INVESTIGATION OF CURING MECHANISM OF FLEXIBLE AQUEOUS POLYMER COATINGS AND EVALUATION OF MONTMORILLONITES AS ANTI-TACKING AGENTS

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To my parents and family,
with love and gratitude

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Table of Contents

1 Introduction

1.1 General

The coating of pharmaceutical dosage form started in the early ninth century B.C., with Egyptian. The pills and hand shaped spherical mass containing drug, sugar and other diluents were the primary dosage form at that time. These dosage forms were coated with a variety of materials including talc, gelatin, sugar, gold and silver. Most of these coatings were ineffective due to a chemical attack in the digestive tract.

The candy making industry was the first to develop and enhance the art of coating and later on the pharmaceutical industry adapted the art of sugar coating for its own purposes. The first sugar coated pills were developed in 1854 in Philadelphia, the USA. Enteric coatings were started in 1880. In 1953, the first compression coated tablets were introduced and in 1954 the foundation for the film coatings was developed (Johnson, 2007).

1.2 Coating applications

There exist numerous reasons for the coating of food and pharmaceutical products e.g., vegetables and fruits are being coated to protect them from temperature, moisture and attack of microbes. Various types of oil based waxes, gums, gelatin, carbohydrates and proteins are used to coat vegetables and fruits. For example, amylose ester of fatty acids/protein bilayer has been used to coat the dried food to prevent stickiness (Grunnerson and Bruno, 1990).

The pharmaceutical dosage forms are also coated to protect the incorporated active ingredients against light, oxygen, moisture, mechanical burden and the degradation in gastric juice. Economic and safety reasons have to be taken into consideration such as product appearance, identification, taste and odour masking of bitter drugs. A variety of release profiles and mechanisms can be adapted: enteric coating, colon targeting, pulsatile release, extended release or fast dissolving. In order to achieve the desired release profile, different polymers have to be selected, which are characterized by different solubility and swelling properties in water, gastric and intestinal fluids.

1.3 Controlled release drug delivery systems

Controlled release, sustained release, sustained action, prolonged action, extended action and time release are the terms used to represent the systems that are designed to achieve a prolonged therapeutic effect by slow and continuous release of active ingredients over extended period of time (Coswar, 1974; Patwardhan and Das, 1983). This period may vary from days to months (in the case of parenteral dosage forms) or hours (in the case of orally administered dosage forms) (Urquhart, 1981).

Controlled release drug delivery systems (DDS) are defined by the FDA as those formulations designed to release an active constituent at rates which differ significantly from those of their corresponding immediate release forms (Gundert-Remy and Moller, 1990).The advantages of controlled release delivery systems include:

- reduced dosing frequency
- reduced total amount of administered drug
- increased safety margin of potent drugs
- reduced incidence of local and systemic side effects and improved patient compliance
- ability to maintain a constant level of active agent for a long period of time

On the other hand, the disadvantages of such systems are:

- does not allow proper termination of therapy
- has less flexibility in dose adjustment
- significant patient variation and economical factors due to costly processes and equipment involved during manufacturing

With regard to the mechanism applied to control the drug release, the design of oral controlled release devices is based on one of the following categories:

- diffusion-controlled systems
- osmotically-driven systems
- chemically-controlled systems

Diffusion-controlled systems

The diffusion–controlled systems can be further divided into membrane–reservoir systems and monolithic-matrix systems. Reservoir systems are made up of a drug core (reservoir) surrounded by a release rate controlling membrane, usually applied by a coating process. In general, the rate controlling membrane consists of a polymeric material plus additives, modifying the properties of the polymer (Chien, 1985). Those polymeric membranes are insoluble in aqueous fluids, but can swell and are permeable for drug molecules allowing diffusion of the drug through the membrane resulting in zero-order drug release, which can be described by the following equation:

$$c = k \bullet t$$

where k is the proportionality factor and c is the concentration of drug released at time t. This relationship is valid if the following prerequisites are taken into consideration: undissolved drug is present in the device, perfect sink conditions, constant surface, membrane thickness and composition, negligible mass transfer coefficient for the portioning of the drug into and out of the membrane.

In contrast, a matrix system consists of a drug homogenously distributed throughout a carrier. The distributed drug may be in the form of monolithic solution or monolithic dispersion depending on the solubility of the drug in the matrix. These systems can be prepared by a variety of methods, e.g., compression, centrifugal pelletization, extrusion and solvent casting or granulation. The drug release from these systems can be approximately described by a square root of time kinetics (Higuchi, 1961; Higuchi, 1963).

Osmotically-driven systems

Osmotically driven systems use osmotic pressure as driving force for the controlled delivery of drugs. A simple osmotic system consists of a core containing drug with or without osmotically active agent, a semi-permeable (i.e. permeable only to water but not to solute) membrane having an orifice for the release of drug. The drug release occurs through the orifice by hydrostatic pressure (Theeuwes, 1985; Marucci et al., 2010; Muschert et al., 2009).

The drug release rate from a simple osmotic system can be described by the following mathematical equation:

$$dM/dt = AK/h\ (\Delta\pi\text{-}\Delta p).C$$

where dM/dt is drug release rate, A is the membrane area, K is the membrane permeability, h is the membrane thickness, $\Delta\pi$ and Δp are the osmotic and hydrostatic pressure difference between the inside and outside of the system, respectively, and C is the drug concentration inside the system.

Chemically-controlled systems

Chemically–controlled systems, such as drug-polymer complexes, ion exchange resins, and prodrugs release the drug by a chemical reaction, e.g., hydrolysis, enzymatic digestion, and ionic dissociation (Sriwongjanyna, 1996). The advantages of those systems include high drug loading, simple drug release mechanism and good stability.

1.4 Controlled release coated dosage forms

Pellets

Pellet has narrated a variety of systematically performed, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. Pelletization is an agglomeration process that converts fine powder or granules of bulk drugs and

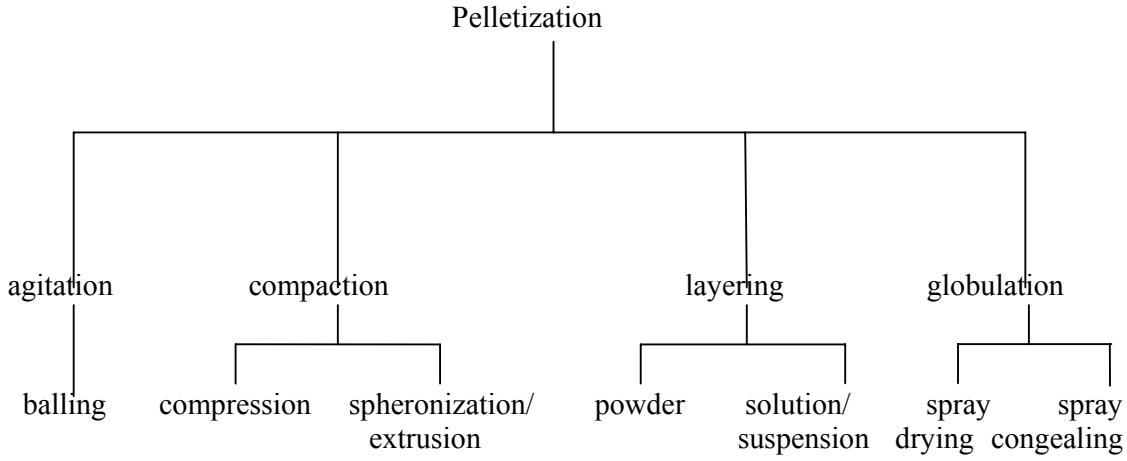


Figure 1: *Classification of pelletization processes.*

excipients into small, free flowing, spherical units, referred to as pellets. Pellets range in size between 0.5-1.5 mm, though, other sizes could also be prepared, depending on the processing

technologies employed (Ghebre-Sellassie, 1989). The most widely used pelletization processes in pharmaceutical industry are schematically illustrated in Figure 1.

Pellets exhibit less risk of local toxicity than tablets due to their uniform distribution throughout the gastrointestinal tract (Khosla and Davis, 1990; Dressman et al., 1998). In the case of single unit dosage forms, the destruction of the film would result in dose dumping and loss of sustained release properties. The pellets are less susceptible to risk of dose dumping compared to the reservoir type single unit dosage forms (Ghebre-Sellassie, 1989; Bodmeier, 1997). Due to improved safety and efficacy of drug, and having flexibility in design and development of dosage form, the pellets are preferred over tablets (Daumensil, 1994; Bodmeier, 1997). The advantages of multiple units over single unit dosage forms are enlisted in Table 1.

Table 1 *Comparison of single and multiple unit dosage forms*

Single unit	Multiple unit
▪ Susceptible to risk of dose dumping and local irritation	▪ Restricted risk of dose dumping or local irritation
▪ Gastric residence time is highly influenced by food intake	▪ Gastric residence time is less influenced by food intake
▪ Inter- and intra variability in rate and extent of absorption	▪ More reproducible absorption

Since pellets are uniformly distributed throughout gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability.

Pellets provide immense flexibility during the development of oral dosage forms. Pellets containing different drugs can be blended and formulated in a single dosage form. This helps in delivery of chemical incompatible drugs, acting at the same or different sites within the gastrointestinal tract. Additionally, the pellets of different release rate can be combined to achieve desired release profile (Ghebre-Sellassie, 1989). Importantly, the drug loading up to 90% with good content uniformity is achievable (Mesiha and Valles, 1993). Other

technological advantages include low surface area to volume ratio, ideal shape for application of film coatings, good flowability, low friability and narrow particle size distribution (Reynolds, 1970).

Tablets

Tablets are defined as solid dosage forms produced by compaction of a formulation containing the drug and certain filler or excipients selected to aid in the processing and properties of the drug product. Compressed tablets are traditionally used for oral dosage forms, since they are convenient, easy to apply, portable, and less expensive than other dosage forms (Bandelin, 1989). The purpose of tablets is determined by their design.

Conventional film coatings are applied to improve product appearance, comfort of swelling, to provide the moisture protection and unpleasant taste masking of the drug. Generally, prior to the coating the immediate release tablet is formulated. Thus, tablet disintegration mainly influences the effective surface area available for drug dissolution. In the case of immediate release tablets, the quality and quantity of disintegrant play a vital role (Massimo et al., 2000).

Another important reason for the coating of tablets is to protect the drugs and excipients sensitive to moisture (Rudnic and Kottke, 1996; Du and Hoag, 2001). Commonly, hydroxypropyl methylcellulose (HPMC) is applied for this purpose (Plaizier-Vercammen and De Nerve, 1993; Budavari et al, 1996) but also polyvinyl acetate (Kollicoat® SR 30 D) and methacrylic acid copolymers (e.g., Eudragit® L 100) are being used for moisture protective properties (Lehmann, 1997). Importantly, care has to be taken for the selection of coating polymer, so that the resulting drug release kinetic within the stomach remains unaltered. Thus, the moisture protective coatings must rapidly dissolve and/or rupture upon contact with the release medium. Polymeric film coatings surrounding the drug-containing tablets can be applied to mask the bitter and/or unpleasant taste of drugs leading to improved patient compliance (Roy, 1994; Besse et al., 2001). HPMC is the most commonly used polymer for this purpose (Nagai et al., 1997; Kokubo et al., 2001).To improve the taste masking properties, ethylcellulose is also used as coating material (Bodmeier and Siepmann, 1999) and frequently added to HPMC-based coatings (Lehmann, 1994; Siepmann et al., 2007). Also thin acrylic films can be applied (Lehmann, 1994; McTeigue et al., 2002).

Soft gelatin capsules

Several advantages of soft gelatin capsules derive from the fact that the drug is in liquid form or at least dissolved, solubilized, or suspended in a liquid vehicle. In addition, a higher degree of homogeneity is possible in liquid systems that can not be in powder blends (Augsburger, 1995). Thus, the preparation of drugs into soft gelatin capsules can solve many troubles involved in the tabletting (e.g., poor compaction, lack of content or weight uniformity, and other powder flow or mixing problem). Soft gelatin capsules are appropriate for use with compounds that are sensitive to oxidation or those that are photosensitive because the gelatin shell can provide a barrier to oxygen and can be rendered opaque by use of opacifiers. As in the solid state the photochemical process occurs on the product surface, a capsule and a tablet have different light scattering characteristics and different ratios of surface area to volume resulting in a variation in the photodegradation of the active principle (Tonnesen, 2001). Another derived advantage from the liquid nature of the fill is an immediate release of the contents with potential enhanced bioavailability. The proper choice of vehicle may promote fast dispersion of capsule contents and drug dissolution (Augsburger, 1995). The most commonly used vehicles for soft gelatin capsules fills are oils and polyethylene glycols. Migration of water and plasticizer from the shell to shell could lead to crystallization of poorly soluble drugs, as well as brittleness in the capsule shell. Thus, selecting appropriate filling materials and shell composition is important in the design of soft gelatin capsule dosage forms (Shah et al., 1992).

1.5 Mechanism of drug release from coated pellets

The major mechanism of drug release from coated pellets form is given by the solubility of the polymer in the gastrointestinal tract. Additionally, the drug release is also influenced by the pKa of polymer, coating thickness, and acidic and basic excipients of the pellet core. For the water insoluble polymers, the drug release follows different phases. The medium first hydrates/penetrates the coating, dissolve the drug and produces a saturated drug solution, assuming sufficient drug in the pellet core. Then drug diffuses at a constant release rate out of the core as long as a saturated solution is present.

Several possible mechanisms following this principle are given below (Dressman et al, 1995):

a) Solution/diffusion through the continuous plasticized polymer phase

This mechanism is followed by the systems that form a continuous phase in which plasticizer and excipients are homogenously dispersed. This mechanism is favourable for the coating of organic solution, which forms complete film without cracks and where the drug has relatively high affinity for the polymer compared to water. The release rate can be described as under:

$$J= P_m/\sigma\ (C_s\text{-}C_b)$$

$$P_m = D\varepsilon/\tau\beta\ K= D\ K$$

Where J is the flux, σ the coating thickness, P_m the permeability coefficient, C_s and C_b are the concentration of drug at the drug-coating interface and the bulk respectively, D the molecular diffusivity of the drug, K the distribution coefficient of the drug between polymer and fluid in the core, ε the volume fraction of the chain openings, β the chain immobilization factor, t the tortuosity factor and D the apparent diffusivity.

b) Solution/diffusion through plasticized channels

This mechanism seems to be unlikely, because the formation of continuous plasticizer channels represents an extreme condition and the plasticizer will be mostly distributed more or less uniformly throughout the polymer. Moreover, the drug solubility in the plasticizer channels would have to be higher than in water.

c) Diffusion through aqueous pores

The drug releases through the aqueous pores when the coating is not homogenous and pores are formed due to incomplete film formation. This usually happens in the case of aqueous polymeric coating when unfavourable processing conditions are used. The permeability coefficient P_p can here be expressed as:

$$P_p = \varepsilon_p\ D_p/\tau_p$$

ε_p is the volume fraction of the aqueous channels and τ_p is the tortuosity of the aqueous channels, D_p is the aqueous diffusivity of the drug.

d) Osmotically driven release

Drug release can be driven by an osmotic pressure difference between core and release medium for a porous coating. This is important for highly water soluble core materials, such as sucrose in nonpareils and highly water soluble drugs. The release rate of the drug through pores of the coating can be described by:

$$J = K\ \sigma\ \Delta\pi\ (C_i\text{-}C_m)$$

Where K is the filtration coefficient, σ the reflection coefficient of the coating, $\Delta\pi$ the osmotic pressure difference, C_i and C_m the interior and media concentrations, respectively.

However, several studies stated that the overall drug release mechanism, acting with the investigated dosage forms with water-insoluble polymers, is a combination of two or more of the above mentioned mechanisms (Hoffman, 1986; Ozturk et al, 1990). Additional other factors like swelling of the core or the film are capable to contribute to the release mechanism of these systems. It was believed that swelling of the coating was accompanied by an osmotic driven release mechanism for ethylcellulose-coantaining membrane (Hjartstam and Hjertberg, 1998).

1.6 Coating equipment and process parameters

1.6.1 Coating equipment

Several coating technologies are being used for the coating of solid cores (Mehta, 1989; Christensen and Bertelsen, 1997). Conventional coating pans, which are traditionally used for sugar coating, have been improved by different modifications for a better air flow, drying capacity and coating uniformity. For example, perforated pans allow an intensive contact of the drying air with the cores. Hi-coater (Vector), Accela Cota (Thomas) and Dria-Coater or the Glatt are the famous coating machines.

Fluidized bed equipment is available for the coating of smaller cores, such as pellets, granules and poweder. Different applied techniques include the top, bottom (Wurster) or tangentially (rotary granulator) spraying mode (Jones, 1994; Deasy, 1991). A typical description of a fluidized bed coater with top and bottom spray nozzles is given in Figure 2. The top spray process is less efficient in film-coating than the Wurster and tangential process (Mehta et al, 1986) and also less effective in drug layering than rotary equipment (Iyer et al, 1993). The rotary granulator technique allows pelletization and subsequent coating as a one step process (Vecchio et al, 1998). These methods use water or organic liquids as solvents or dispersion media which must be removed by drying during coating process.

In the hot melt coating technique the coating material is applied in a melted state onto the substrate. The main advantage of this method is the reduced processing time, because no solvent is required. Hydrophobic coating materials, such as waxes, fatty bases and hydrogenated oils are used, which should have a melting point less than 80 °C and an

acceptable thermostability. Hot melt coating can be performed in a modified fluidized-bed coater, where the melted material is delivered onto the substrate without solidification (Achanta et al, 1997; Jozwiakowski, 1990).

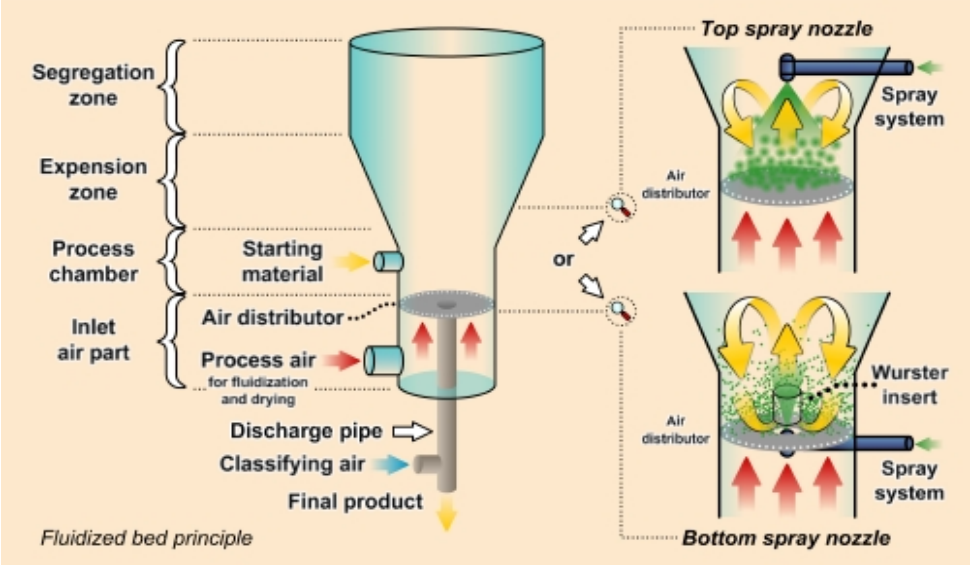


Figure 2: *A fluidized bed coater with top and Wurster bottom spary nozzles.*

Dry coating is a novel coating method, which applies the micronized ploymer powder directly onto tablets or pellets with a powder feeder, while simultaneously spraying a plasticizer. In the first step, polymer particles are deposited onto cores and in the second step they are cured by heating for a short time to achieve film formation. This technique was first developed for the manufacturing of enteric coated dosage forms. It has the advantage of reduced processing time and less need of energy due to the absence of solvent evaporation (Obara et al, 1999). A special technique is the electrostatic tablet coating, which uses an electrical field for the powder deposition onto core and afterwards particles are formed into a film by applying of heat.

Another solvent free coating method is based on photocurable polymers. Wang and coworkers used a liquid photocurable formulation based on norbone-endcapped polydimethylsiloxane, which was applied onto nonpareil beads in a laboratory-scaled pan-coater. A relatively impermeable coating was achieved by crosslinking the silicone based polymer upon ultraviolet irradiation (Wang et al, 1995).

1.6.2 Process parameter

The manufacturing of coated dosage form is a complex process and homogenous film has to be formed onto the core to control the drug release. In fact, several processes take place simultaneously during the coating process. These include atomization of the spraying liquid and droplet formation, contact and spreading over the surface of the substrate, evaporation of the liquid and coalescence of the particles to form a film (Christensen and Bertelsen, 1997; Jones, 1988). The air volume in fluid-bed processes should promote the particle movement, prevent agglomeration and dry the coated substrate. Several studies have been made to investigate and optimize critical process parameters for manufacturing of coated dosage forms, which could have a significant influence on the release of controlled release dosage forms.

Some critical parameters of fluidized bed coating are as under:

- Fluidization air volume, which affects fluidization pattern and particle velocity
- Fluidization air temperature, which is important for the evaporation of the solvent and the softening of the latex particles, but is limited because of stickiness of the product
- Fluidization air humidity, which should be kept constant to minimize batch-to-batch variability of the coating process and should be limited to maximize the drying efficiency of the coater
- Solid application rate, which depends on the solid concentration and the liquid spray rate, is restricted by over wetting and the tackiness of the coating
- Atomization air pressure, which controls the droplet size and spraying pattern

Importantly, the properties of the substrate such as density, diameter and stickiness influence the coating process (Christensen and Bertelsen, 1997). The flow of particles in a Wurster column and the uniformity of particle coverage were investigated (Cheng et al., 2000; Cheng, 2000). The release profile was tremendously affected by difference in fluidization pattern and velocities and it has been shown with different coater chamber geometries or spray mode (Yang et al., 1992) or with beads of various sizes. The beads with high density and diameter had thicker films and thus a slower drug release than smaller ones. The release rate was shown to be directly proportional to the surface area of the coated cores (Rangarsson and

Johansson, 1988). Inappropriate process conditions during manufacturing of the coated dosage forms can lead to stability problems.

Product temperature

The product temperature and a subsequent curing phase are of particular importance for aqueous systems, in comparison to organic coating (Lorck et al., 1997). Inlet-air temperature was found to be most critical variable in this regard (Parikh et al., 1993). A too low product temperature can be one determinant, which can affect the completeness of coalescence. The optimal product temperature for complete coalescence should be approximately 10-20 °C above the minimum film formation. The complete coalescence to a homogenous film is only possible, when the polymer chains are mobile enough to facilitate deformation and fusion. Above the optimum temperature, too fast water evaporation on the pellet surface could lead to spray loss. The time necessary for the capillary forces to achieve complete coalescence of the particles could be insufficient, leading to a faster drug release. A low dispersion concentration could lead to a slow drug release because the capillary forces could act longer, since more water was available for evaporation (Laicher et al., 1993). Furthermore, the coalescence temperature can be important for the mechanical properties of films, as shown for Surelease® (Parikh et al., 1993; Obara and McGinity, 1995). Besides at high coating temperatures, the problem of tackiness during coating can also occur because of interaction of drug with spray-dispersion ingredients. This was pronounced, when ibuprofen pellets were coated with Aquacoat® ECD dispersion already at low product temperature (Bodmeier and Paeratakul, 1994). The reason for this behavior could be the formation of a eutectic system with ibuprofen and cetyl alcohol, the stabilizer of Aquacoat® ECD (Schmid, 2000).

1.7 Polymer coating systems

Polymer is generally dissolved in a suitable solvent, aqueous or non-aqueous for application as a coating material. The high cost of organic solvent, high price of solvent recovery systems, strict air quality controls, and environmental toxicity and explosiveness have motivated pharmaceutical and food supplement to not use organic solvents during the coating process. Presently, the water-insoluble polymers are available in a form which makes them usable from aqueous systems. As a result, aqueous-based systems have been developed and used instead of organic polymer solutions because of their environmental and economic advantages. However, because water has a high heat of evaporation, aqueous-based systems

that might require processing times seemed initially to have a serious economical disadvantage despite of their environmental advantages. In addition to the conventional liquid-based systems, dry powder coating has been developed as an alternative technology. It is generic designation for a variety of processes for applying a coating to substrate using polymeric powder. One major advantage of this coating system is that it is environmentally benign, producing none of the organic or aqueous waste streams, which normally are presented in conventional liquid-based coatings. The continuous success for dry powder coating is also related to its known economical advantages, including reduction in processing time and in costs of environmental safety, compliance and energy use (Leong et al., 1999; Obara et al., 1999).

Organic coating

Organic solvents are preferred over aqueous to form a continuous film especially for water insoluble polymers. Alcohols (e.g., ethanol, isopropanol) are the mostly commonly used solvents. As some polymers consist of structural units that form hydrogen bonds, the water is good co-solvent. 3-5% of water is suggested to be added to a mixture of ethanol-acetone for polymethacrylate copolymers (Lehmann et al., 1989). An important aspect is the relatively high viscosity of polymeric solutions, which depends on the molecular weight and affinity of the polymer to the solvents. High viscosity polymer solutions are obtained due to spreading of polymer chain when the solvent has high affinity to the polymer chain. With the solvent which has a lower affinity to the polymer, some polymer chain aggregation and shrinkage of the polymer leads to lower viscosity. For that reason, the mixtures of the solvents can provide better dissolution properties of the polymer as well as lower solution viscosity, in relation to the concentration of the solid polymer.

For an organic polymer solution, a continuous film can be formed throughout the surface of the substrate after the solvent is evaporated. In contrast to polymer latexes, polymer in organic solution will form the film at room temperature, irrespective of the Tg of the polymer. The gel formation is the most important phase, and the solvents that can not gel yield poor films, which were indicated by poor transparency (Spitael and Kinget, 1980). Since the polymer coils in good solvents will interpenetrate to a more compact structure than the poor one, the compact molecules in solution will remain compact in the film state. It should be noted that the sprayed films show comparatively a higher degree of porosity than the casted films,

because the droplet-like nature created during spraying, which remains apparent in the resulting final film structure (Spitael and Kinget, 1977).

Using the mixed solvent system, it contains a good solvent of high evaporation rate under the coating conditions. It is sometimes very useful in the mechanism of film formation upon coating phase. The corresponding processes are as follows: firstly, a droplet of polymer solution reaches the core surface; it has a high spreading tendency due to the low viscosity of the diluted polymer solution, secondly, the more volatile solvent is a better choice for the polymer due to its quick evaporation, the polymer solution in the poor solvent becomes less sticky and gelation takes place at higher polymer concentration. However, there is also higher tendency of the polymer to retain the solvent of higher affinity in the film (Lehmann, 1994).

Dry powder coating

Paint industries have been interested in the preparation of films from dry powder formulations. Powder coating, which directly attaches polymer particles without using any organic solvents, is a promising alternative approach. Compared to liquid-borne coatings, the film formation process of dry powder coating is different since it is happening in the molten phase. Softening, melting and cure completion are the principal stages in the film formation of powder coating (Leong et al., 1999; Wulf et al., 2000; Pfeffer et al., 20001). A new alternative procedure known as dry powder coating has been developed with potential applications for film-coated dosage forms. In an effort to adjust to the new trends and enhance the versatility of the polymer a novel coating technology with micronized hydroxypropyl methylcellulose acetate succinate (HPMCAS) powder coating onto drug-loaded pellets and tablets was developed by Obara and his co-workers (Obara et al., 1999). Compared to an aqueous HPMCAS dispersion, the enterically coated pellets and tablets with HPMCAS powder require a higher polymer amount for achieving gastric resistance. A big advantage of dry powder coating is shorter processing time.

Aqueous dispersion coating

Polymeric material that is insoluble in water is commercially manufactured as aqueous colloidal dispersion for extended release coatings. They are classified as true latexes or pseudo latexes depending on the technique of production. With organic coating, the polymer pattern is fully-entangled chains because the polymer is dissolved in the molecular state. The film formation in organic coating process occurs due to simple loss of the solvent due to close association of solvent to polymer. In contrast to aqueous dispersion systems where water

serves only as a carrier for the dispersed particles and not as solvent, the continuous phase does not have a high level of interaction with the polymer molecules. Particle deformation must occur in order to obtain a complete film formation (Osterwald, 1985; Iyer et al., 1990; Sun et al., 1999).

1.8 Aqueous polymer dispersions

Aqueous polymer dispersions have been gaining a tremendous attraction for the coating of solid dosage form for last two decades. They provide the possibility of applying water insoluble polymer to substrates without using organic solvents, thus preventing the environmental risks associated with them. Aqueous polymer dispersion coatings offer the following advantages over organic polymer solution coatings:

Table 2 *Comparison of organic solution and aqueous dispersion polymeric coatings*

Organic coating	Aqueous coating
▪ Expensive process due to use of organic solvents	▪ Economical process because water is used as a solvent
▪ High risks of environmental hazards and toxicity	▪ No risk of environmental hazards at all
▪ Not possible to coat high solid content	▪ High solid contents with low viscosity can be applied

Aqueous colloidal polymer dispersions are classified as true latexes or pseudolatexes on the basis of production technique. These latexes are prepared by emulsion of a monomer or by emulsification of performed polymer. Different emulsification methods are available to prepare colloidal dispersions. These methods include solution emulsification (solvent evaporation), phase inversion and self emulsification. All these emulsion polymerization processes require the addition of initiators that function by free radical, anionic or cationic polymerization mechanisms. They are also stabilized with aid of anionic or nonionic surfactants. The conversion of water insoluble polymers into colloidal aqueous polymer dispersion was developed at emulsion polymer institute, Lehigh University under direction of

Dr. John W. Vanderhoff (Vanderhoff et al., 1979) and it was applied to pharmaceutical polymers at Physical Pharmacy Department, Purdue University.

1.8.1 Polymers

1.8.1.1 Polyvinyl acetate

A new aqueous polymer dispersion, Kollicoat® SR 30 D, produced by an emulsion polymerization process, was developed and is available with a solid content of 30%. It consists of 27% polyvinyl acetate, 2.7% polyvinyl pyrrolidone (PVP) as a pore former, and 0.3% sodium laurylsulfate (Kollicoat® SR 30 D technical information, 2007). The dispersion can be used for pH-independent extended release formulations or with thin film coatings for taste masking purposes (Dashvesky et al., 1999; Kolter and Ruchatz, 1999). In blended films, the polymer is used for the development of particular kinds of drug release systems, e.g. colon targeting (Rock et al., 2000). If unplasticized, it has a MFT of 18 °C and results in brittle films in dry state. Plasticizers are added to improve mechanical properties of the coating and the final MFT depends on the type and amount of plasticizer added.

1.8.1.2 Acrylates

Acrylates are used in different industries. Poly (methyl methacrylate) is a well known synthetic material, known as Plexiglas, which has important technical properties, such as hardness, low specific gravity and an excellent long term-stability. For pharmaceutical purposes, acrylates of different chemical compositions and solubility properties are available under the trademark Eudragit® (Eudragit® technical information, 2010). (Meth) acrylate copolymers, which are insoluble over the entire physiological pH range, are especially used for extended release dosage forms.

Eudragit® NE 30 D

The neutral poly (ethylacrylate-methylmethacrylate) [poly(-EA-MMA)] with ratios of 2:1 (Eudragit® NE 30 D/ NE 40 D) is present in aqueous latex dispersions, produced by emulsion polymerization. It is mainly used for transdermal formulation or buccal patches, wet granulation and film coating. Soft films are formed from polymer dispersion without the need of a plasticizer below room temperature. For coating, anti-tacking agents are useful to reduce the stickiness of the polymer.

Eudragit® RL/RS 30 D

Cationic polymers of poly (ethylacrylate-methylmethacrylate) trimethylammonio ethylmethacrylate chloride [poly(-EA-MMA-TAMCl)] with ratios of 1:2:0:1 (Eudragit® RS 30 D), and 1:2:0:2 (Eudragit® RL 30 D), respectively, are pseudo latexes with a solid content of 30%. The colloidal polymer particles are stabilized by the positively charged quaternary ammonium groups, which have chloride ions as counterions. Since Eudragit® RL 30 D possesses the double amount of ionized groups; it is more hydrophilic and has a higher tendency of swelling in water than Eudragit® RS 30 D. Drug release can be controlled from coated dosage forms by the film thickness and by the mixing proportions of Eudragit® RL 30 D and RS 30 D, which determines the film permeability.

1.8.1.3 Ethyl cellulose

Ethylcellulose is a hydrophobic coating material used for controlled drug release, moisture protection and taste masking. It is a semi-synthetic polymer manufactured from cellulose and transferred with sodium hydroxide to alkali cellulose (Rekhi and Jambhekar, 1995). Ethylcellulose is insoluble in gastro-intestinal tract and assures pH independent drug release profiles due to its neutral side chains (Siepmann et al., 2007). It is widely used in oral drug delivery as film former, since it is non-toxic, non-allergenic and non-irritant. Ethyl cellulose water permeability is very low around one tenth of cellulose acetate (Bindschaedler et al., 1983).

1.8.2 Mechanism of film formation

Film formation from aqueous polymer dispersions is entirely different from the conventional organic coatings, where the polymer solution undergoes a sol gel transition upon solvent evaporation to the final film. For latexes, it is complex and quality determinant in pharmaceutical coating. Film-forming polymer latex is deposited from an aqueous colloidal dispersion of discrete polymer spheres and the formation of a continuous film is then entirely dependent on the minimum film formation temperature (MFT) of the polymer. The MFT is defined as the minimum temperature at which latex-cast films become continuous and clear (Lehmann, 1994; Keshikawa and Nakagami, 1994; O' Donnnel and McGinity, 1997) (Eckersley and Rudin, 1990; Steward et al., 2000). Typically, the coalescence of latex particles takes place only above the MFT. In order to achieve MFT above the coating temperature for the aqueous polymer dispersions, the addition of plasticizers is required (Bodmeier et al., 1997). The plasticizers not only improve the flexibility and toughness of the

resulting films, but also soften the dispersed polymer particles and facilitate their deformation and final coalescence (Harris and Ghebre-Sellassie, 1997).

The mechanism of film formation during drying is of theoretical and practical interest since film properties are related to the performance of the resulting coatings (Vanderhoff, 1970; Onion, 1986a; Eckersley and Rudin, 1990; Hogan 1995a; Wheatley and Steuernagel, 1997). The general mechanism of latex film formation is as follows: compaction, deformation, cohesion and polymer chain inter-diffusion. Each stage is characterized by the corresponding phase of the latex layer on the substrate and the associated changes in the evaporation rate of the aqueous dispersion medium.

Theoretical considerations

The film formation process of aqueous polymer dispersions can be described in three phases: 1) evaporation, particle concentration and ordering, 2) particle deformation, and 3) polymer chain inter-diffusion across particle boundaries (Vanderhoff, 1970; Onion, 1986a; Eckersley and Rudin, 1990; Hogan, 1995a; Wheatley and Steuernagel, 1997; Steward et al, 2000). A description of film formation mechanism from aqueous polymer dispersion is elaborated below in Figure 3.

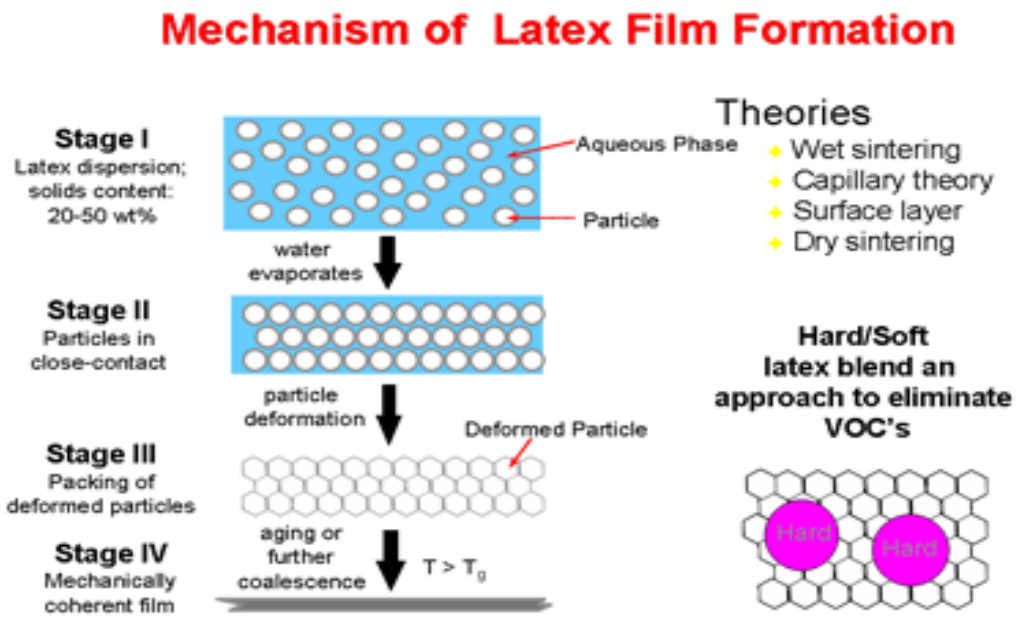


Figure 3: *Mechanism of film formation from aqueous colloidal polymer dispersion.*

Phase1: Water evaporation and particle concentration

The first phase is the longest period of the three phases and last until the polymer has reached approximately 60-70% volume fraction, or until the surface area of the latex's liquid-air interface starts to reduce as a consequences of solid film formation. Initially, the polymer particles move freely with Brownian motion, colliding with one another and rebounding elastically. Water evaporates from the latex surface, concentrating the latex surface and solid contents. The ability of polymer particles to move about becomes more and more limited, until some point they come into contact with one another and all particles motion ceases.

Phase II. Deformation of latex particles

This phase begins when the polymer particles come into contact, and iridescence may be seen on the latex surface. The evaporation rate per unit of open wet latex remains constant, but the overall rate of evaporation decreases significantly during the second phase. Since the drying progresses further, the polymer particles are no longer mobile in the bulk latex and pack in an ordered array, as a hexagonal close packed lattice. It has been suggested that hexagonal close packing is theoretically possible, as well as cubic close packing. However, both shapes are not easily distinguishable, since they share many geometrical features.

Phase III polymer chain inter-diffusion across particle boundaries

This phase starts with the initial formation of a continuous film. The remaining water leaves the film initially via inter-particle channels and then by diffusion through the fused polymer skin, but the rate of evaporation eventually slows down. It is during this final phase that soft latex becomes more homogenous and gains its mechanical properties. As polymer chain inter-diffusion takes place a process variously termed such as maturation, autohesion, or further gradual coalescence (FGC) and particle interface tend to become less distinct. A drastic change in film properties between phase II and III is that the initially brittle cohered particles turn more ductile due to polymer chain entanglements.

In 1958, Voyutskii theory proposed that the surface tension forces (Dillon-Matheson-Bradford) and capillary forces (Brwon) were inadequate to account for the physical properties indicated by the latex films, instead, these resulted from conglomeration or "autohesion" such as mutual inter-diffusion of free polymer chain ends across the particle-particle interface in the coalesced film. As a result, the mutual inter-diffusion of polymer chain ends makes the latex film homogenous and thus improves its physical-mechanical properties.

1.8.3 Additives

Different types of excipients are usually added to aqueous polymeric dispersion before coating for several reasons. Most commonly used are plasticizers, anti-tacking agents and pore formers. These excipients strongly influence film properties, coating process and release rate of the coated dosage form. The coating formulations need to be optimized in order to have optimized coating conditions.

1.8.3.1 Plasticizers

Plasticizers are usually high-boiling point organic solvents used to impart flexibility to brittle and hard polymers. They generally act by reducing cohesive intermolecular forces within the polymer chain leading to different changes in polymer properties. For instance, plasticizers cause reduction in tensile strength, increase in elongation and flexibility and reduction in glass transition temperature. The addition of plasticizers is required to reduce minimum film formation temperature (MFT) below the coating temperature (Bindschaedler et al., 1983). During the plasticization process, the plasticizer diffuses into polymer particles and promotes the particle deformation and coalescence to form homogenous film. For good plasticization effect, the plasticizer should be compatible with the polymeric particles.

Plasticizers, which are not compatible to polymers, can cause coagulation of the dispersion and this phenomenon has been shown for ethyl acrylate/methacrylic acid copolymer formulations (Kollicoat MAE 30 D) (Flößer et al., 2000; Dangel et al., 2000). Therefore, the selection of appropriate type and concentration should be made very carefully. The concentration below the appropriate concentration could have anti-plasticizing effect (Guo, 1994; Guo et al., 1992). Addition of polyvinyl alcohol (PVA) to hydroxypropyl methylcellulose (HPMC) films lead to increase in Tg, because of an increase in crystallinity (Okhamafe and York, 1984).

1.8.3.2 Pore-formers

Pore formers are often added to the coating formulations to adjust the drug release of extended release coatings. Commonly used pore-formers include 1) low molecular-weight materials like sugars (e.g., sucrose, lactose, sorbitol), salts (e.g., sodium chloride, calcium phosphate) and 2) hydrophilic polymers (e.g., polyethylene glycol, polyvinylpyrrolidone and HPMC) or surfactants such as sodium lauryl sulfate (Muhammad et al., 1992; Li et al., 1990; Erdmann et al., 2000). During dissolution, theses pore-formers leach out of the coating

membrane resulting in more permeable membrane and increase in drug release. The concentration of the pore former can control the release kinetics, as shown for ethyl cellulose coatings and different polysorbates as additives (Samani, 1999). The drug release from Aquacoat coating was increased by using urea as pore-former which made the film more porous (Appel and Zentre, 1991). Also the drug release from the Aquacoat coatings was stabilized under stress conditions by adding pore-formers (Siepmann et al., 2007; Siepmann et al., 2008; Muschert et al., 2009). Calcium phosphate is an example for an inorganic salt, which is insoluble in dispersions with a neutral or alkaline pH. In the acidic artificial gastric fluid, it is soluble and leaves a microporous membrane coating (Bodmeier and Paeratakul, 1991; Bodmeier and Paeratakul, 1990).

In a recent study, Aquacoat ECD and Kollicoat SR 30 D dispersions were found to be stable with up to 50% addition of polyvinylpyrrolidone and polyvinyl alcohol-polyethylene glycol graft copolymers (Dashevsky et al., 2010).

1.8.3.3 Anti-tacking agents

Anti-tacking or separating agents and pigments are commonly added to aqueous polymer formulations to reduce agglomeration or sticking of coated particles during the coating process. Talc, magnesium stearate, glyceryl monostearate (GMS) and titanium dioxide are most commonly used pigments as anti-tacking agents in aqueous film coating.

Talc is used as an anti-adherent agent, which is known to have a tendency for sedimentation and blocking of nozzles during the spraying process. Therefore, the coating dispersion should be continuously kept under stirring during the coating process. The amount of pigments in the aqueous dispersion must be optimized without exceeding the maximum carrying capacity of the polymer or critical pigment volume concentration (CPVC). The pigment concentration has a strong influence on the final film properties such as a mechanical strength and permeability (Patton, 1979). An increase in drug release rate was found, which was explained with the adsorption capacity, the high specific surface area and the high affinity of colloidal silica for polar components like water (Vecchio et al., 1995). Polymer dispersions can have a high binding capacity for pigments. To prevent sticking, up to 200% talc, based on dry polymer mass, were incorporated into coatings of Eudragit® RL/RS 30 D plasticized with high levels (up to 30%) of TEC (Maejima and McGinity, 2001).

GMS was shown to have a ten-time higher anti-tacking effectiveness than talc and can be used at lower concentrations. The addition of talc and GMS lead to decrease in flexibility of

and the effect was increased as a function of concentration (Wesseling and Bodmeier, 1999; Peterit et al., 1999). Magnesium stearate was effective as anti-tacking agent for methylcellulose coated granules but it strongly increased the drug release by making film rough. An orange peeling effect of film coating was observed, when the granules swelled in the release medium (Wan and Lai, 1993). During coating, fine particles have a particular high tendency of agglomeration. This could be reduced by adding NaCl to an aqueous spray solution of hydroxyl propylcellulose (Fukumori, 1993). It was suggested that the suppression of agglomeration was caused by a reduction of viscosity of the spray solution through salting out of the polymer (Yuasa, 1997).

1.8.4 Adhesive force of polymeric coatings

Adhesion force between a polymer and substrate is very important pre-requisite for the coated dosage forms (Nadkarni et al., 1975; Rowe, 1977; Felton and McGinity, 1999). The decrease in adhesion force due to accumulation of moisture at coating-substrate interface potentially affects the mechanical protection and the stability of the coated dosage forms (Okhamafe and York, 1985). Therefore, to have a stable product over long period of time, the adhesion force between coated polymer and substrate should not be changed during storage.

Generally, the adhesion of the polymer-substrate have been affected by two major forces 1) the strength of interfacial bonds and 2) the internal stresses within the film. The factors that affect these two parameters will also have a significant influence on the adhesion of the coatings. A distinction must be made between “fundamental” and “practical” adhesion. The former refers to the intermolecular interactions between the polymer and the substrate (Mittal, 1980) and the latter refers to the numerical value that results from a variety of testing methods, including shear and tensile tests.

The earliest method for determine the adhesive force of polymeric coating to substrate surfaces was the “Scotch tape” test where a piece of adhesive tape was applied to the coating surface and then peeled off (Strong, 1935). It was obviously qualitative method and did not provide accurate measurement of adhesive force. However, the first quantitative method to determine the adhesion force was developed by Heavens in 1950. In this method, the tip of hard stylus is drawn across the surface of film and critical load required to completely detach the film from substrate is determined and related to polymer adhesion. Another important way of determining quantitative adhesive force is the “butt adhesion” method. In this method, double sided-adhesive tape is placed between the tablet surface and the upper plate and a

uniform displacement rate should be used to remove the film from substrate (Rowe, 1980). Felton and McGinity used a Chatillon digital force gauge and motorized test stand to conduct butt adhesion experiments (Figure 4). The apparatus was connected to a personal computer and force-deflection diagrams were constructed from the data, which allowed the visualization of the development of the force within the sample during the adhesion experiments.

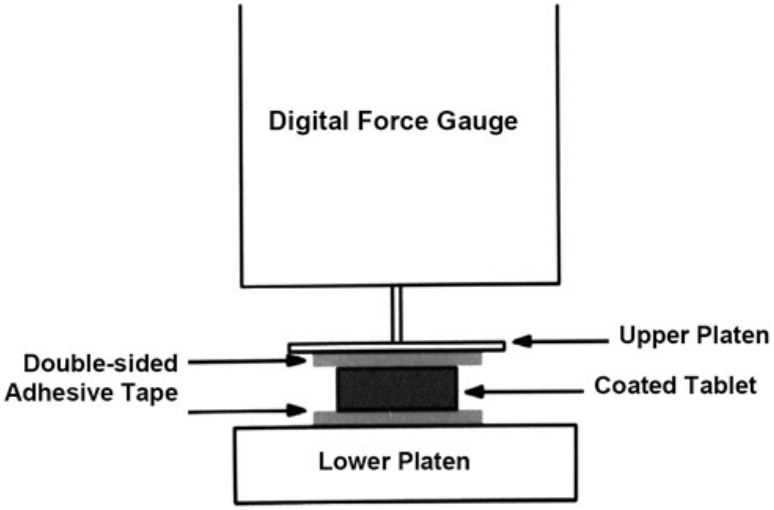


Figure 4: *Schematic representation of a butt adhesion test.*

The adhesive force can also be affected by the shape of the tablets. The force required to remove the film from the surface of the biconvex tablets was lower than the same films coated onto flat-faced tablets (Rowe, 1977). However, the flat faced tablets are preferred due to proper sticking of adhesive tape (Fisher, 1976; Lehtola, 1995; Felton and McGinity, 1996). Felton and McGinity used flat-faced punches with a beveled edge to achieve a more uniform adhesion of the polymeric film.

Film thickness could also influence the adhesive force. It was shown that for films up to a thickness of 35 μm resulted in decreased adhesion of an organic-based cellulosic polymer, while films greater than 35 μm in thickness exhibited increased adhesion with increased film thickness and similar results were reported for aqueous and organic-based hydroxypropyl cellulose and aqueous-based acrylic polymeric films (Felton and McGinity, 1996; Johnson, 1986).

The surfactants are used to enhance the wettability of polymer dispersions on tablets (Felton et al., 1997). The adhesion of polymeric coatings could also be affected by the drug-excipients and drug polymer interactions (Sarisuta et al., 2006; Khan and Fell, 2001).

1.8.5 Curing

The process in which coated dosage forms are stored at elevated temperatures to promote further gradual coalescence of the film is known as curing. It can also be defined as the input of energy into film-coated system after the desired film coat level is applied (Hamed and Sakr, 2003). Curing of film-coated dosage forms is an important component in the film-formation mechanism from aqueous latexes. During coating process, the curing takes place to a certain extent itself. However, this is fairly inadequate. To assure the completion of coalescence, the dosage form is generally exposed to elevated temperature after the coating. This can be done in the coating machine using a process known as post-coating fluidization (Harris and Ghebre-Sellassie, 1986) or by placing the coated dosage forms in an oven (Goodhart et al., 1984; Lippold, et al., 1989).

As the film formation process from the aqueous polymeric dispersions depend on capillary forces to draw together and deform the latex particles and is highly influenced by the amount of water in the polymeric film and environmental temperature. The increased temperature and amount of water in the polymeric films decrease the Tg of colloidal particles, resulting in an increased mobility of the polymer chains, which in turn enhances the further gradual coalescence of the latex particles. As a result, better film formation takes place. On the other hand, decreased temperature and reduced amount of water in polymeric film will not produce enough capillary forces to bring together and deform latex particles, which in turn results in incomplete film formation. Therefore, in order to achieve complete film formation, which facilitates to have stable release profile, the proper curing conditions are required. This is known as “conventional curing”. This conventional curing is most commonly recommended for the aqueous polymers, which have high glass transition temperature (Tg) and minimum film formation temperature (MFT). Heating of the films above Tg facilitates polymer movement and relaxation. For example, curing at 60 °C for at least one hour was recommended for Aquacoat® ECD coated dosage forms by the manufacturer (FMC, the USA) and it has also been reported in literature (Bodmeier and Paeratakul, 1991; Gilligan and Wan, 1991).

The curing process is dependent on both the time and temperature used during the curing process. The curing rates can be accelerated by increasing the storage temperature and relative humidity because of fast kinetic factors responsible for coalescence (Dressman et al., 1995; Körber et al., 2010; Amighi and Moes, 1996b; Bianchini et al., 1993).

Drug release from Kollicoat® SR 30 D coated pellets was unchanged by increasing the curing time (Dashevsky et al., 2005). This was attributed to complete film formation during coating process due to a low MFT of plasticized Kollicoat® SR 30 D coatings. In contrast, a strong curing effect depending on the plasticizer type and curing conditions has also been reported with Kollicoat® SR 30 D coated pellets (Shao et al., 2002).

A curing at 60 °C for 8 h was found to be sufficient to form complete film with Aquacoat® ECD coated pellets (Wesseling and Bodmeier, 2001) which could be further minimized by increasing the plasticizer concentrations (Bodmeier and Paeratakul, 1994b; Amighi and Moes, 1996a).

Additionally, the controlled humidity can accelerate the curing step significantly. This happens because water facilitates polymer particle coalescence and it acts as plasticizer for many polymers (Liu and Williams, 2002b; Williams III and Liu, 2000).

The extent of curing effect can also be affected by the type of plasticizer and coating level. For example, drug release decreased with increasing harshness (time, temperature and relative humidity) of curing conditions, when using triethyl citrate as a plasticizer whereas with dibutyl sebacate and Myvacet this relationship was only seen at low coating levels (Yang et al., 2010).

Furthermore, the drug migration into the coatings can also occur during the curing step which results an increase in drug release rather than decrease. In order to overcome this problem, a sub coating was applied between drug layer and polymer coating (Hamed and Sakr, 2003).

With Eudragit NE 30 D coated pellets, the crystallization of surfactant occurs depending on the curing conditions (Bajdik et al., 2003). It has also shown that Eudragit NE 30 D coatings are more sensitive to change in release profile at low curing temperatures (Kucera et al., 2009; Lin et al., 2003).

1.8.6 Storage stability

The purpose of long term stability is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug

substance or a shelf life for the drug product under recommended storage conditions (European medicine Agency; ICH guidelines). The long term stability data is particularly needed for the registration of new chemical entities. In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment, and subsequent use. Different storage conditions are recommended by international committee on harmonization (ICH). For example, 25°C ± 2 °C/60% RH ± 5% RH for 12 months, 30 °C ± 2 °C/65% RH ± 5% RH for 6 months and 40 °C ± 2 °C/75% RH ± 5% RH for 6 months are less, intermediate and accelerated long term stability conditions respectively.

Contradictory results have been reported in the literature regarding the effect of long-term storage on drug release from coated dosage forms. The ibuprofen release from coated pellets was increased after storage (Bodmeier and Paeratakul, 1994) and theophylline release was decreased upon storage (Yuen et al., 1993; Goodhart et al., 1984; Bando and McGinity, 2006).

The change in release profile over long term storage can be caused by the numerous factors. For instance, incorporation of inadequate amount of plasticizer in the formulation can result in polymer films that are brittle and need longer curing times to exhibit stable films. It has been shown that theophylline release from coated pellets with Eudragit RS 30D containing 10% or 20% triethylcitrate (TEC) depended on plasticizer concentration (Amighi and Moes, 1996b). Another reason could be the physical instabilities in the coating that leads to cracks and chipping of the coating. In addition, the researchers have attributed these problems to an increase in water contents of the films rather than a decrease (Chowhan et al., 1982). In the case of Aquacoat® ECD coatings, the faster drug release was associated with brittle films or the formation of micro-ruptures in the film during storage (Wesseling and Bodmeier, 2001). The decrease in the free volume of the film and increased compaction of polymer structure due to further gradual coalescence as the ageing progresses was also reported one reason for unstable release profile (Guo et al., 1993). This could also lead to change in water vapor permeability of the films (Guo et al., 1991). Additionally, the presence of endogenous excipients in the aqueous polymeric dispersion can also lead to serious stability issues such as increase in drug release rates. It has been shown that crystallization of the surfactants affects the dissolution rate of the drug from coated pellets (Amighi and Moes, 1997, Bajdik et al., 2003).

The decrease in drug release was reported upon storage under elevated humidity (Siepmann et al., 2007; Wu and McGinity, 2000) which was linked to better film formation due to further gradual coalescence resulting in decreased permeabilities for water and drug.

The storage at 40 °C-75% RH of Kollicoat® SR 30 D coated pellets also resulted in a decreased drug release due to continuous film formation (Shao et al., 2002). In contrary, an extended lag time without any significant change in release profile was observed with Kollicoat® SR 30 D coated pellets upon 1 month storage at 40 °C-75% RH (Ensslin et al., 2008).

On the contrary, storage stability at 40 °C-75% RH from Aquacoat® ECD: HPMC coated pellets was improved only by using thermal/humidity curing or very high temperature (80 °C) during 24 h (Körber et al., 2010).

In some recent studies, the storage stability of aqueous polymeric coated pellets was improved by adding pore-formers to the coating formulations. The enhanced stability was attributed to the presence of more trapped water in these systems during film formation which facilitates particle coalescence (Kranz and Gutsche, 2009; Muschert et al., 2009; Siepmann et al., 2008).

The incorporation of talc up to 200% in the coatings also provided a stable release profile from Eudragit® RS 30 D coated pellets. In fact, the polymeric particles were embedded in the skeleton of talc around the pellets, which led to an inhomogeneous film formation. Upon curing, the smoothness of film was further decreased due to the densification of polymeric particles and the drug released through the pores without any change (Maejima and McGinity, 2001; Ahmed et al, 2008).

1.9 Tackiness problems

Tackiness is defined as the property of a material to form a bond of measurable strength with another material which happens to be in immediate contact. Tack can also be defined as the ability of two materials to resist separation after bringing their surfaces into contact for a short time under light pressure (Wetzel, 1957). The strength of tack is dependent on the extent of inter-diffusion of molecules across interface (Voyutskii, 1971). Additionally, the extent of deformity of polymer chain and Vander Wall forces has a huge impact on tack strength. Autohesion or autohesive is the term used to describe the tack between two chemically similar surfaces. Commonly, during the coating of dosage forms with aqueous polymeric dispersions, the sticking of substrates occurs during the coating process and upon curing/storage. This

sticking problem is more likely observed with small substrates like mini-tablets, pellets and granules, also with sticky and flexible polymers (Eudragit® RS & RL 30 D, Eudragit® NE & NM 30 D and Kollicoat® SR 30 D etc) due to the tackiness of polymeric films. This leads to a massive problem of handling the coated substrate caused by sticking to each other and with the walls of Wurster and chamber. In some worse cases, a stoppage of process is caused by irreversible agglomeration of several coated substrates or a complete batch (pellets and granules) especially at higher product temperatures and plasticizer contents (Bodmeier and Paeratakul, 1991). Moreover, tackiness increases the number of coating defects and impairs the quality and efficiency of the coated batch. Therefore, a suitable balance has to be established between sufficiently high product temperatures and non-agglomeration (Wesseling et al., 1999).

In order to reduce the problems of sticking, different pigments and anti-tacking agents are added to dispersions before coating. In this case, the most commonly used anti-tacking agents are talc, magnesium stearate and glycerol monostearate (GMS). Talc and magnesium stearate are used in higher amounts (50%–100%), while GMS is used in smaller quantities (10%–20%) but it has a disadvantage of multiple steps preparation before adding into the aqueous dispersions. Talc and magnesium stearate are usually not fully dispersed in the formulation due to their hydrophobic nature and, as a result, blockage of nozzle is sometimes evident during coating.

1.10 Montmorillonites

Montmorillonites (MMTs) belong to the smectite group of clays and is made up of silica tetrahedral sheets layered between alumina octahedral sheets (Lagaly and Ziesmer, 2003; Leszczyńskaa et al., 2007; Joshi et al., 2010). The general chemical structure of montmorillonites is shown in Figure 5. The imperfection of the crystal lattice and the isomorphous substitution induce a net negative charge that leads to the adsorption of alkaline earth metal ions in the interlayer space. Such imperfection is responsible for the activity and exchange reactions with organic compounds. MMTs also contain dangling hydroxyl end-groups on the surfaces (Khalil et al., 2005).

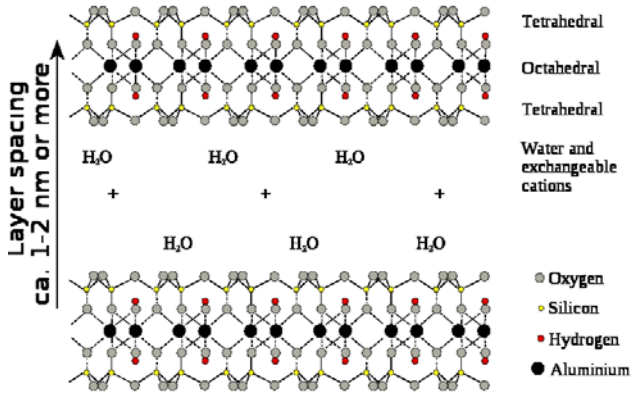


Figure 5: *Chemical structure of montmorillonites.*

MMTs have a large surface area and a high aspect ratio; exhibit good adsorption ability, cation exchange capacity and drug carrying capability. MMTs are mostly used to enhance mechanical properties, reduce flammability and improve gas barrier properties in plastic and paper industry (Majumdara et al., 2003). In pharmaceutical field, researchers have investigated MMTs for different purposes such as for the formation of drug-clay and polymer-clay intercalated nanocomposites to attain controlled release (Pospisil et al., 2001; Menga et al., 2009; Joshi et al., 2009; Brostow et al., 2010; Pongjanyakul and Rongthong, 2010), and to small extent as a filler, glidant and lubricant. However, no work so far has been done to investigate the anti-tacking properties of MMTs.

Cloisite® Ca^{++} and Nanofill® 116 are two naturally occurring MMTs with Ca^{++} and Na^{+} on their surfaces, respectively. Both of these MMTs have a large surface area, a high aspect ratio and can be completely dispersed in water due to their higher hydrophilicity (Rockwood, 2010).

1.11 Research objectives

The present was divided into two parts. The major objectives of the first part were:

i) To investigate and understand the curing mechanism of Kollicoat® SR 30 D and Eudragit® NE 30 D coated pellets (flexible coatings). In this regard, effect of starter core, drug solubility, drug loading, adhesion of coating to core and flexibility of coating, on curing was evaluated in detail.

ii) To purpose different approaches to eliminate the curing effect of Kollicoat® SR 30 D and Eudragit® NE 30 D coated pellets. In addition, storage stability under stress conditions was also focused.

The objectives of the second part were:

i) To investigate and evaluate the anti-tacking effect of two naturally occurring montmorillonites (MMTs) (Cloisite® Ca^{++} and Nanofill® 116) in comparison with talc, a conventionally used anti-tacking agent, using different aqueous polymer dispersions.

ii) To compare the anti-tacking effect of the MMTs and talc on mechanical properties of casted films, coating processability of aqueous polymer dispersions and drug release from coated pellets.

2 Materials and Methods

2.1 Materials

The experimental materials were obtained from different commercial suppliers and were used as received.

Cores

Non-pareils (Suglets® sugar spheres NF; 710-850 µm, NP Pharma S.A., Bazainville, France), microcrystalline cellulose cores (Celphere® CP 708; Asahi Kasai Chemical, Tokyo, Japan).

Drugs

Propranolol HCl, theophylline, carbamazepine, metoprolol tartrate (BASF AG; Ludwigshafen, Germany), tramadol HCl (Heumann pharma GmbH, Germany).

Polymers

An aqueous dispersion of polyvinyl acetate (Kollicoat® SR 30 D; BASF AG, Ludwigshafen, Germany), polyvinyl alcohol-polyethylene glycol graft copolymer, (Kollicoat® IR; BASF AG, Ludwigshafen, Germany), an aqueous dispersion of ethyl acrylate and methyl methacrylate copolymer (Eudragit® NE 30 D and Eudragit® NM 30 D; Evonik, Darmstad, Germany), an aqueous dispersion of ethyl acrylate and methyl methacrylate copolymer with a low content of a methacrylic acid ester (Eudragit® RL 30 D and Eudragit® RS 30 D; Evonik, Darmstad, Germany), hydroxypropyl methylcellulose (HPMC) (Methocel® E5; Colorcon, Orpington, UK), hydroxypropyl methylcellulose (HPMC) (Pharmacoat® 606; Shin-Etsu Chemical, Tokyo, Japan).

Plasticizer

Triethylcitrate (TEC) (Citroflex®-2; Morflex, Greensboro, NC, USA).

Other excipients

Talc (Luzenac pharma, Europe, Toulouse, France), Magnesium stearate (Caelo, Caeasar & Loretz GmbH, Hilden, Germany), two naturally occurring montmorillonites (MMTs) with calcium ions (Cloisite® Ca^{++}) and with sodium ions (Nanofill® 116) (Rockwood additives, Moosburg, Germany), Titanium dioxide (Evonik, Darmstad, Germany), lactose (Ludipress®; BASF, Ludwigshafen, Germany), Silicon dioxide (Aerosil® 200; Evonik, Darmstad, Germany), Sodium chloride (Natriumchlorid; Carl Roth GmbH, Karlsruhe, Germany), Silica gel (Silica Gel Orange; Carl Roth GmbH, Karlsruhe, Germany).

Solvents

Isopropanol.

Buffer

0.01N HCl.

2.2 Methods

2.2.1 Preparation of drug layered pellets

The model drugs (carbamazepine, theophylline, propranolol HCl, tramadol HCl and metoprolol tartrate) were layered onto non-pareil and microcrystalline cellulose cores. Drug layering solutions (15% w/w solid contents) were prepared in an isopropanol: water (88:12) mixture using HPMC (E5) (5% w/w based on drug mass) as a binder. Drug layering was performed in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany) to achieve 2%, 5%, 10%, 20%, 30% and 50% weight gain (based on initial weight of cores). Optionally, in the case of propranolol HCl layering, the binder HPMC (E5) was increased to 25% w/w (based on drug mass) or a sub coating of HPMC (E5) 10% w/w (based on initial drug layered pellets) was applied. The process parameters were as follows: batch size = 900 g, inlet temperature = 52 °C, product temperature = 32 ± 2 °C (carbamazepine and theophylline) or 40 ± 2 °C (propranolol HCl and tramadol HCl) or 50 ± 2 °C (metoprolol tartrate), air flow = 80-100 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 1.2 bar, spray rate = 6-8 g/min, final drying at 40 °C for 15 min.

2.2.2 Coating of pellets

Kollicoat® SR 30 D

The aqueous dispersion was plasticized with TEC (10% w/w based on dry polymer mass) and talc (35%-100% w/w based on dry polymer mass) or titanium dioxide (20%-35% based on dry polymer mass) were added as anti-tacking agents to avoid sticking during the coating process. The final solid contents were adjusted to 15% w/w by adding deionized water. The coating was performed in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to obtain coating level of 20% w/w (based on dry polymer mass). The coating parameters were as follow: batch size = 900 g, inlet temperature = 34 °C, product temperature = 28-30 ±2 °C, air flow = 72 m^3/h, nozzle diameter = 1.2 mm, spray pressure = 2 bar, spray rate = 6-8g/min, final drying at 40 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with pellets to avoid sticking.

Eudragit® NE 30 D

Talc (35%-100% w/w based on dry polymer mass) or titanium dioxide (20%-35% based on dry polymer mass) were added as anti-tacking agents into polymer dispersion and the final

solid contents were adjusted to 15% w/w by adding deionized water. The coating was performed in a fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) to achieve coating level of 20%w/w (based on dry polymer mass). The coating parameters were as follow: batch size = 80 g, inlet temperature = 28 °C, product temperature = 18-20±2 °C, air flow = 0.2 m^3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 0.8-1g/min, final drying at 20 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with pellets to avoid sticking

2.2.3 Preparation of films

Sprayed films

The coating dispersions of Kollicoat® SR 30 D and Eudragit® NE 30 D were also used to prepare films with the help of an Airbrush having a nozzle diameter of 0.75 mm (Paasche Chicago, IL, USA) onto teflon plates (14x14 cm^2) under controlled drying conditions. The thickness of the films (50-100 µm) was measured using a foil thickness gauge (Minitest 600; Erischen, Hemer, Germany). The films were cured at 60 °C or 60 °C-75 % RH for 24 h and were stored in a desiccator for 48 h until further use.

Casted films

The aqueous polymer dispersions of Eudragit® RL & RS 30 D and Kollicoat® SR 30 D were plasticized with 10% and 20% of triethylcitrate (based on dry polymer mass) for 12 h. No plasticizer was added to Eudragit® NE & NM 30 D dispersions. Cloisite® Ca^{++}, Nanofill® 116 and talc were dispersed in 10%, 20% and 35% (based on dry polymer mass) concentrations in deionized water using ultra-turrax for 5 minutes, and then added into the polymer dispersions. The solid contents were adjusted to 15% w/w by adding deionized water and the whole formulations were stirred for 12 h. The films were casted onto teflon mounted levelled glass plates (area of casting = 16 X 16 cm^2) by pouring 60 g of the final formulations. The films were dried in an oven (Heraeus T 6120, Hanau, Germany) for 48 h at 40 °C and 35% relative humidity (RH) and then were further equilibrated at ambient condition for 2 h. After peeling the films from teflon surface, the thickness of the films (330-360 µm) was measured with a foil thickness gauge (Model 497, Erichsen, Hemer, Germany).

2.2.4 Preparation of model tablets

The model tablets of 10 mm diameter were prepared using lactose. 0.5% Mg stearate was added as a lubricant. The mixture was mixed using kitchen aid for 10 minutes and the tablets

were prepared on a single punch rotary machine (Korsch, Berlin, Germany). The hardness of tablets was kept constant (90 N) and was measured using a hardness tester (Erweka, Heusenstamm, Germany). The tablets were drug layered and polymers coated like the pellets, in a drum coater (Lab-coater GC-300, Switzerland). The tablets were cured at 60 °C or 60 °C-75 % RH for 24 h and were stored in a desiccator for 48 h until further use.

2.2.5 Coating processability of polymer dispersions

The coating processability of different aqueous polymeric dispersions (Kollicoat® RS 30 D, Eudragit® RL and RS 30 D, Eudragit® NE 30 D and NM 30 D) was evaluated using a fluidized bed coater (Mini-Glatt, Wurster insert, Glatt GmbH, Binzen, Germany). For each process, 70 g of propranolol HCl layered sugar cores were used. The composition of tested formulations was exactly similar to the one for the casted films. The coating processability was evaluated based on the flow of pellets, agglomeration tendency, spray rate, product temperature, nozzle blockage and yield.

2.2.6 Characterization of the coated pellets

2.2.6.1 Curing of pellets

The coated pellets were cured at 60 °C and 60 °C-75 % relative humidity (RH) for 24 h in aluminium pans in an oven. 75% RH was attained by pouring saturated solution of sodium chloride in a desiccator. After curing, the pellets were equilibrated in a desiccator for 24 h before further use

2.2.6.2 Tackiness of coated pellets

3g of the coated pellets were put into aluminium pans and into glass bottles (100 ml of pH-2 media) without addition of any anti-tacking agent. The aluminium pans and bottles were placed at 40 °C, 40 °C-75 % RH, 60 °C and 60 °C-75 % RH for 24 h. After the curing, the pellets were passed through a sieve of 2 mm mesh size. The tackiness (agglomeration tendency) was evaluated based on the weight of agglomerated and non-agglomerated pellets.

2.2.6.3 In vitro drug release

In vitro drug release in 0.01 N HCl (900 ml) was performed using the USP paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) at 37 °C (rpm=100, n=3). At pre-determined time intervals, the 3ml samples were collected and analyzed UV-spectrophotometrically (propranolol HCl: λ = 289, theophylline: λ = 270, carbamazepine: λ =

289 and metoprolol tartrate: λ = 274) (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany). Optionally, the osmolality of release medium was adjusted to 1000-1500 mOsmol/kg with sodium chloride.

2.2.6.4 Macroscopic/SEM pictures and video monitoring

The macroscopic pictures of pellets before and after the drug release were taken using a light macroscope (Inteq® informationtechnik, GmbH, Berlin, Germany). Additionally, the video monitoring of pellets during drug release was performed using an image analyzing software (IQ Easy measure®, Inteq® informationtechnik, GmbH, Berlin, Germany). In order to observe the thickness of different drug loadings and proper distribution of anti-tacking agents in the coating, the scanning electron micrograph (SEM) analysis of the cross-section of the coated pellets was performed. Also the macroscopic pictures of the coated pellets were taken before and after curing to investigate the agglomeration tendency.

2.2.6.5 Water uptake and weight loss

The water uptake was determined by using approximately 500 mg (accurately weighed) pellets by the following method: USP paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) (900 ml 0.01 N HCl, 37 °C, 100 rpm, n=3). After predetermined time points, the pellets were filtered, carefully blotted and weighed (wet weight). The wet pellets were then dried in an oven at 60 °C for 24 h and finally in a desiccator for 48 h and weighed (dry weight). The water uptake and weight loss was calculated as follows:

Water uptake (%) = (wet weight – dry weight)/dry weight * 100

Weight loss (%) = (initial weight – dry weight)/initial weight * 100

2.2.6.6 Osmolality inside pellets

The osmolality was determined using approximately 500 mg (accurately weighed) pellets by the following method: USP paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA) (900 ml 0.01 N HCl, 37 °C, 100 rpm, n=3). At predetermined time points, the pellets were filtered and the surface water was removed using a vacuum pump. After that, the pellets were homogenized, centrifuged and the osmolality of the filter liquid was measured using an osmometer (Osmomat 030, Gonotec GmbH, Berlin, Germany).

2.2.6.7 Swelling studies

The pictures of pellets at definite time intervals were selected from the video recordings and the diameter of 50 pellets was measured under light macroscope (Inteq, Berlin, Germany). % swelling was calculated as follows:

Swelling % = ($Volume_{wet}$ – $Volume_{dry}$)/$Volume_{dry}$*100 %

2.2.7 Characterization of films

2.2.7.1 Water uptake and weight loss

The water uptake and weight loss of the sprayed films was determined by the same method used for the pellets.

2.2.7.2 Permeability

The permeability of uncured and cured sprayed films was determined using a diffusion cell apparatus. The film was tightly fixed between the donor and acceptor compartment. The donor compartment was completely filled with a saturated solution of the drug and the cell was placed into plastic box containing 900 ml of 0.01 N HCl. The whole set up was transferred in a horizontal shaker (GFL shaking incubator 3033; GFL mbH, Burgwedel, Germany) (37 °C, 80 rpm, n=3). At predetermined time intervals, the 3 ml samples were collected and analyzed UV-spectrophotometrically (Shimadzu UV-2101PC UV-Vis Scanning spectrophotometer; Shimadzu Europe, Duisburg, Germany).

2.2.7.3 Mechanical properties

The mechanical properties of the spayed and casted films were measured by a puncture test using Texture Analyzer (Stable Micro Systems, Surrey, U.K.). The films were fixed on a film holder (n=6). The load cell (50 kg) was used and the puncture probe (spherical end: 5mm diameter) was attached to the load cell. The puncture probe was driven downward with a cross head speed of 0.1 mm/s to the centre of the film holder's hole. Load versus displacement curve were recorded until the rupture of the films and used to determine the mechanical properties as follows:

$$\text{Puncture strength} = F/A$$

where F is the load required to puncture the film and A is the cross-sectional area of the edge of the film located in the path

$$\% \text{ elongation at break} = \frac{\sqrt{R^2 + D^2} - R}{R} \times 100$$

Where R is the radius of the film exposed in the cylindrical hole of the holder and D is the displacement to puncture.

2.2.7.4 Tackiness of casted films

The test specimen (n=6) were placed with one end of each polymer film in clamps (width 2.5 cm^2 of Texture analyzer (Stable Micro Systems, Surrey, U.K.) as illustrated in Figure 6.

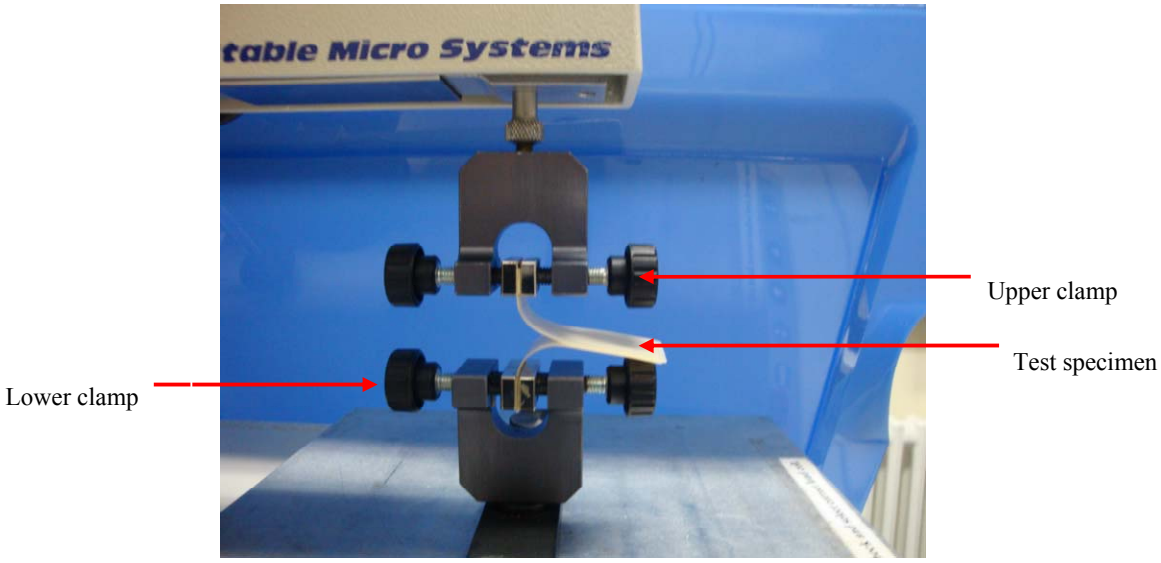


Figure 6: *Set up for determination of force (F)-displacement (d) curves from polymeric films.*

The upper clamp, which was attached to a driving load cell (50 Kg maximum load), was driven upwards at a crosshead speed of 15 mm/min while the lower clamp remained in the original position. The force needed to separate the polymer films was recorded. The average value was obtained from the constant force portion of the force vs. displacement (Wesseling et al., 1999).

A typical force vs. displacement diagram exemplifies the detachment force in Figure 7. The curves were divided into three phases. In first phase a steep increase in force was recorded resulting into maximum force. This was the point just prior to detachment of the films from each other. The second phase reflected a slight decrease in the force followed by the last

phase with a continued constant force until the films were completely separated. The last phase represented the detachment of the films from each other. The recorded force values in the last phase of the curve were averaged and considered as a measure of the tackiness of the polymer films.

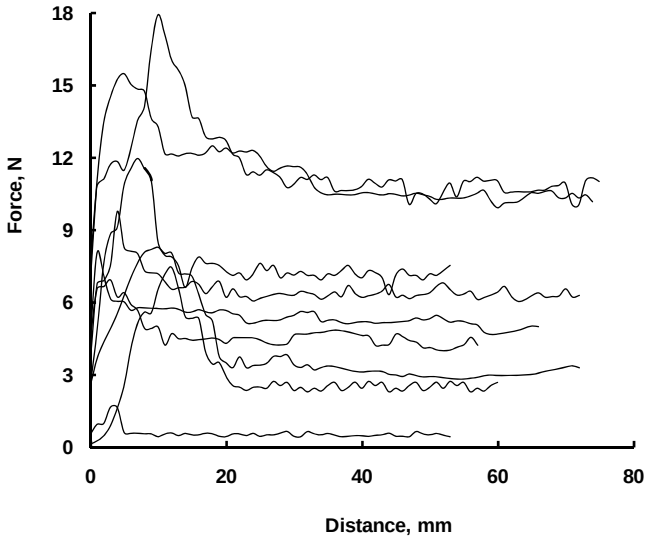


Figure 7: *Example of force vs. displacement curves showing detachment force of polymer films.*

2.2.7.5 Macroscopic pictures

The distribution of anti-tacking agents in the casted polymeric films was observed under Inteq-macroscopic (IQ Easy measure®, Inteq®, informationtechnik, GmbH, Berlin, Germany). Additionally, the macroscopic pictures of the coated pellets were taken before and after curing to investigate the agglomeration tendency.

2.2.8 Characterization of the model tablets

2.2.8.1 Adhesive force of the coating

The adhesive force of the coating of the uncured and cured tablets was determined using a Texture Analyzer (Stable Micro Systems, Surrey, U.K.). The coating of the tablets was cut from the centre (7mm) with the help of round sharp knife and the probe was fixed to the

coating with double sided adhesive tape. The force was recorded at the point of detachment of the coating from the tablet (n=6).

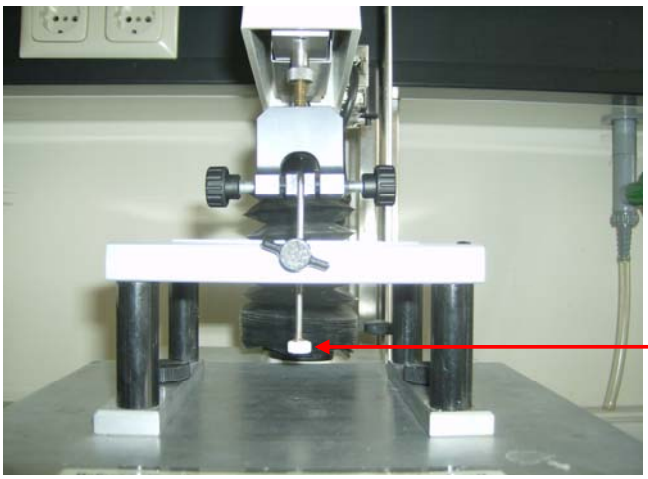


Figure 8: *Set up for determining the adhesive force of coating using a model tablet.*

2.2.9 Evaluation of curing effect

The presence of curing effect was evaluated by using f_2 similarity factor $f_2 < 50 \rightarrow$ curing effect and $f_2 > 50 \rightarrow$ no curing effect (Moore and Flanner et al.; 1996; Polli et al., 1997).

$$\text{Similarity factor } (f_2) = 50 \bullet \log \{[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\}$$

where f_2 is similarity factor, n is the number of observations, R_t is percentage of drug dissolved from reference formulation (uncured), and T_t is percentage of drug dissolved from test formulation (cured).

2.2.10 Determination of contact angle

The contact angle (CA) on the surface of the MMTs and the talc was measured by pouring deionized water and the polymer dispersions using a CA analyzer (Krüss, GmbH, Hamburg, Germany). 1 g of the each tested powder was put on a horizontally levelled glass slide and the surface of the powder was smoothened with a spatula. After that, a drop of deionized water

was placed on the surface of the tested powder with the help of a microsyringe. The CA on both sides of the drop was measured to assume symmetry and horizontal level. The same procedure was repeated for the polymer dispersions. The measurements were performed in triplicate.

3 Results and discussion

3.1 Curing mechanism of Kollicoat® SR 30 D coatings

The main objective of this part of work was to investigate the curing mechanism of Kollicoat® SR 30 D coated pellets using sugar cores [known as nonpareil (NP) cores] and propranolol HCl as a model drug. In this regard, effect of osmotically active cores, drug loading, adhesion of coating to the cores and flexibility of coating on curing was investigated in detail. Additionally, the drug release mechanism from the coated pellets, water uptake and the mechanical properties of free films were evaluated in order to have a deep insight of curing phenomena. The curing effect of Kollicoat® SR 30 D coated pellets has been reported (Shao et al., 2002) but so far no clear understanding of the curing mechanism has been provided.

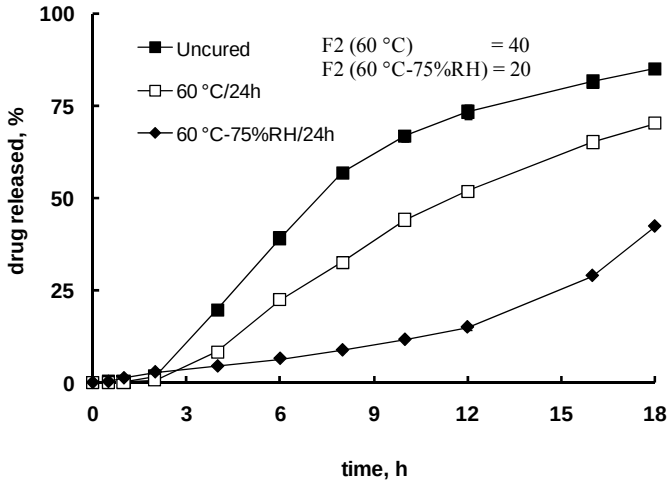
3.1.1 Drug release from Kollicoat® SR 30 D coated pellets

The curing effect was investigated using propranolol HCl (10% w/w based on initial weight of cores) loaded sugar pellets (710-850 μm) coated with Kollicoat® SR 30 D (20% w/w based on dry polymer mass). The coated pellets were cured at 60 °C (elevated temperature) and 60 °C-75%RH (elevated temperature and humidity) for 24 h and the drug release was performed in 0.01 N HCl (pH-2) medium. The presence of curing effect was assessed by comparing the release profiles of uncured and cured pellets using f_2 similarity factor; $f_2 < 50 \rightarrow$ curing effect and $f_2 > 50 \rightarrow$ no curing effect (Polli et al., 1997).

The drug release from the coated pellets was significantly decreased after curing and the effect was more pronounced at 60 °C-75%RH (Figure 9A). The f_2 similarity values of 40 and 20 were obtained after curing at 60 °C and 60 °C-75%RH, respectively, which were suggestive of a strong curing effect. Moreover, the t_{50} of the pellets cured at 60 °C-75%RH was delayed to 18 h in comparison with 7 h of the uncured pellets. However, in order to evaluate the shape of profiles after the complete drug release, the dissolution studies were further continued till 36 h (Figure 9B). Importantly, both the uncured and cured pellets showed a typical sigmoidal release pattern with a lag time of 2 h followed by a continuous release phase and lastly a plateau. The sigmoidal release profile from the oral controlled

release pellets and tablets has been observed several times (Ensslin et al., 2008; Narisawa et al., 1997; Ito et al., 2005; Wei et al., 2006). Interestingly, the macroscopic pictures of the uncured and cured pellets after the drug release showed a big difference in swelling and the

A)



B)

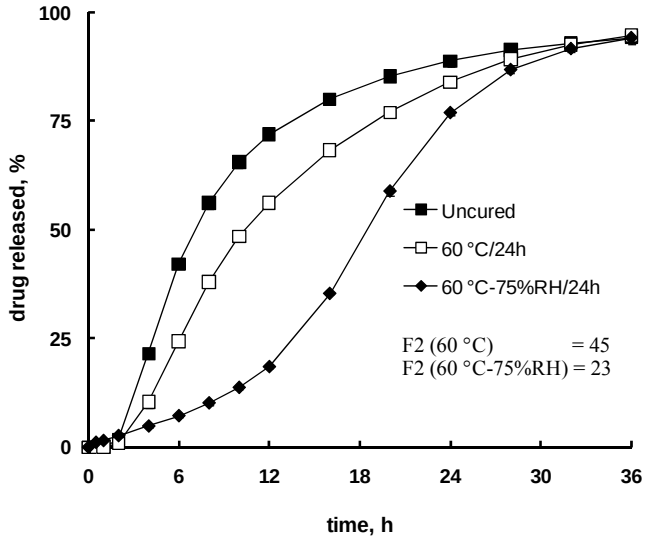


Figure 9: *Drug release from uncured and cured propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30D (TEC 10% w/w, talc 35% w/w),coating level 20% w/w, A) 18 h release and B) 36 h release.*

effect was more pronounced after curing at 60 °C-75%RH. The uncured pellets had moderate swelling whereas the pellets cured at 60 °C-75%RH were extensively swollen like balloons. This significant difference in the swelling led to an interesting aspect which needed to be further investigated.

Kollicoat® SR 30 D is a flexible polymer having a minimum film formation (MFT) of 18 °C which is further reduced to 1 °C by the addition of triethylcitrate (TEC) 10% (w/w based on dry polymer mass) before coating. Due to a low MFT and a high recommended product temperature of 28-32 °C, the film formation is claimed to be completed after the coating process (Kollicoat® SR 30 D technical information, 2007) which supposed that the further gradual coalescence, a conventional known cause for curing, of the film might not be the reason for the observed curing effect. In order to find out the exact reason, the further supportive studies like the water uptake of pellets/free films, the mechanical properties and the permeability of free films, osmolality inside the pellets and the video monitoring of the pellets were carried out.

Importantly, the curing effect at 60 °C-75%RH was more pronounced therefore it was more focused in further studies.

3.1.2 Water uptake and weight loss of coated pellets/free films

The water uptake and weight loss studies of the free films and the coated pellets were performed. The results showed that the water uptake of the uncured and cured pellets was almost similar till 6 h and afterwards the cured pellets started to absorb more water which increased continuously as a function of time (Figure 10A). For example, the pellets cured at 60 °C-75%RH showed a water uptake of approximately 800% after 18 h whereas the uncured pellets took about 250%. In comparison, the weight loss of the uncured and cured pellets was in accordance with the drug release results (Figure 10B). However, the decreased water uptake of the uncured pellets resulted in increased release rate whereas the increased water uptake of the cured pellets revealed decreased release rates. This indicates that there might be a change in the permeability and mechanical properties of coatings upon curing which were further investigated. The water uptake and weight loss of the free films did not show significant change after curing (Figure 10C & D). This suggests that the higher water uptake of the cured pellets might not be linked to only changes in the films upon curing.

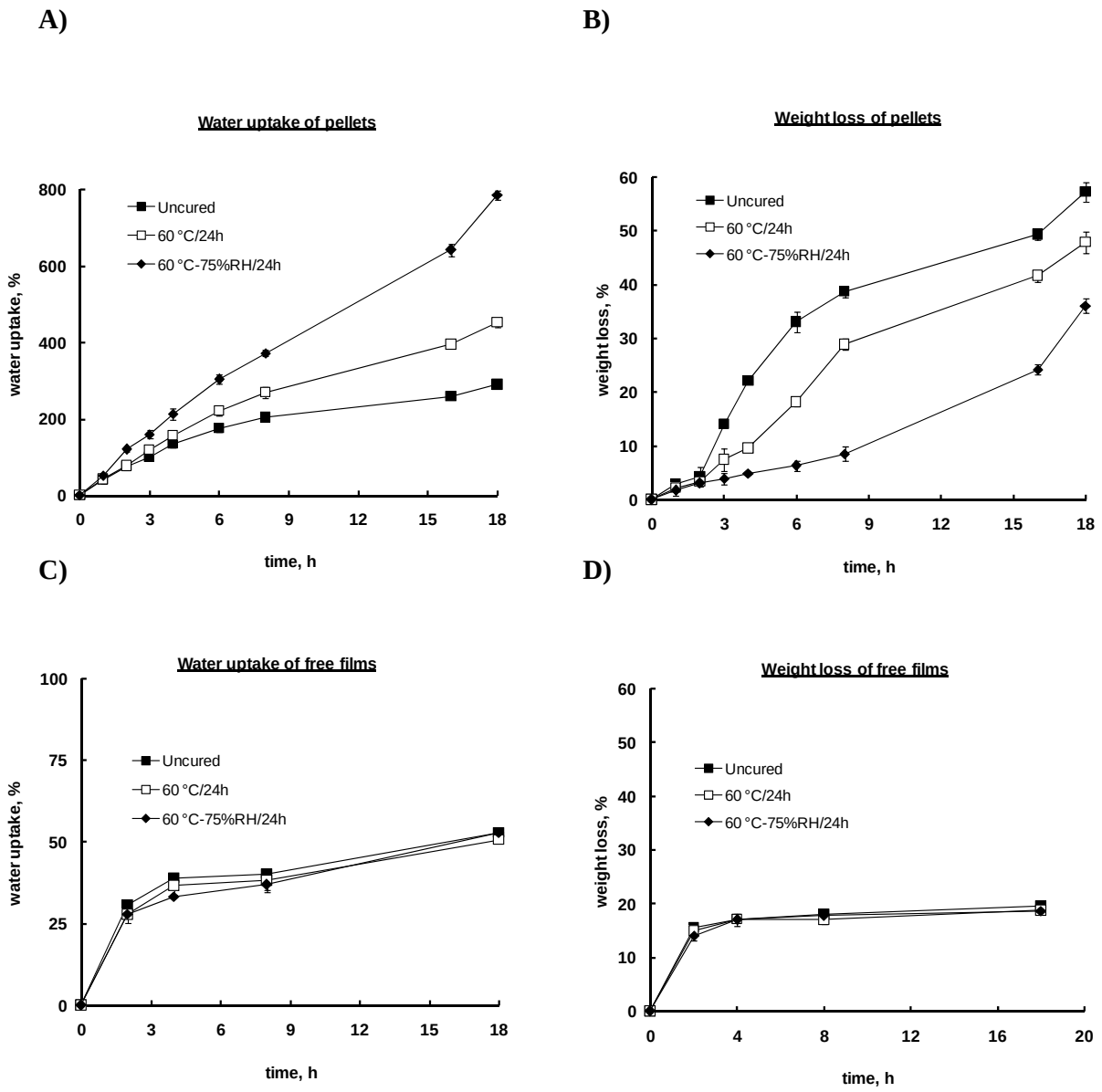


Figure 10: *A) Water uptake and B) Weight loss of uncured and cured propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w), coating level 20% w/w, C) Water uptake and D) Weight loss of uncured and cured Kollicoat® SR 30 D free films (TEC 10% w/w, talc 35% w/w), film thickness 100-110 µm.*

3.1.3 Mechanical properties and permeability of films

The changes in the coating upon curing were evaluated by determining the mechanical properties and the permeability of sprayed free films. For that purpose, the mechanical properties of the films were determined both in dry and wet state and the results are enlisted in

Table 3. In the dry state, no significant differences were observed in the mechanical properties of the uncured and films cured at 60 °C-75%RH. However, the films cured at 60 °C showed a significant decrease in the puncture strength and % elongation which could be due to the loss of water at elevated temperature (Wu et al., 2000; Zheng et al., 2003). However, the mechanical properties of the uncured and cured films were almost similar in the wet state which is an indicative of no changes in the flexibility of coatings upon curing.

The permeability of the uncured and cured films was determined using a diffusion cell apparatus. The saturated solution of propranolol HCl was filled in the donor compartment and the samples collected from the acceptor compartment were analyzed UV spectrophotometrically to calculate the amount of permeated drug. It is important to state that a negligible amount of the drug could permeate through both the uncured and cured films suggesting no changes in the permeability upon curing (data not shown). However, the permeability of polymeric film often decreases upon curing as the film undergoes further gradual coalescence which causes an increase in film density and tortuosity (Gutierrez-Rocca et al., 1993; Guo et al., 1991; Zheng et al., 2005) but this phenomenon usually applies to brittle polymers where the film formation may not complete and a post thermal curing step is often required to promote the complete film formation.

Table 3 *Effect of curing on the mechanical properties of Kollicoat® SR 30 D free film (TEC 10% w/w, talc 35% w/w) (thickness = 100 ± 5µm).*

Testing state	Curing condition	Mechanical properties, n = 9	
		Puncture strength, N/mm^2	Elongation, %
		M. V. ± S. D.	M. V. ± S. D.
Dry state	Uncured	8.0 ± 0.3	189.7 ± 7.5
	60 °C/24h	6.6 ± 0.1	97.1 ± 5.1
	60 °C-75%RH/24h	9.0 ± 0.8	197.6 ± 5.1
Wet state	Uncured	7.8 ± 2.2	333.6 ± 8.2
	60 °C/24h	7.6 ± 1.9	317.4 ± 6.2
	60 °C-75%RH/24h	8.1 ± 1.2	340.6 ± 7.2

Clearly, no changes in the mechanical properties of the films in the wet state and in the permeability of the films upon curing eliminated the speculation that “the further gradual coalescence of the polymer particles might be the reason for the observed curing effect”. This

also confirmed that the film formation from the Kollicoat® SR 30 D formulations was complete after the coating process. Further, the videos monitoring of the pellets during dissolution was performed to assess the difference in their swelling behaviour. In addition, osmolality inside the pellets was determined to understand the drug release mechanism.

3.1.4 Video monitoring of coated pellets during drug release

The videos of the uncured and cured pellets during dissolution were recorded to observe differences in their swelling behaviour. The video recordings were thoroughly analyzed and, surprisingly, the swelling behaviour of the uncured and pellets cured at 60 °C-75%RH was found to be completely different. In this regard, some pictures from the video recording at definite time interval were selected and put together in Figure 12. The detailed swelling behaviour of the uncured and pellets cured at 60 °C-75%RH is described below in two scenarios:

First scenario (observed for uncured pellets): It was noticed that the coatings of the uncured pellets started to swell locally after medium penetration. This began to happen after nearly 1 h start of dissolution, and the coating continued to swell/extend towards that particular direction which eventually ruptured followed by a collapse (called as localized swelling and rupturing). In fact, majority of the uncured pellets underwent this procedure within 2-3 h and a few of them in 3-4 h which correlates closely with the lag time. This could be explained by the fact that the propranolol HCl 10% loading formed neither a thick nor a thin layer around the sugar

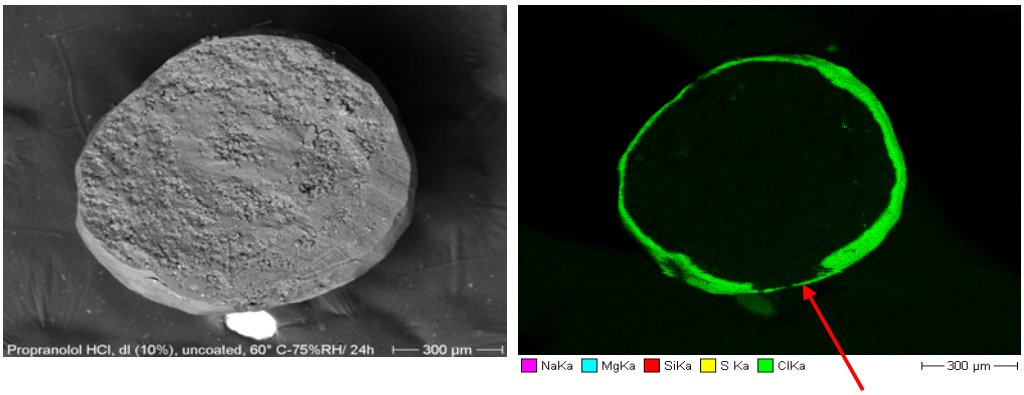


Figure 11: *SEM images of cross section of sugar pellets loaded with propranolol HCl 10% w/w.*

cores. Hence, the medium rapidly penetrated only at "weak point" where probably the drug layer was thin (confirmed from SEM images in Figure 11) which resulted in rapid solubilisation of the sugar cores and arising of osmotic pressure towards that "weak point" (Figure 12). This is why the coating only started to swell extensively towards that particular direction (approx. 300% as estimated from the pictures) until ruptured by exceeding the elongation limit and then finally collapsed (Figure 12). Therefore, the drug released through visible macro ruptures by an osmotically driven mechanism. Moreover, despite of the visible macro ruptures, the drug release followed a typical sigmoidal pattern rather than an immediate release which also confirms the collapsing of coating due to its higher flexibility.

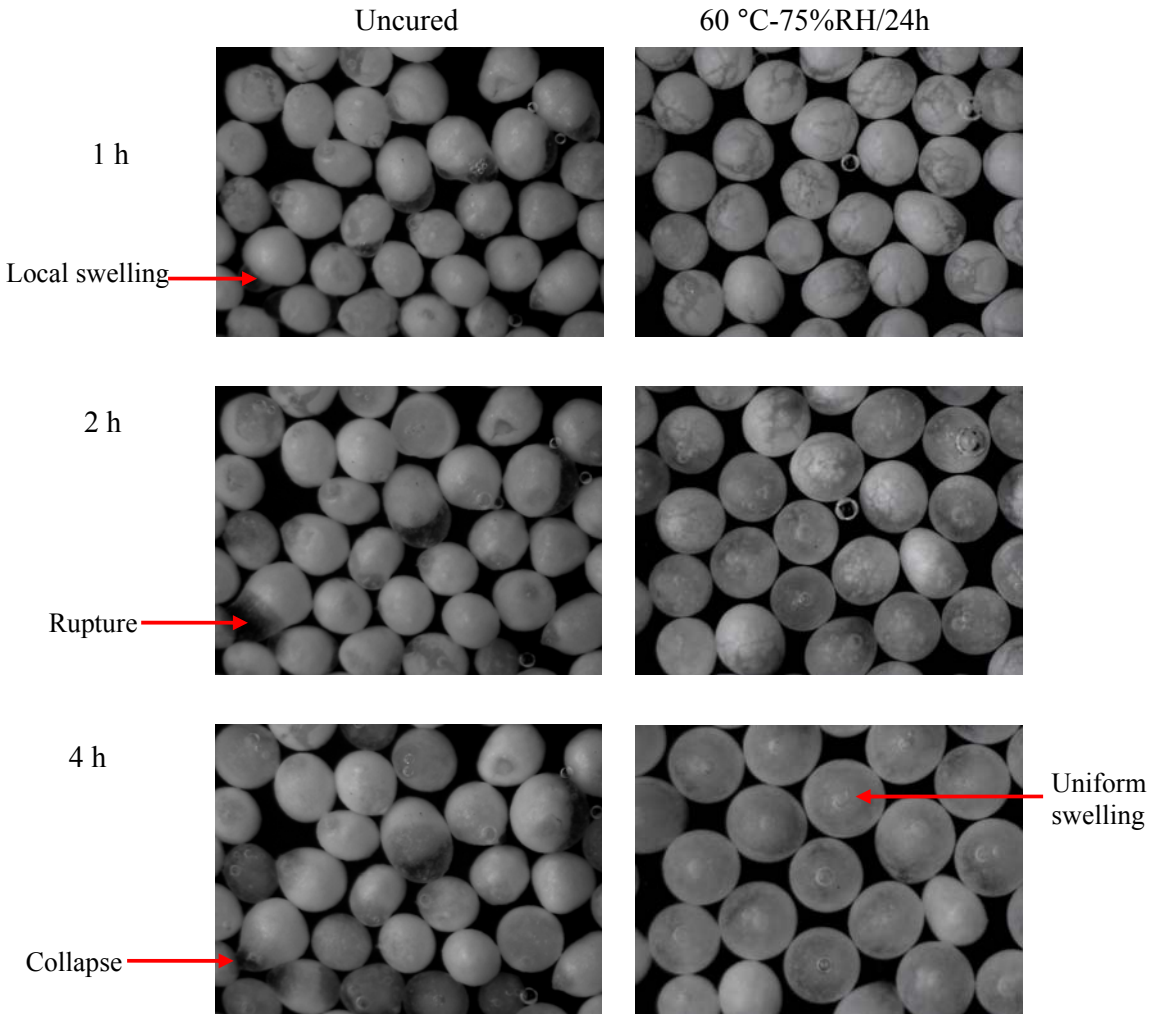


Figure 12: *Pictures from video monitoring of uncured and cured (60 °C-75%RH/24 h) propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30D during dissolution (TEC 10% w/w, talc 35% w/w), coating level 20% w/w.*

Second scenario (observed for pellets cured at 60 °C-75%RH): The pellets cured at 60 °C-75%RH revealed entirely different swelling behaviour in comparsion with the uncured. For example, the localized swelling and rupturing of the coatings was not seen at all. In contrast, the cured pellets started to swell uniformly after the medium penetration and continued as a function of time without exceeding the elongation limit (approx. 150% estimated from the pictures). This occurred because the osmotic pressure inside the pellets was distributed equally towards all directions and no visible macro cracks were observed in the coatings. This indicates that the drug released after a certain lag time necessary for the thinning of the coating and the formation of non-visible micro pores. The coating extended until equilibrium of inner/outer liquids and did not collapse. Due to this, the pellets appeared extremely swollen (5 times) after release. A sigmoidal release pattern from the cured pellets also suggests an osmotically driven drug release mechanism.

However, the pellets cured at 60 °C exhibited a dual type of swelling behaviour during dissolution. Some of the pellets underwent localized swelling/rupturing whereas others followed a low uniform swelling. As a result, the drug release profile from these pellets was slower than the uncured and faster than the pellets cured at 60 °C-75%RH which also suggests that elevated temperature with elevated humidity was the main reason for the extensive uniform swelling and ultimately for the strong curing effect.

Moreover, the extensive uniform swelling of pellets upon curing at 60 °C-75%RH could be possibly due to decrease in the adhesive force of coating which was further investigated.

3.1.5 Swelling of coated pellets

The swelling extent of pellets during dissolution was measured for the better understanding of the drug release mechanism. The increase in diameter and % swelling as a function of time are shown in Figure 13A & B. The result depicted that both the uncured and cured pellets had the same extent of swelling till 2 h, afterwards the cured pellets started to swell more. Interestingly, the swelling of the uncured pellets was decreased to a small extent after 4 h while the pellets cured at 60 °C continued to swell slowly. In comparison, the pellets cured at 60 °C-75%RH exhibited a significant increase in swelling as a function of time. After the dissolution, the uncured pellets had a swelling less than 100% whereas the pellets cured at 60 °C-75%RH showed a swelling of over 500% (Figure 13B). The first increase followed by decrease in swelling of the uncured pellets agrees with the rupturing and the collapsing of the

coating which, in turn, also closely correlates with the lag time and to the osmotically driven release mechanism. On the other hand, the extensive uniform swelling of the pellets cured at 60 °C-75%RH was an indication of the absence of macro rupture and the slow release of drug via micro crack in the coating. A small increase in the swelling of 60 °C cured pellets

A)

B)

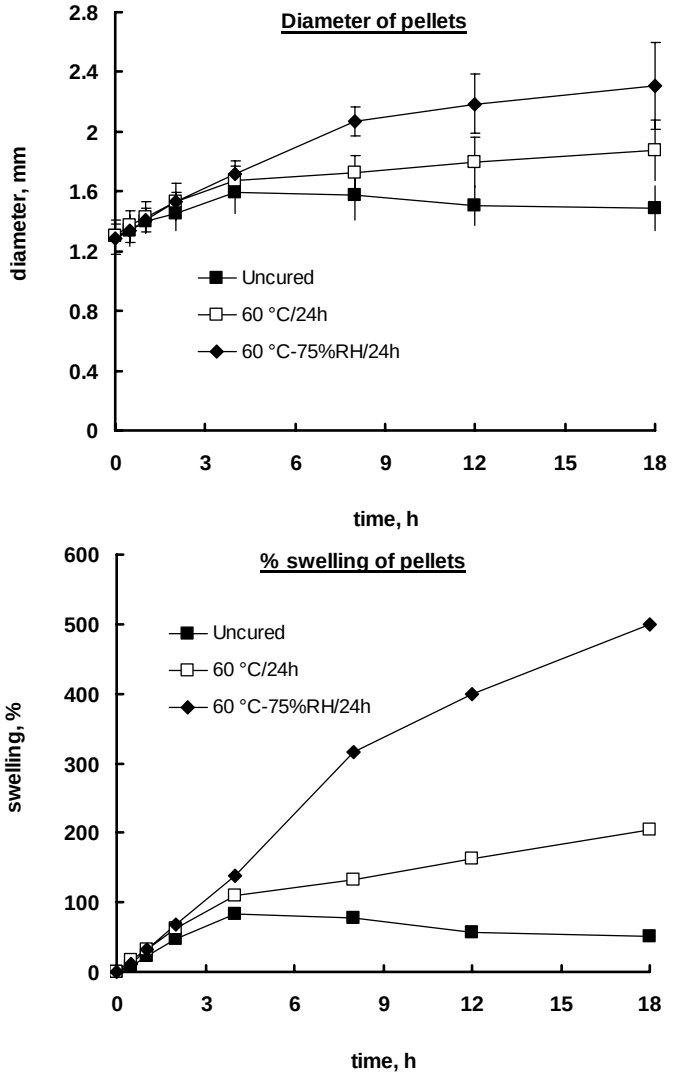


Figure 13: *A) Increase in diameter and B) % increase in swelling of uncured and cured propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D during dissolution (TEC 10% w/w, talc 35% w/w), coating level 20% w/w.*

represents that the low uniform swelling was dominant over the localized, which led to a decrease in drug release in comparison with the uncured pellets.

3.1.6 Osmolality inside coated pellets

To assess the effect of osmotic pressure difference on the curing, the osmolality inside the uncured and cured pellets was measured. Surprisingly, the osmolality inside the uncured and cured pellets was almost similar despite of a big difference in drug release, water uptake-weight loss and swelling behaviour (Figure 14). This could be due to that the increased drug release of the uncured pellets was balanced by the decreased water uptake whereas the decreased drug release of the cured pellets was equilibrated by the increased water uptake and, as a result, the osmolality inside the pellets remained unchanged. In spite of the similar osmotic pressure inside the uncured and cured pellets, the difference in the swelling behaviour could be explained by the following fact: in case of the uncured pellets, the localized swelling/rupturing of the coating occurred due to applying of osmotic pressure towards one particular direction whereas the uniform swelling of the pellets cured at 60 °C-75%RH cured was caused by the equal distribution of the osmotic pressure towards the whole coating.

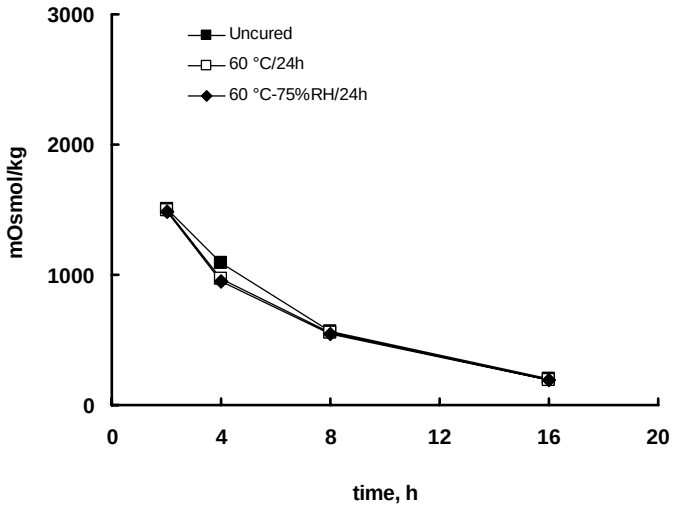


Figure 14: *Osmolality inside uncured and cured propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w), coating level 20% w/w.*

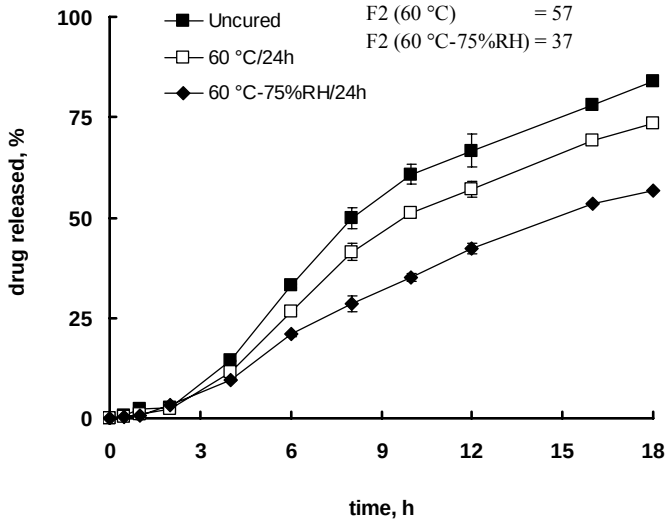
However, an osmotically driven drug release mechanism from both the uncured and cured pellets was confirmed. The similar osmotically driven mechanism from the pellets coated with Kollicoat® SR 30 D and with some other polymers has been reported (Ensslin et al., 2008; Ozturk et al., 1990; Narisawa et al., 1996).

3.1.7 Drug release in a high osmolality medium

In order to suppress the localized swelling of the uncured pellets caused by a higher inside osmotic pressure, the drug release was carried out in a high osmolality medium. The osmolality (30 mOsmol/kg) of pH-2 medium was raised to 1000 and 1500 mOsmol/kg by adding sodium chloride (NaCl). As expected, the curing effect was minimized as a function of increasing the osmolality of medium. For example, the curing effect was eliminated at 60 °C (f_2=57) and was reduced to some extent at 60 °C-75%RH by using a medium of 1000 mOsmol/kg osmolality (f_2=37) (Figure 15A). In contrast, the curing effect was completely overcome both at 60 °C (f_2=55) and 60 °C-75%RH (f_2=53) by further increasing osmolality to 1500 mOsmol/kg (Figure 15B). Additionally, the drug release was slowed down due to the decreased pressure inside the pellets confirming the osmotic driven mechanism.

The release profile of the uncured pellets approached closer to the cured ones using 1500 mOsmol/kg medium, which also indicates the suppression of macro rupture in coatings of the uncured pellets (later confirmed under video monitoring). The overall swelling of pellets was significantly decreased due to decreased osmotic force.

A)



B)

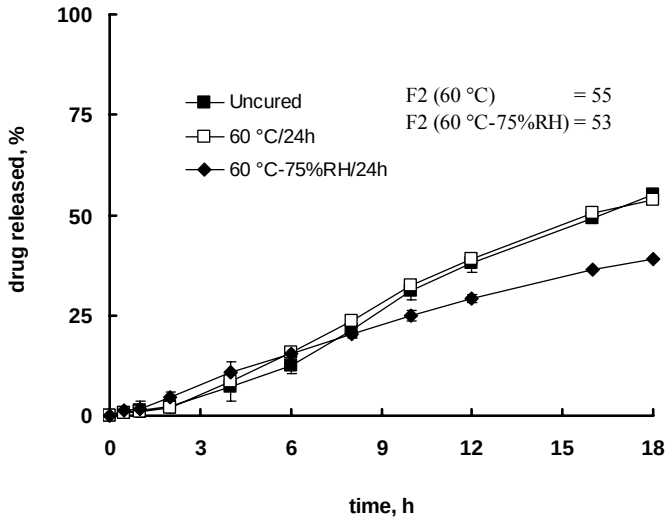


Figure 15: *Drug release from uncured and cured propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w),coating level 20% w/w, A) Release in 1000 mOsmol/kg pH-2 medium and B) Release in 1500 mOsmol/kg pH-2 medium.*

3.1.8 Determination of the adhesive force of coating

The adhesive force of coatings to the core was measured in order to evaluate the changes upon curing. It was difficult to determine the adhesive force of coatings using the pellets. Therefore, the model tablets were prepared exactly similar to the pellets and the detachment force of the coating was measured on a Texture Analyzer (Stable Micro Systems, Surrey, U.K.).

The results revealed that the adhesive force of the coating was significantly decreased after curing at 60 °C-75%RH/24 h (Figure 16) which could be due to the weakening of interfacial bonding of the coating to the core caused by the penetration of water and the creation of new stresses within the polymeric film. Another reason could be the change in swelling coefficient of the core and coating. The similar results have been reported when a decrease in adhesion of pigmented and non-pigmented cellulosic films occurred during storage at 37 °C and 75%RH (Okhamafe and York, 1985). In contrast, the adhesive force was decreased to a small extent after curing at 60 °C-24 h. This suggests that humidity plays a major role for decreasing the adhesive force of coatings and a small decrease at 60 °C-24 h might be caused by the increased internal stresses within coatings due to evaporation of residual water in polymeric films (Felton and McGinity, 1997).

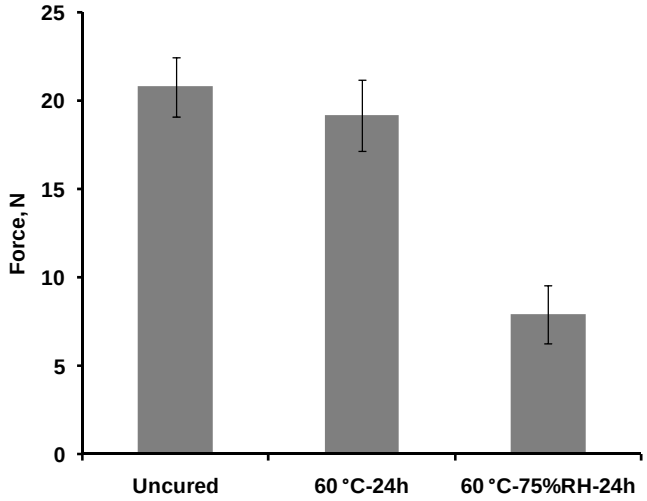


Figure 16: *Effect of curing on the adhesive force of the Kollicoat® SR 30 D coating (TEC 10% w/w, talc 35% w/w) using model tablets (n=9), coating level 20% w/w.*

It can be stated that the decreased adhesive forces of the coating upon curing at 60 °C-75%RH/24h led to the extensive uniform swelling of the pellets which could be the one reason for the observed curing effect.

3.1.9 Effect of drug loading

The effect of thickness of drug layer on curing was evaluated by layering propranolol HCl onto sugar cores in different loadings ranging from 2% to 50%. The drug layered cores were coated, cured and the release studies were carried out. The results depicted that very low (2%-5%) and very high (30%-50%) drug loadings did not show curing effect whereas 10% (discussed earlier) and 20% displayed a strong curing effect (Figure 17A-F). No curing effect with low and high drug loadings could be explained because of similar swelling behaviour of uncured and cured pellets observed during video monitoring. The details are as under:

2% and 5% drug loadings: the uniform swelling of both uncured and cured pellets was observed without any signs of localized swelling. This could be due to the quick dissolution of thin drug layer (confirmed from SEM images in Figure 18A) permitting the rapid penetration of medium from all sides. Consequently, the osmotic pressure was distributed equally towards the whole coating and the pellets underwent uniform swelling. Moreover, the release profiles of 2% and 5% drug loaded pellets were nearly similar like the release profile of 10% loaded pellets cured at 60 °C-75%RH (Figure 17A-C). This could be because of their similar swelling and release patterns.

10% and 20% drug loadings: the pellets with 10% and 20% drug loading had a strong curing effect due to a completely different swelling of the uncured and cured pellets (which has been explained in section 3.1.4) (Figure 17C & D).

30% and 50% drug loadings: the uncured and cured pellets with high drug loadings also followed uniform swelling during video monitoring. This could be due that 30% and 50% loading made a thick drug layer (confirmed from SEM images in 18B) which delayed the penetration of medium to the cores. As a result, the gradually increasing osmotic pressure was directed towards the whole coating and the pellets showed uniform swelling. The drug released from the uncured and cured pellets through the same mechanism without any curing effect (Figure 17E & F).

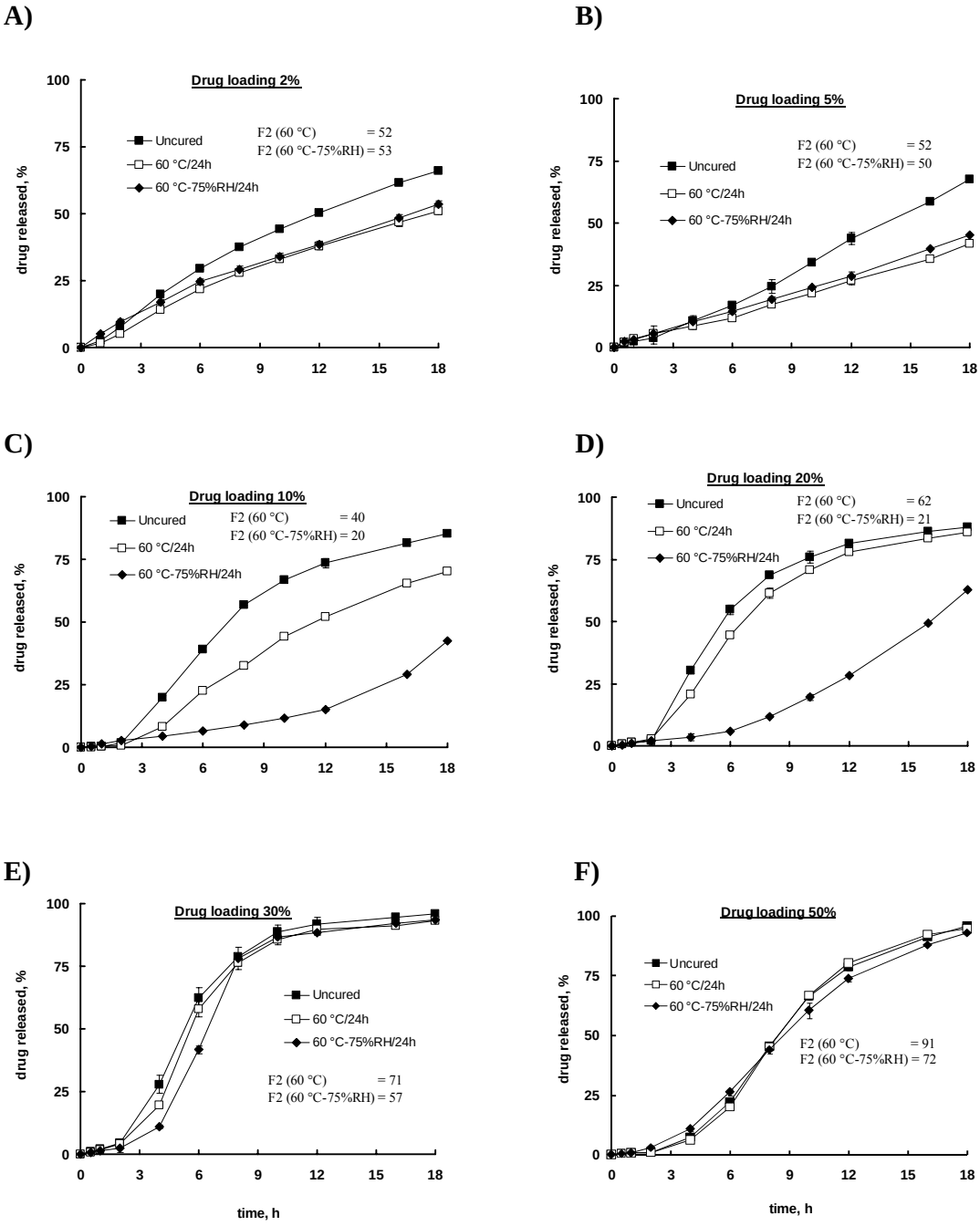


Figure 17: *Effect of drug loading on curing effect of propranolol HCl w/w loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w), coating level 20% w/w, A) 2%, B) 5%, C) 10%, D) 20%, E) 30% and F) 50%.*

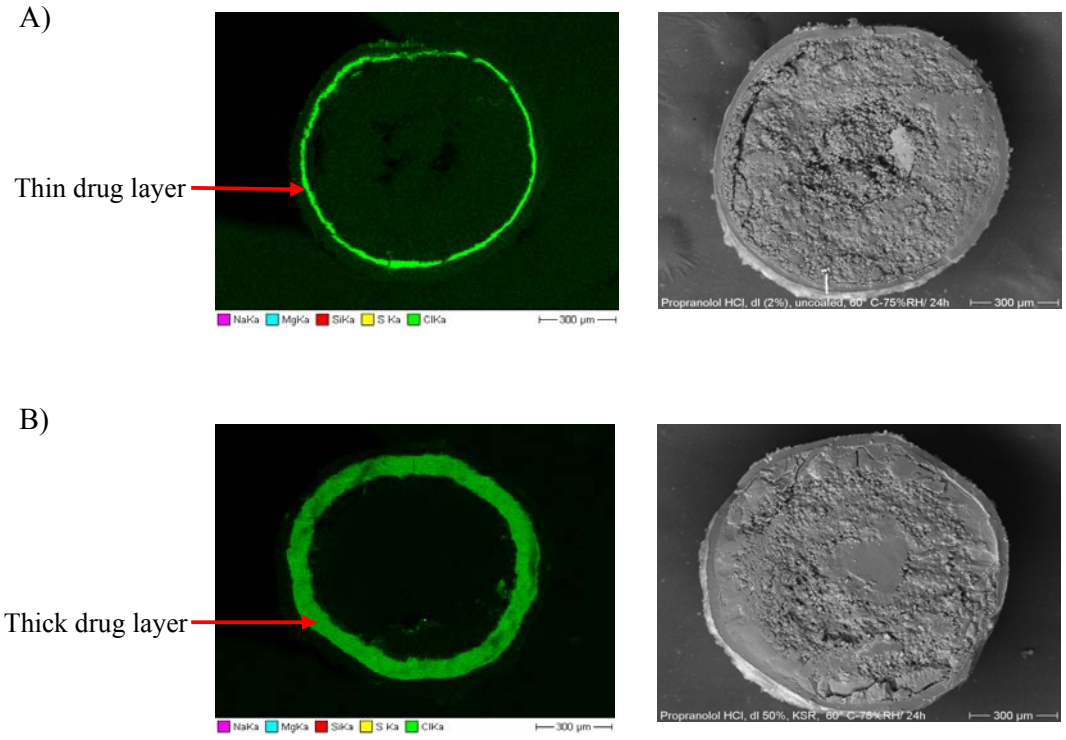


Figure 18: *SEM images of cross section of sugar pellets with different propranolol HCl w/w loadings, A) 2% and B) 50%.*

Despite of the similar swelling behaviour of 2%, 5%, 30% and 50% drug loaded pellets, the faster release rates with 30% and 50% drug loadings could be due to the excessive amount of drug.

Clearly, the curing effect was observed when both the uncured and cured pellets followed a completely different swelling behaviour which, in turn, was strongly depended on drug layer thickness/loading.

3.1.10 Effect of the type of drug layering (solution vs. suspension)

To explain the effect of type of drug layering (solution vs. suspension) on the curing, the drug layering from suspension was also applied. It was supposed that the drug layer from solution might have cracks that resulted in localized swelling of the uncured pellets. In comparison, the layering from suspension could result the simple deposition of drug particles onto the cores. However, the release results depicted no effect of type of drug layering on the curing

(Figure 19). Moreover, the video monitoring did not show any difference in swelling behaviour of solution vs. suspension layered pellets. The slightly faster release from the suspension layering could be linked to batch variability during the coating process.

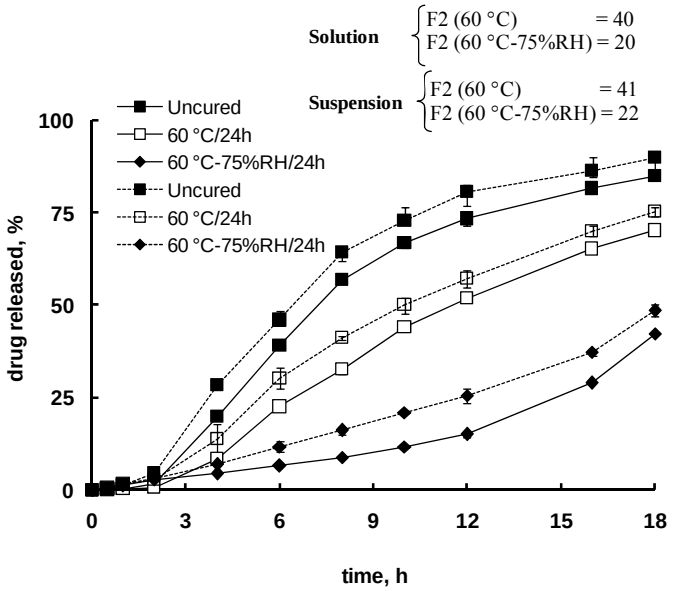


Figure 19: *Effect of type of drug layering (solution vs. suspension) on curing effect of propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w),coating level 20% w/w, (-) line represents drug release from solution layering and (….) line shows drug release from suspension layering.*

3.1.11 Curing as a function of time

The curing effect as a function of time was investigated and the results are shown in Figure 20A-D. Surprisingly, the pellets cured at 60 °C and 60 °C-75%RH showed significant decrease in drug release after 0.5 h and 6 h, respectively, which was further increased as a function of curing time. These findings confirmed that only 0.5 h exposure to 60 °C-75%RH was enough to induce a curing effect which reached to its maximum limit after 6 h. The video monitoring revealed that the swelling behaviour of 6 h cured pellets was in a close resemblance with 24 h cured ones. These results are in agreement with an increase in curing effect as a function of time with theophylline pellets coated with the blend of Eudragit® RS 30 D and Eudragit® L 100-55 (Wu and McGinity, 2003).

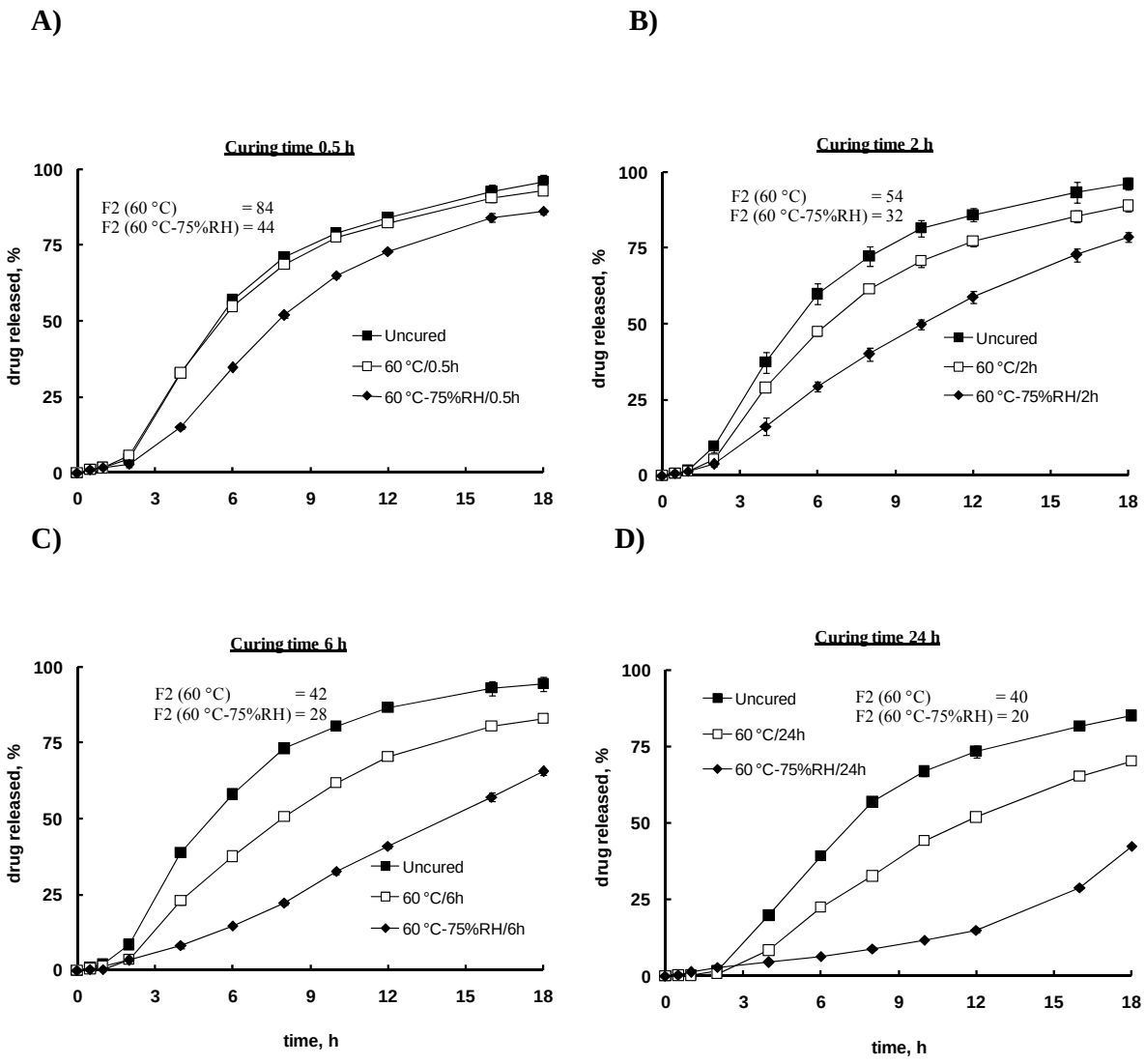


Figure 20: *Effect of curing on propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30D as a function of curing time (TEC 10% w/w, talc 35% w/w), coating level 20% w/w, A) 0.5 h, B) 2 h, C) 6 h and D) 24 h.*

3.1.12 Conclusions

The Kollicoat® RS 30 D coated pellets showed a strong curing effect within a drug loading range of 10%-20%. Importantly, the curing effect was not associated with a conventionally known cause for curing "further gradual coalescence of the polymeric films". This was confirmed by no changes in the permeability (complete film formation) and in the mechanical properties of the films upon curing. The main reason for the observed curing effect was found to be a completely different swelling behaviour of the uncured and cured pellets during release. The uncured pellets had a localized swelling whereas the cured pellets showed an extensive uniform swelling caused by the decrease in adhesive force of the coating upon curing. Additionally, an osmotically driven drug release mechanism from the coated pellets was predicted.

3.2 Effect of starter core, drug solubility and drug loading on the curing effect of Kollicoat® SR 30 D coatings

Drug release from polymer coated pellets is often occurred by three mechanisms: i) diffusion through intact polymeric film, ii) through water-filled channels and iii) through micro/macro cracks within polymeric film. The type of involved drug release mechanism is mainly dependent on the properties of starter cores (e.g. osmotic activity, water uptake and swelling), and drug solubility/loading. Accordingly, the type of starter core and drug solubility could also play a critical role on the curing mechanism of aqueous polymer coatings especially when the further gradual coalescence of films is not the reason for curing. In this regard, either no or very little work without explanations has been done up-to-date. In previous section, the strong curing effect of Kollicoat® SR 30 D coated pellets was observed by using osmotically active sugar cores and propranolol HCl (212 mg/ml) as a model drug within 10%-20% drug loadings Therefore, the aim of this part of work was to further investigate in detail the effect of starter core, drug solubility and drug loading on the curing effect of Kollicoat® SR 30 D coated pellets.

3.2.1 Effect of starter core and drug solubility

To explain the effect of starter core on the curing effect of Kollicoat® SR 30 D coated pellets, osmotically active sugar cores (called as SC cores) and osmotically inactive microcrystalline cellulose cores (called as MCC cores) of the same size were used. In order to investigate the effect of drug solubility, the following drugs were used: a poorly soluble (carbamazepine-0.2 mg/ml), a drug with intermediate solubility (theophylline-12 mg/ml) and two freely soluble drugs (tramadol HCl-500 mg/ml and metoprolol tartrate->1000mg/ml). Both the SC and MCC cores were loaded with 10% of different drugs and were coated 20% with Kollicoat® SR 30 D. The curing effect was evaluated by comparing the release profiles of uncured and cured pellets using f_2 similarity factor. The dissolution studies were carried out till 48 h due to the two main reasons: i) to observe the complete shape of release profiles and ii) to get an appropriate release profile for poorly and intermediate soluble drugs.

The results depicted that the SC cores had a strong curing effect with carbamazepine and theophylline (Figure 21A & B). However, tramadol HCl and metoprolol tartrate did not show curing effect (Figure 21C & D). Interestingly, the drug release was increased with

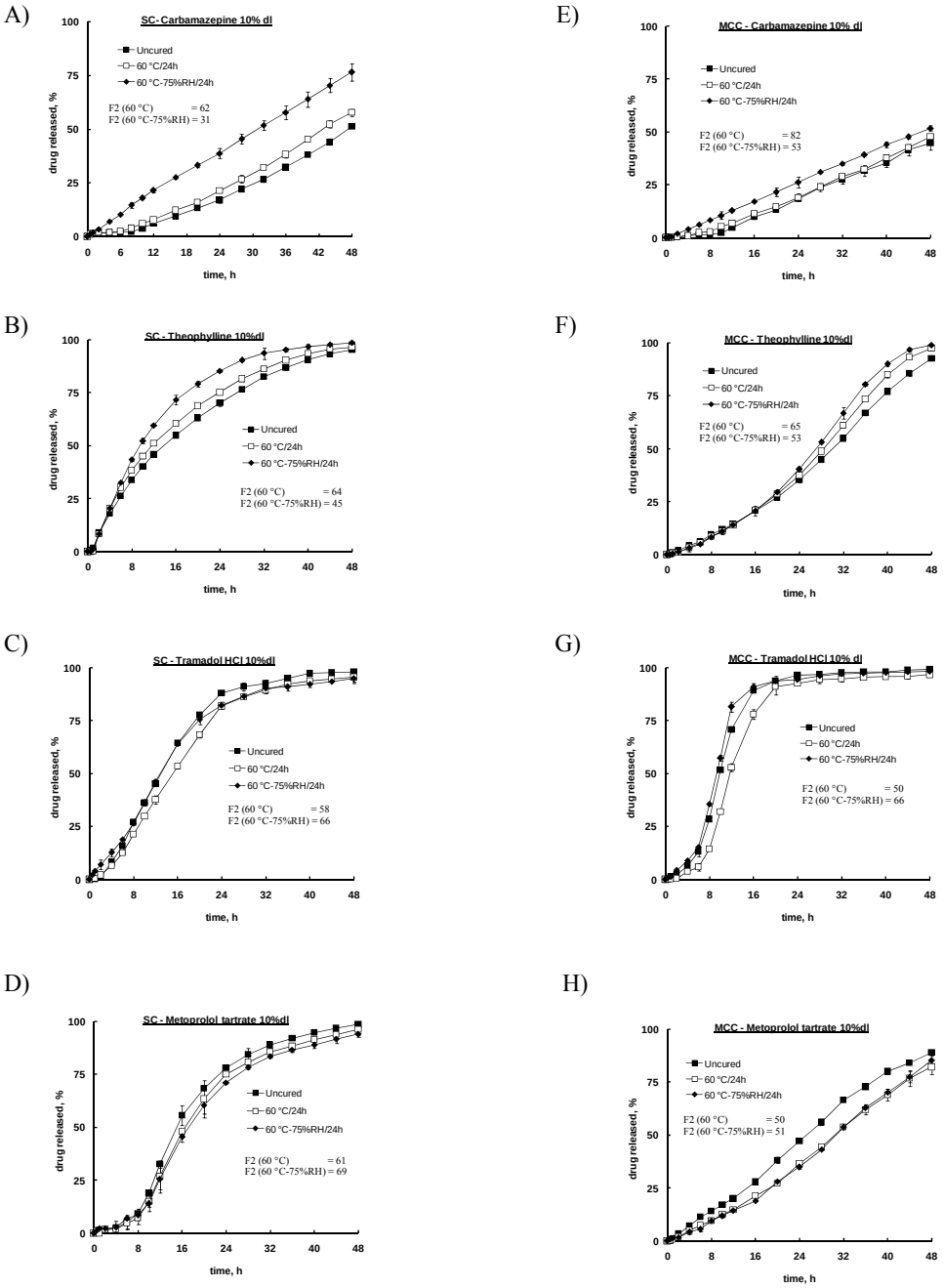


Figure 21: *Effect of starter core and drug solubility on the curing effect of Kollicoat® SR 30 D coated pellets (TEC 10% w/w, talc 35% w/w), drug loading 10% w/w, coating level 20% w/w, A) SC-carbamazepine, B) SC-theophylline, C) SC-tramadol HCl, D) SC-metoprolol tartrate, E) MCC-carbamazepine, F) MCC-theophylline, G) MCC-tramadol HCl and H) MCC-metoprolol tartrate.*

carbamazepine and theophylline after curing compared to propranolol HCl (shown earlier in section 3.1.1). In addition, the shape of release profiles with SC cores was strongly influenced by drug solubility. For example, carbamazepine followed a zero order release due to its very poor solubility while a sigmoidal release pattern was obtained with theophylline, tramadol HCl and metoprolol tartrate.

The coated pellets using MCC as a starter cores did not exhibit any curing effect irrespective of drug solubility (Figure 21E-H). However, a high variability in the release rates is an indication of strong effect of drug solubility. Almost zero order release patterns were obtained with carbamazepine, theophylline and metoprolol tartrate while tramadol HCl revealed a pulsatile type release profile. The investigation of the exact reasons for the different release patterns was beyond the scope of study. The further supportive studies like water uptake-weight loss and swelling behaviour during dissolution were carried out for the better understanding of curing mechanism.

3.2.2 Water uptake and weight loss of coated pellets

The water uptake and weight loss results of SC cores are shown below in Figure 22A-C. Clearly, the water uptake of the coated pellets increased significantly after curing at 60 °C-75%RH and an obvious correlation was found between water uptake and drug solubility. For instance, the water uptake of the carbamazepine pellets cured at 60 °C-75%RH was 326% after 18 h in comparison with 424% of theopylline and 772% of metoprolol tartrate. The lower water uptake of carbamazepine pellets could be attributed to its poor solubility and higher lipophilicity that hindered the penetration of medium into the SC cores whereas the higher water uptake of metoprolol tartrate pellets could be linked to its higher solubility and hydrophilicity that permitted the free ingress of medium. In comparison, the decreased weight loss of metoprolol tartrate pellets was in accordance with the decreased release rates upon curing. However, the decreased weight loss of carbamazepine and theophylline up to 18 h was not in agreement with the increased release rates after curing. This could be explained as follows: with uncured pellets, probably sugar released faster than the poorly soluble drugs through macro cracks formed in coatings due to rapid penetration of medium to cores at weak points of drug layer. However, with pellets cured at 60 °C-75%RH, the penetration of medium to the core was hindered by poorly soluble drug layer due to uniform swelling of coatings caused by decrease in adhesive force upon curing, as a result, mainly drug released via micro cracks till 18 h. This also explains increase in drug release of carbamazepine and

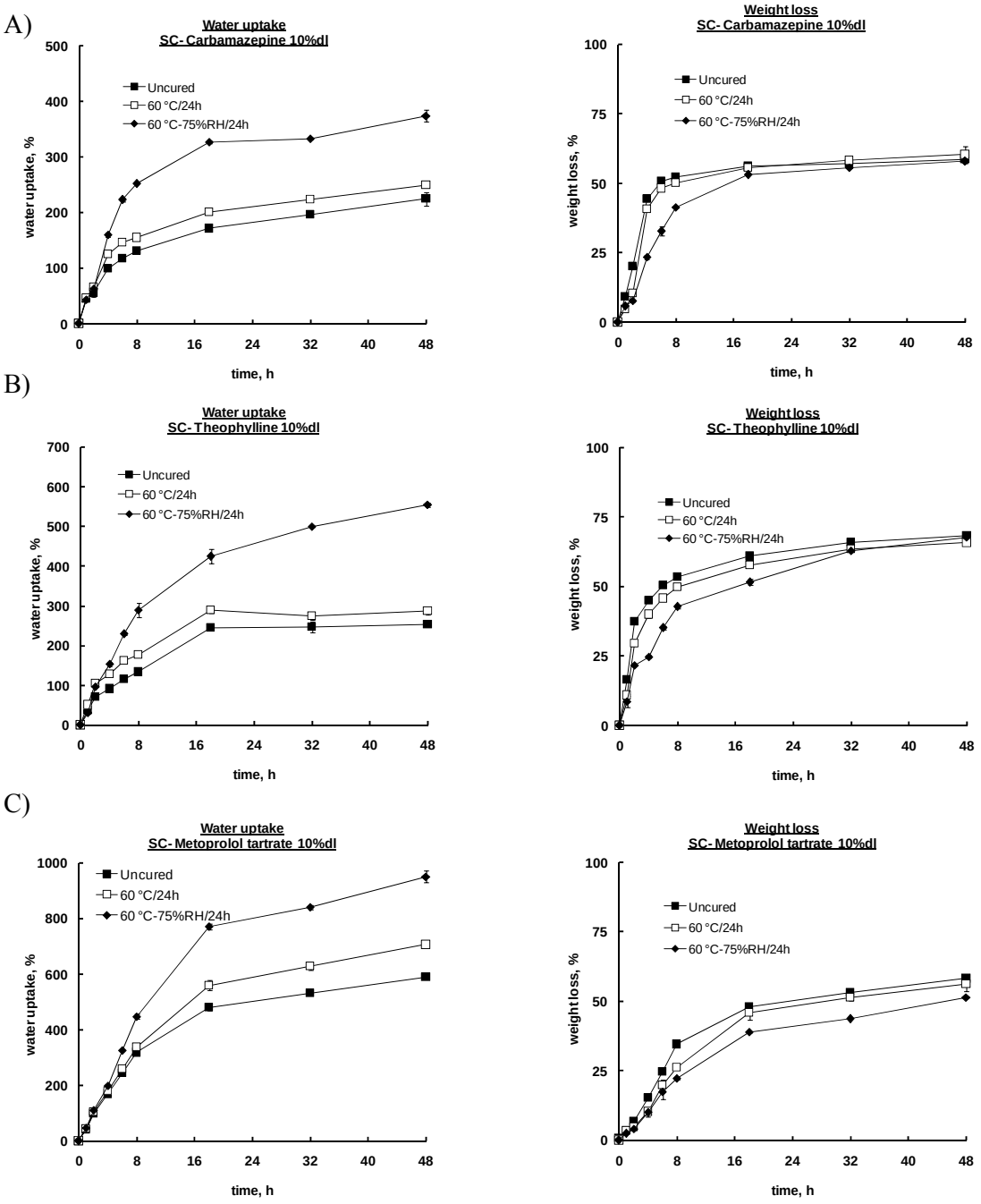


Figure 22: *Effect of drug solubility on the water uptake and weight loss of Kollicoat® SR 30 D coated uncured and cured sugar pellets (TEC 10% w/w, talc 35% w/w), drug loading 10% w/w, coating level 20% w/w, A) carbamazepine, B) theophylline and C) metoprolol tartrate.*

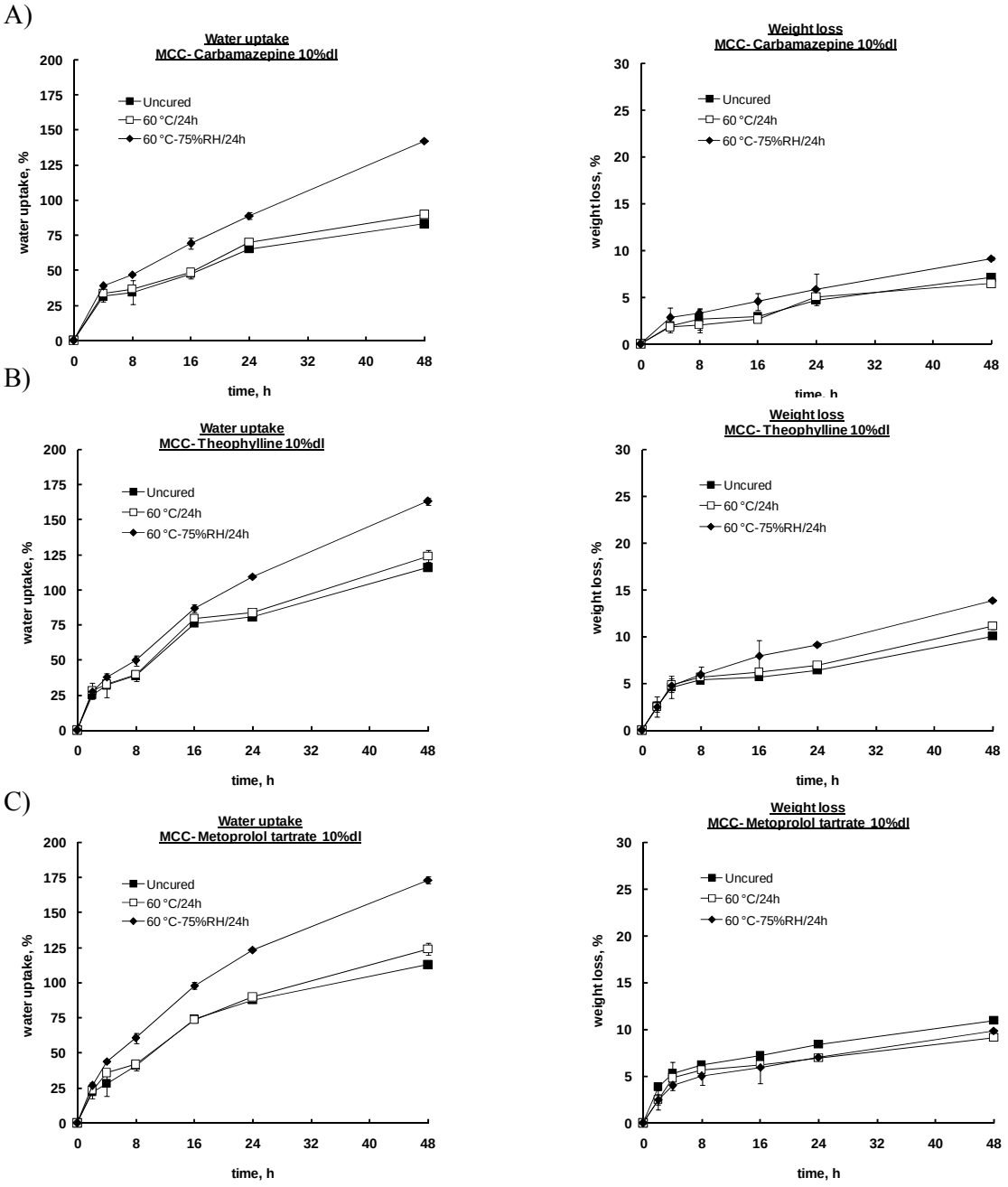


Figure 23: *Effect of drug solubility on the water uptake and weight loss of Kollicoat® SR 30 D coated uncured and cured MCC pellets (TEC 10% w/w, talc 35% w/w), drug loading 10% w/w, coating level 20%, A) carbamazepine, B) theophylline and C) metoprolol tartrate.*

theophylline after curing in contrast to propranolol HCl.

The water uptake of MCC pellets was significantly lower than the SC pellets which might be due to the insoluble nature of MCC cores (Figure 23A-C). However, a small increase in water uptake of the pellets cured at 60 °C-75%RH was observed as a function of drug solubility. For example, the water uptake of carbamazepine pellets after 24 h was 89% compared to 123% of metoprolol tartrate which could be due to difference in drug solubility and lipophilicity. However, the weight loss of uncured and cured MCC pellets was in close agreement with the drug release results irrespective of drug solubility.

3.2.3 Video monitoring of coated pellets during drug release

The video monitoring of the uncured and cured SC and MCC pellets during dissolution were performed to see the effect of starter core and drug solubility on the swelling behaviour. The description of video analysis is as under:

SC cores: The video monitoring of the uncured pellets of carbamazepine and theophylline revealed a localized swelling of the coating caused by the rapid ingress of medium at the point where drug layer was weak. In contrary, the pellets cured at 60 °C-75%RH exhibited a uniform swelling due to decrease in the adhesive force of coatings. However, the pellets cured at 60 °C showed a mixed type of swelling behaviour (localized and low uniform) of the coating (All three types of swelling behaviour have been described in detail for propranolol HCl in section 3.1.4.). The selective pictures at definite time points from the video monitoring of carbamazepine are presented in Figure 24A as an example.

However, both the uncured and cured pellets of tramadol HCl and metoprolol tartrate with 10% drug loading clearly displayed an extensive uniform swelling (Figure 24B.) This could be explained by the higher solubilities of these drugs that resulted in a rapid dissolution of the drug layer, as a result, the medium reached to the core immediately from all sides causing an equal distribution of osmotic pressure towards the whole coating and eventually uniform swelling. This is why with both uncured and cured pellets the drug released through micro cracks in the coating without any curing effect.

Furthermore, in order to confirm the importance of effect of drug solubility on swelling behaviour and extent, SC cores were directly coated with Kollicoat® SR 30 D. As expected, both of the uncured and cured pellets displayed an extensive uniform swelling similar to the metoprolol tartrate pellets. This confirmed the effect of drug solubility on swelling behaviour

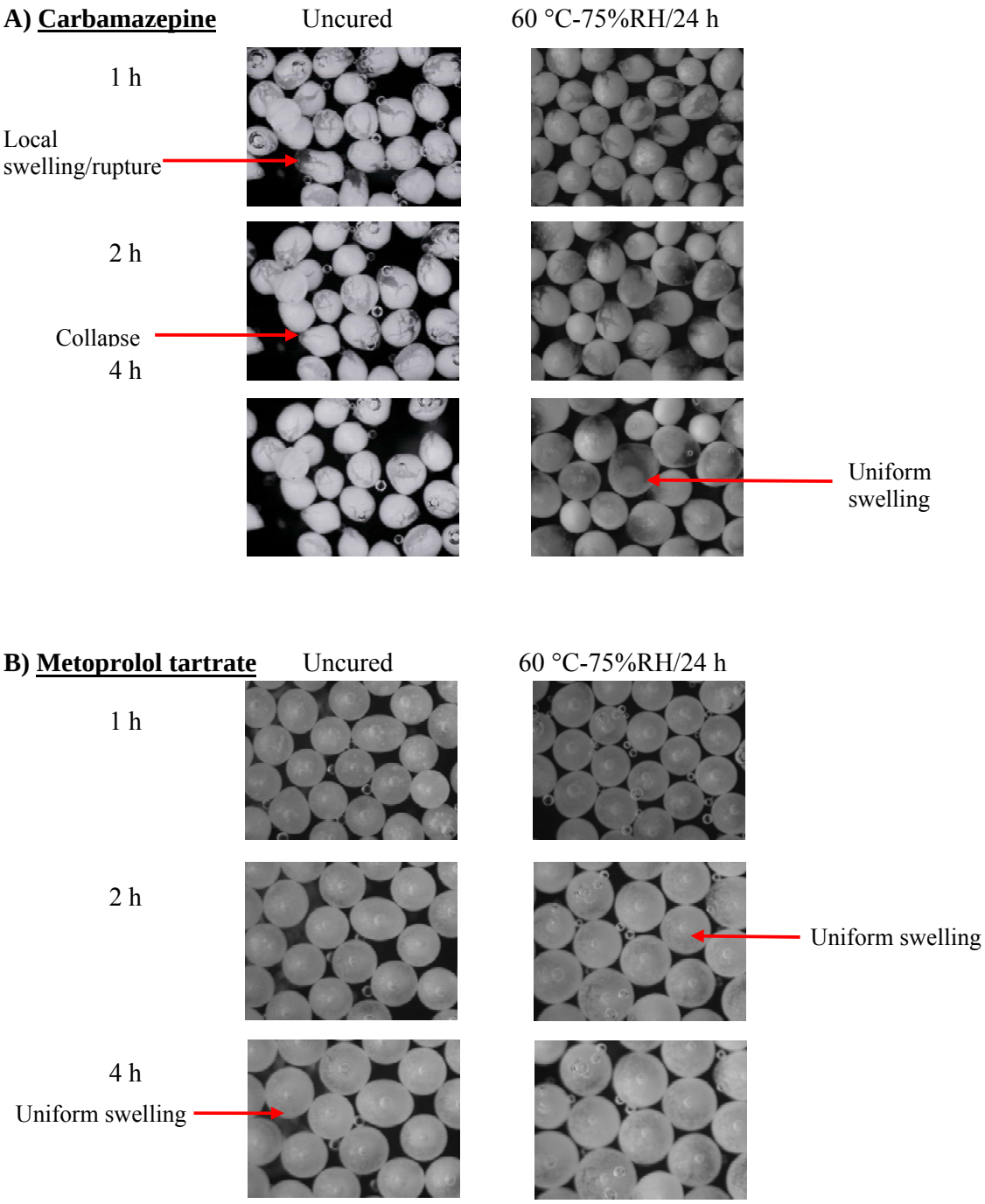


Figure 24: *Pictures from video monitoring of the uncured and cured SC pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w) during dissolution, drug loading 10% w/w, coating level 20% w/w, A) carbamazepine and B)metoprolol tartrate.*

and in turn on curing effect. Clearly, the overall swelling of the pellets was increased by increasing drug solubility (data not shown).

MCC cores: The video monitoring of MCC pellets did not show a big difference between the swelling behaviour of the uncured and cured pellets. Neither the uncured pellets underwent a localized swelling nor the cured ones showed an extensive uniform swelling like of the SC pellets. The selective pictures at definite time points from the video recordings of carbamazepine are shown in Figure 25. However, a few tiny micro cracks were noticed in the coating of uncured pellets whereas the cured pellets as well showed some evidence of expulsion of the drug via micro cracks.

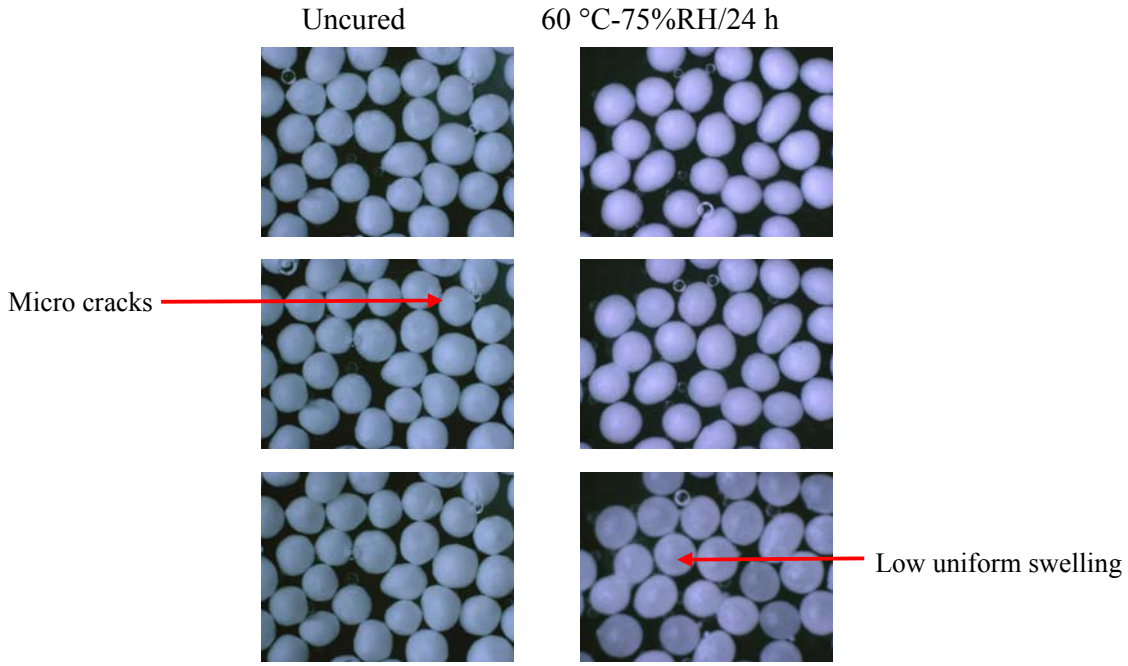


Figure 25: *Pictures from video monitoring of the uncured and cured carbamazepine (10% w/w) loaded MCC pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w) during dissolution, coating level 20% w/w.*

Importantly, the SC pellets had a curing effect when both the uncured and cured pellets followed entirely a different swelling behaviour which, in turn, depends on the drug solubility and loading. In comparison, the no significant difference in swelling of the uncured and cured pellets, independent of drug solubility and loading, with same release mechanism could be the main reason for no curing effect with MCC cores.

3.2.4 Effect of drug loading

The effect of drug solubility in combination with drug loading on curing was also evaluated. In this regards, the drugs with different solubilities were layered onto SC cores in different loadings (2%, 10%, 20%, 30% and 50%). The drug layered cores were coated with 20% of Kollicoat® SR 30 D and the presence of curing effect, the swelling extent and the behaviour of pellets during dissolution are enlisted in Table 4.

The results depicted that the curing effect was strongly dependent on drug solubility and drug loading. The curing effect was seen with drug solubility ranging from 0.2 mg/ml (carbamazepine) to 212 mg/ml (propranolol HCl) (data for propranolol HCl has shown earlier) in a drug loading range of 10%-20%. Moreover, no curing effect was observed with freely soluble drugs (tramadol HCl-500 mg/ml and metoprolol tartrate-> 1000 mg/ml) in all the investigated loadings. The presence or absence of curing effect can be explained as following:

Curing effect: As it has been concluded earlier that the curing effect occurred only when uncured pellets showed a localized swelling whereas cured pellets followed a uniform swelling. The present results also depict that the curing effect of carbamazepine, theophylline and propranolol HCl pellets in a drug loading range of 10%-20% is associated with their different swelling behaviour during dissolution before and after curing. In all these cases, the video monitoring revealed the localized swelling of the uncured pellets in comparison with the extensive uniform swelling of the cured pellets (which has been described earlier). However, outside this range like 2%, 30% and 50%, similar swelling behaviour of the uncured and cured pellets is an indicative of no curing effect. This could be due to that 2% drug loading formed a thin layer while 30% and 50% made a thick layer around the pellets, thus, either permitting immediate or delaying the penetration of medium to the core and eventually preventing the localized swelling of uncured pellets. Furthermore, the low uniform swelling of carbamazepine and theophylline in 30% and 50% drug loadings might be associated with their low drug solubility and high lipophilicity.

No curing effect: The video monitoring showed that the uncured and cured pellets of tramadol HCl and metoprolol tartrate followed a similar swelling behaviour in all the investigated drug loadings. This occurred because of higher solubilities of tramadol HCl and metoprolol tartrate that caused rapid dissolution of drug layer irrespective of thickness, resulting in the immediate penetration of medium from all sides. Due to this the uncured pellets always had a uniform swelling in all drug loading. However, the increased uniform swelling of the cured pellets was due to the decrease in adhesive force of the coating. It is important to mention that the swelling behaviour of tramadol HCl and metoprolol tartrate pellets was almost similar like the Kollicoat® SR 30 D coated sugar cores.

Table 4 *Effect of drug solubility and drug loading on the curing effect and swelling behaviour of Kollicoat® SR 30 D coated sugar pellets (TEC 10% w/w, talc 35% w/w), coating level 20% w/w.*

Drug solubility, mg/ml	**Drug loading, %**	**Curing effect (f_2 value)**		**Swelling behaviour (% swelling after release)**	
		60 °C	60 °C - 75%RH	Uncured	60 °C - 75%RH
Carbmazepine, 0.2	2	no (82)	no (50)	Uniform (175)	Uniform (295)
	10	no (62)	**yes (31)**	**Local (40)**	**Uniform (295)**
	20	no (78)	**yes (45)**	**Local (54)**	**Uniform (274)**
	30	no (77)	no (52)	Low uniform (100)	Low uniform (145)
	50	no (70)	no (51)	Low uniform (98)	Low uniform (139)
Theophylline, 12	2	no (75)	no (54)	Uniform (180)	Uniform (305)
	10	no (64)	**yes (45)**	**Local (56)**	**Uniform (325)**
	20	no (71)	**yes (43)**	**Local (69)**	**Uniform (301)**
	30	no (81)	no (60)	Low uniform (123)	Low uniform (169)
	50	no (76)	no (62)	Low uniform (99)	Low uniform (158)
Tramadol HCl, 500	2	no (89)	no (68)	Uniform (521)	Huge uniform (689)
	10	no (58)	no (66)	Uniform (501)	Huge uniform (685)
	20	no (60)	no (61)	Uniform (489)	Huge uniform (650)
	30	no (63)	no (52)	Uniform (478)	Huge uniform (634)
	50	no (77)	no (55)	Uniform (435)	Huge uniform (618)
Metoprolol tartrate,	2	no (57)	no (53)	Uniform (520)	Huge uniform (720)
> 1000	10	no (61)	no (69)	Uniform (533)	Huge uniform (729)
	20	no (70)	no (59)	Uniform (487)	Huge uniform (708)
	30	no (77)	no (55)	Uniform (490)	Huge uniform (696)
	50	no (78)	no (75)	Uniform (428)	Huge uniform (650)
Sugar cores	-	-	-	Uniform (538)	Huge uniform (780)

3.2.5 Conclusions

The pellets with MCC cores did not show curing effect irrespective of drug solubility while SC pellets revealed a strong curing effect depending on drug solubility and drug loading. The curing effect with SC pellets was observed in those cases when both the uncured and cured pellets exhibited a completely different swelling behaviour during dissolution which was potentially influenced by drug solubility and drug loading. In addition, the drug solubility also had a pronounce influence on the swelling of SC pellets.

3.3 Approaches to overcome the curing effect of Kollicoat® SR 30 D coatings

The objective of this part of work was to overcome the curing effect of Kollicoat® SR 30 D coated pellets. It has been concluded in the previous sections that the multiple factors are responsible for the observed curing effect e.g. osmotic activity of starter cores, drug solubility, drug loading and decrease in the adhesive force of coatings to the core upon curing. In order to eliminate the curing effect of Kollicoat® SR 30 D coated pellets, the different approaches were adopted accordingly.

3.3.1 Seal coating of starter cores

To suppress the osmotic activity, the SC cores were seal coated 20% with Kollicoat® SR 30 D because of its higher flexibility to withstand the osmotic pressure. Afterward, the seal coated SC cores were drug layered and polymer coated.

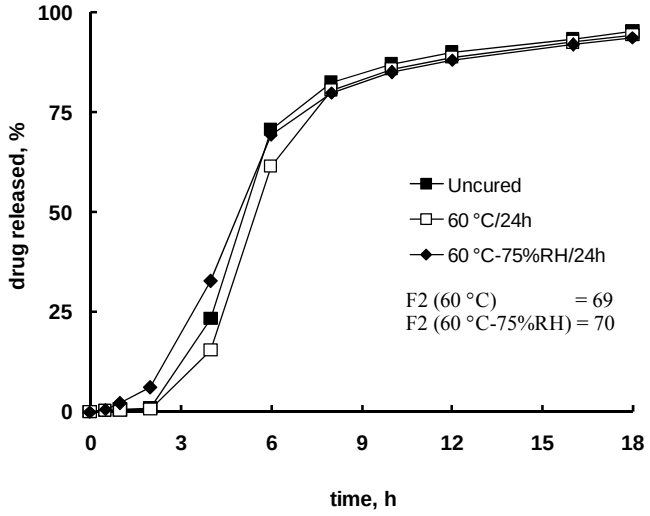


Figure 26: *Effect of seal coating of sugar cores on the curing effect of Kollicoat® SR 30 D coated pellets (TEC 10% w/w, talc 35% w/w), seal coating level 20% w/w, drug loading 10% w/w, coating level 20% w/w.*

The release results did not show curing effect both at 60 °C and 60 °C-75%RH. Moreover, the video monitoring displayed the similar swelling behaviour of the uncured and cured pellets

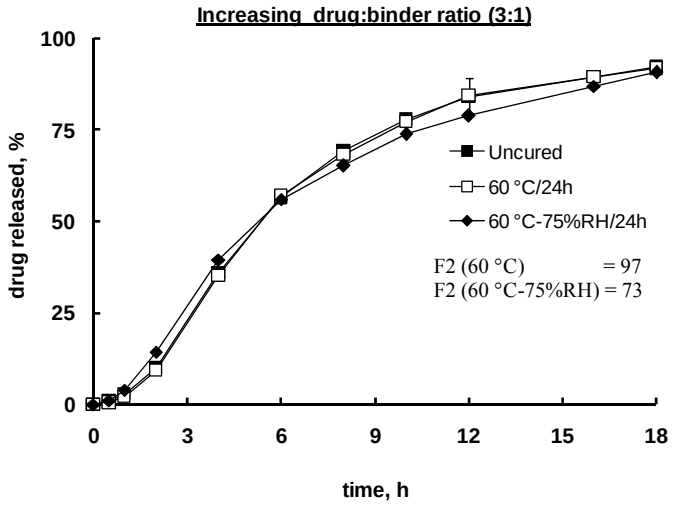
which reflects that the localized swelling of the uncured pellets was restricted after the seal coating of SC cores. In contrast, the curing effect could not be successfully eliminated when SC cores were seal coated 20% using Aquacoat® ECD (data not shown). This could be possibly related to the brittle coatings of Aquacoat® ECD which might not withstand the osmotic pressure. Clearly, the presence of localized swelling in uncured pellets suggested the rupturing of Aquacoat® ECD seal coatings.

3.3.2 Improving the adhesion of coatings

The decrease in adhesion of the coating to the core upon curing was found to be one of another cause of the observed curing effect. In order to hinder the decrease in adhesion of coating upon curing, the drug to binder ratio was increased from 9:1 to 3:1. Alternatively, a 10% sub coating of HPMC was also applied.

The release results depicted that the curing effect was successfully overcome by increasing the drug to binder ratio or by applying a 10% sub coating of HPMC (Figure 27A & B). The video monitoring revealed that uncured pellets showed a localized swelling and rupturing of the coatings but the extensive uniform swelling of the cured pellets at 60 °C-75%RH was reduced significantly. Furthermore, the water uptake and the extent of swelling of the cured pellets came closer to the uncured ones (data not shown).

A)



B)

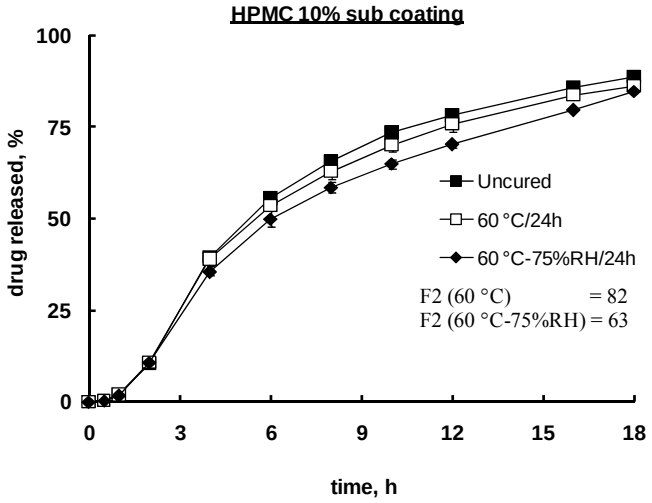


Figure 27: *Effect of A) increased drug:binder ratio (3:1) and B) a 10% sub coating of HPMC on the curing effect of propranolol HCl (10% w/w loaded) sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w, talc 35% w/w), coating level 20% w/w.*

In addition, the adhesion of the coating was determined by preparing the model tablets. The results showed that the adhesion of coating was decreased to a small extent upon curing and, the uncured tablet also exhibited an increase in the adhesive force which is a representative of

a strong binding of the coating to the core (Figure 28). This could be due to increase in interaction between the primary and secondary hydroxyl groups of HPMC with the polymer coatings. The increased concentrations of HPMC phthalate has been found to adhere strongly to MCC tablets (Missaghi et al., 2004; Lehtola et al., 1995; Row, 1981)

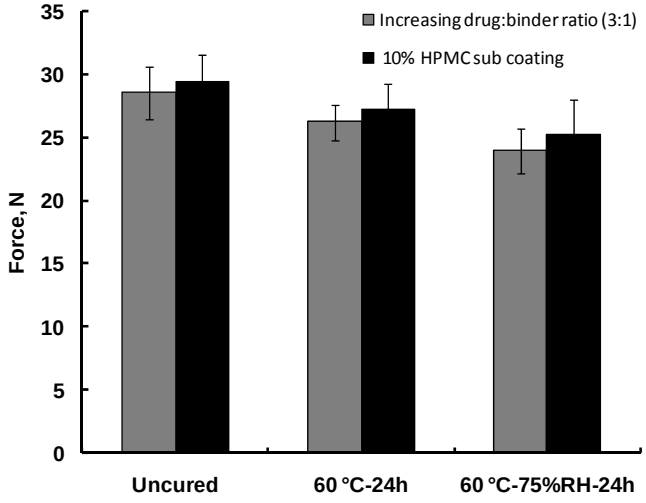


Figure 28: *Effect of curing on the adhesive force of Kollicoat® SR 30 D coatings after increasing drug to binder ratio (3:1) and applying a 10% w/w sub coating of HPMC (TEC 10% w/w, talc 35% w/w),coating level 20% w/w, the test was performed using model tablets (n=9).*

3.3.3 Making the coatings brittle

This approach was adopted to reduce the flexibility of Kollicoat® SR 30 D coatings by incorporating the higher amount of talc and using titanium dioxide. Interestingly, by adding 75% of talc to the coating formulations, the curing effect was eliminated at 60 °C but not at 60 °C-75%RH (Figure 29A). However, when the amount of talc was further increased to 100%, a stable release profiles indicated the complete absence of curing effect (Figure 29B). The difference in the water uptake of the uncured and cured pellets was minimized significantly (data not shown). Moreover, the video monitoring revealed that the extent of swelling of the cured pellets decreased effectively which indicates that the presence of higher amount of talc made the coating brittle and rough. The decrease in flexibility of coatings with

100% addition of talc was also confirmed by the mechanical properties of free films (data not shown). With 100% addition of talc, since the coating mainly consisted of talc and polymer

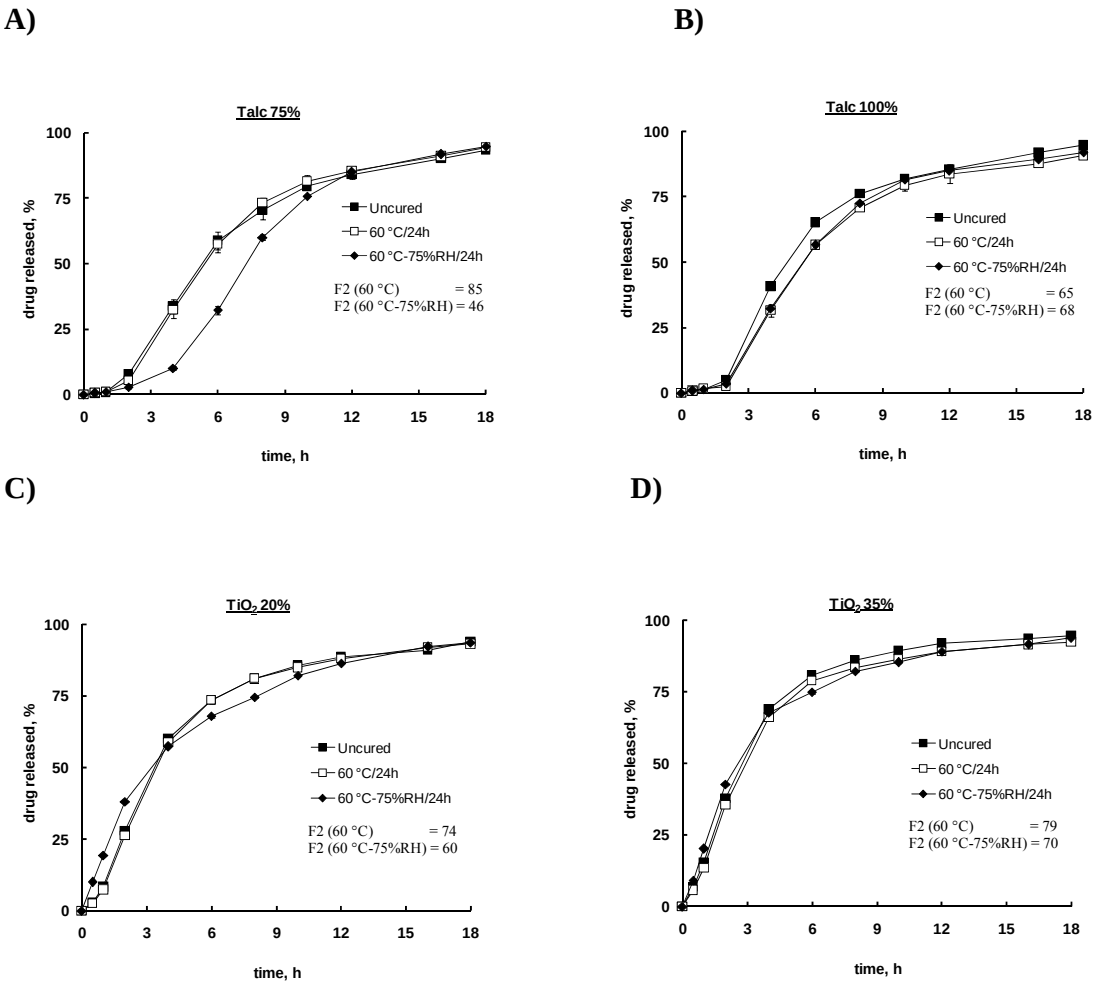


Figure 29: *Effect of incorporating higher amount of talc (w/w) and using TiO_2(w/w) as an anti-tacking agent on curing effect of propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w), coating level 20% w/w, A) Talc 75%, B) Talc 100%, C) TiO_2 20% and D) TiO_2 35%.*

latex and the particle size of the polymer latex was much smaller than that of talc, the talc would form the skeleton of the controlled release coating and the polymer latex would be distributed within the talc during coating process. During the curing, the polymer particles present within the talc matrix were more densified around talc particles resulting in more porous coating (Maejima and McGinity, 2001). It has also been reported that the surface of

polymer coating became rough after curing by using higher amount of talc. No curing effect suggested that the release rates through the micro cracks of the cured and via the macro cracks of the uncured coatings were equal.

Furthermore, the effect of higher amount of talc 100% on the adhesive force of the coatings was determined using model tablets and a decrease in overall adhesive force of the coating was found. This happened because talc is a hydrophobic substance that is generally added to the coating formulations to reduce the stickiness. The hydrophobic talc particles become embedded within the polymeric film and interfere with hydrogen bond formation between the tablet surface and the film coating. Additionally, talc causes stiffening of the film and increases the internal stresses within the polymer, as has been evidenced by an increase in the Tg of the polymer (Okhamafe and York, 1984; Okhamafe and York, 1985). However, the adhesion of the coating was not affected upon curing (Figure 30) which could be due to that the hydrophobic skeleton of talc hindered the penetration of water. As a result, the interfacial cleavage of bonding between the polymer and the tablet surface could be prevented and no significant decrease in adhesion occured.

Another strategy was adopted to replace hydrophobic talc with hydrophilic small sized titanium dioxide (TiO_2) due to its better wetting and dispersibility. The curing effect was completely eliminated by 20% addition of TiO_2 to the coating formulations and by further increasing the concentration to 35%, the release profile remained almost unchanged. In addition, the video monitoring expressed a low uniform swelling of the uncured and cured pellets suggesting a pronounced reduction in the flexibility of coatings. This reflects that the elimination of curing effect with smaller quantities of TiO_2 could be linked to its better covering of polymeric particles that resulted in reduction of flexibility.

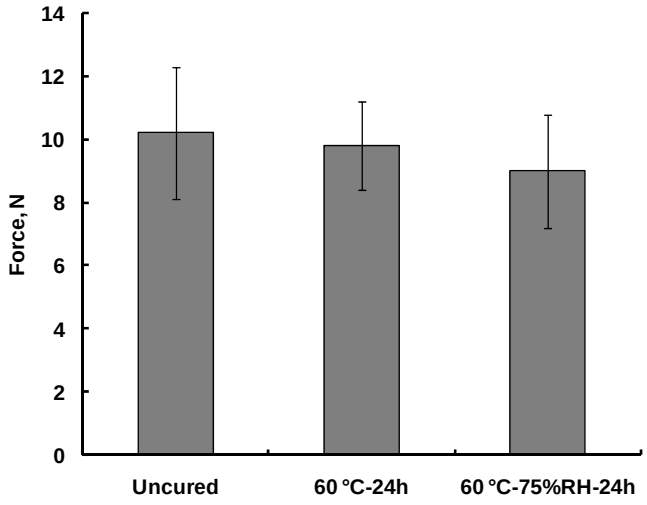


Figure 30: *Effect of curing on the adhesive force of Kollicoat® SR 30 D coatings after incorporating talc 100% w/w in the coating (TEC 10% w/w), coating level 20% w/w, the test was performed using model tablets (n=9).*

3.3.4 Use of pore-formers in coatings

This strategy was applied to make the coating porous in order to avoid the localized swelling of the uncured pellets upon leaching out of water soluble additives. Commonly used water soluble additives are low-molecular weight materials (e.g., sucrose, lactose, sodium chloride and calcium phosphate etc) and hydrophilic polymers including polyethylene glycol, polyvinylpyrrolidone and cellulose ethers such as HPMC. However, HPMC (Pharmacoat® 606) and another hydrophilic polymer [poly(vinyl alcohol)-poly(ethylene glycol) (PVA-PEG) graft copolymer, the trade name Kollicoat® IR] were added in different concentrations (5%, 7.5% and 10%) to coating formulations. Clearly, the coated pellets did not show curing effect by the addition of Pharmacoat® 606 to the coating formulations in all concentrations (Figure 31A-C). However, f_2 values represented the most stable release profiles with 7.5% addition of Pharmacoat® 606. The curing effect of carbamazepine pellets was not eliminated by 7.5% and 10% addition of Pharmacoat® 606. However, 20% of Pharmacoat® 606 addition provided a stable release profile. No elimination of the curing effect with 7.5% and 10% addition of

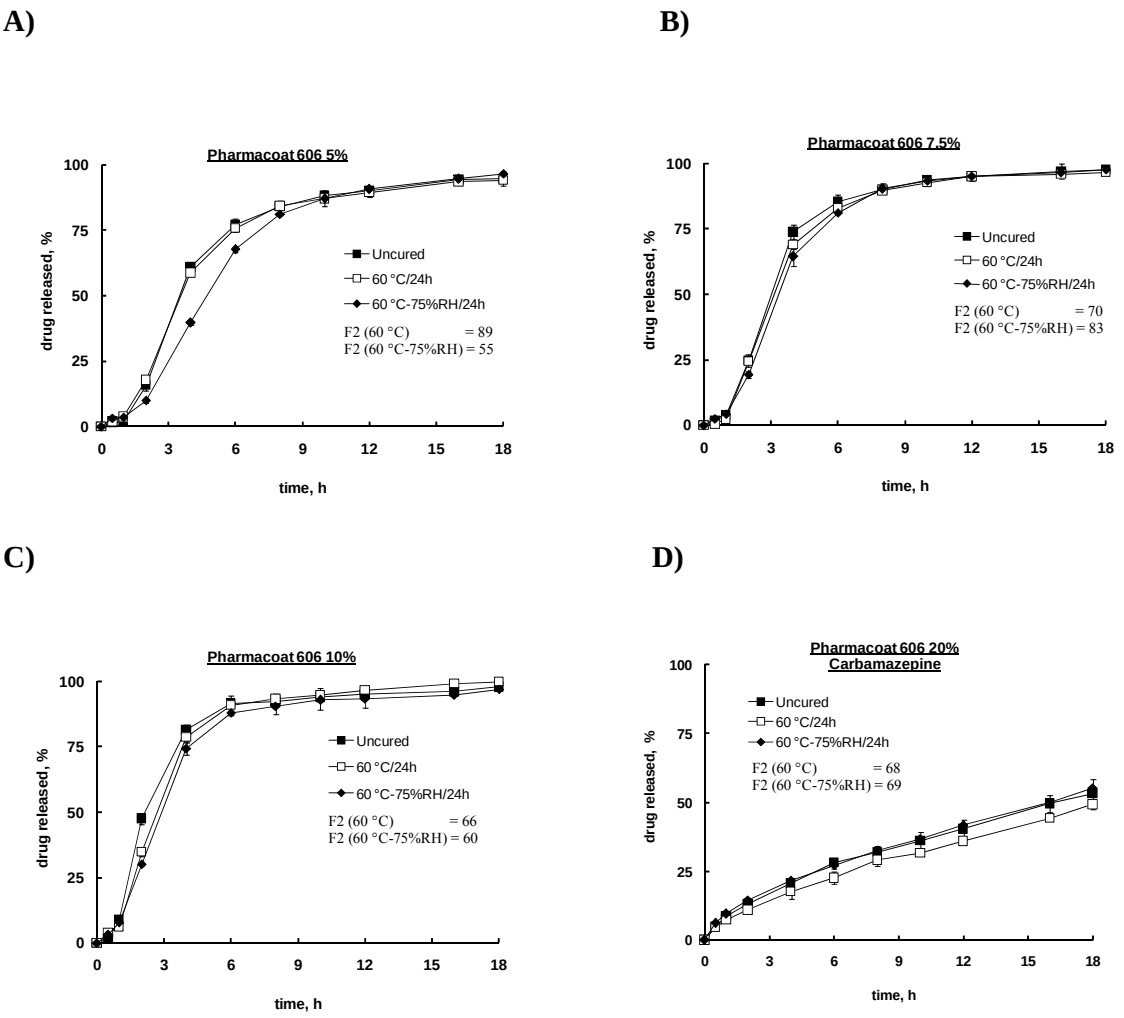


Figure 31: *Effect of addition of pore former on the curing effect of propranolol HCl and carbamazepine loaded sugar cores coated with Kollicoat® SR 30D, drug loading 10%, coating level 20%, A) propranolol HCl-Pharmacoat® 606 5%, B) propranolol HCl-Pharmacoat® 606 7.5%, C) propranolol HCl-Pharmacoat® 606 10% and D) carbamazepine-Pharmacoat® 606 20%.*

Pharmacoat® 606 could be due to the poor solubility of carbamazepine. The drug release rates were increased by adding pore-formers due to an increase in the permeability of coatings. In addition, the video monitoring showed a low uniform swelling of the uncured and cured pellets due to the porous coatings. An increase in permeability of ethylcellulose coatings by HPMC addition has been shown (Lindstedt et al., 1989; Wong et al., 1991). Also, the release of theophylline from matrix pellets coated with Aquacoat® ECD was shown to be stable by

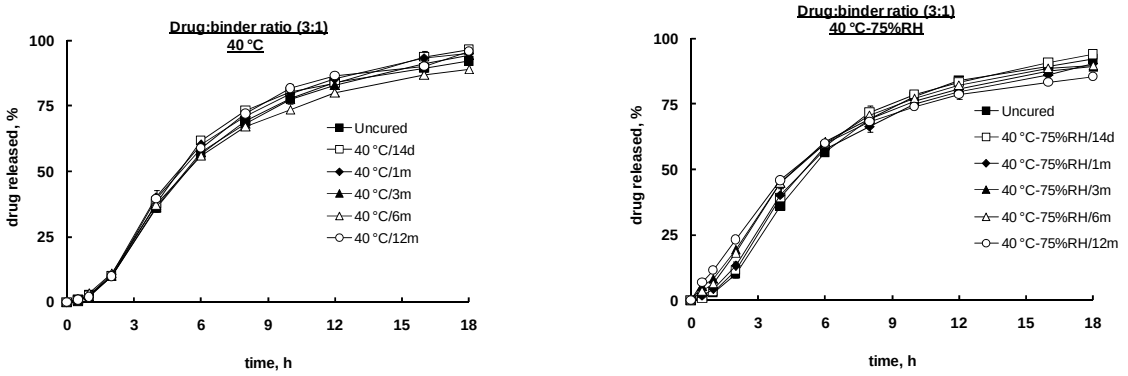
10% addition of Kollicoat® IR to the coating formulations (Siepmann et al., 2007; Siepmann 2008; Muschert et al., 2009) In comparison, the drug release was not stabilized by the addition of Kollicoat® IR to the coating formulations and only the release rates were changed as a function of Kollicoat® IR concentration.

3.3.5 Long term storage stability

The long term storage stability of Kollicoat® SR 30 D coated pellets, which did not exhibit curing effect, were evaluated. In this regard, two batches i) in which drug to binder ratio was increased from 9:1 to 3:1 and ii) in which higher amount of talc 100% was incorporated in the coating, were selected and the stability studies were continued up to 12 months under stress conditions.

The results showed that both the batches were stable at 40 °C and 40 °C-75%RH till 12 months (Figure 32A & B) which confirms the right selection of approaches in accordance with the identified reasons for the curing mechanism. This shows that Kollicoat® SR 30 D coatings are potentially stable over long term storage under stress conditions once the short term curing effect is eliminated.

A)



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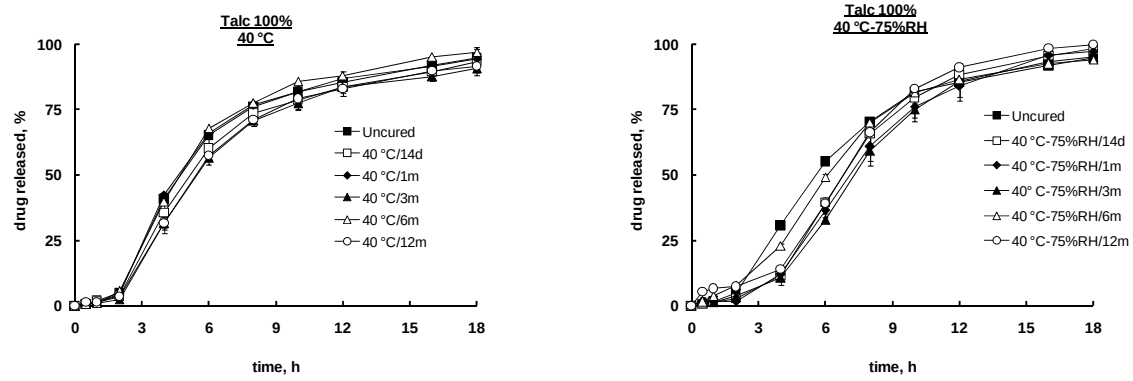


Figure 32: *Effect of long term stress storage conditions on the stability of propranolol HCl (10% w/w) loaded sugar pellets coated with Kollicoat® SR 30 D (TEC 10% w/w), coating level 20% w/w, A) Increasing drug:binder ratio (3:1), B) Incorporating 100% w/w talc in the coating.*

3.3.6 Conclusions

The curing effect of Kollicoat® SR 30 D coated sugar pellets was successfully eliminated by seal coating of cores to suppress their osmotic function, increasing drug to binder ratio or applying a sub coating to resist a decrease in the adhesion of coating upon curing, reducing flexibility of coatings by using higher amount of talc or alternatively by small sized hydrophililc TiO_2 and by adding hydrophilic polymers to make the coatings porous. In addition, the coated pellets were stable over long term storage under stress conditions.

3.4 Curing mechanism of Eudragit® NE 30 D coatings

The objective of this part of work was to investigate the curing mechanism of Eudragit® NE 30 D, another flexible polymer with a low Tg, coatings. The curing effect of Eudragit® NE 30 D coated pellets has been reported in literature but only a few aspects like curing time, curing temperature and crystallization of nonoxynol, a stabilizer in dispersion, has been elaborated without a clear understanding (Angela et al., 2003; Lin et al, 2001; Lin et al., 2003; Kucera et al., 2009; Bajdik et al., 2003). Therefore, the curing mechanism of Eudragit® NE 30 D coated sugar pellets was investigated for better understanding using propranolol HCl as a model drug.

3.4.1 Drug release and supportive studies

The drug release from Eudragit® NE 30 D coated pellets was decreased significantly after curing (Figure 33A). The f_2 values of 35 and 30 represented a pronounced curing effect at 60 °C and 60 °C-75%RH, respectively. The supportive studies like water uptake-weight loss, swelling studies and video monitoring were further carried out.

The water uptake of the uncured and cured pellets was nearly similar till 2 h and, after that, the water uptake of the cured pellets increased gradually as a function of time (Figure 22B). In comparison, the increased weight loss of the uncured pellets and decreased weight loss of the cured pellets was in accordance with the release results. However, the difference in the water uptake of the uncured and cured pellets was not that big like observed for the Kollicoat® SR 30 D coated pellets. The water uptake of Eudragit® NE 30 D pellets cured at 60 °C-75%RH after 18 h was approximately 200% compared to 800% of the Kollicoat® SR 30 D coated pellets. Although, Eudragit® NE 30 D is even more flexible than Kollicoat® SR 30 D, the difference in water uptake could be attributed to completely different chemical composition of the polymer dispersions. However, the uncured and cured coated pellets of Eudragit® NE 30 D followed a completely different swelling behaviour during video monitoring like the Kollicoat® SR 30 D coated pellets. The local swelling of the uncured pellets with small visible cracks was seen whereas the pellets cured at 60 °C-75%RH exhibited low uniform swelling (Figure 34). Nevertheless, the overall swelling of Eudragit® NE 30 D coated pellets was significantly lower than Kollicoat® SR 30 D coated pellets.

Furthermore, the drug release was performed in a high osmolality medium (1500 mOsmol/kg) to hinder the localized swelling. The decreased release rates with no curing effect suggest the

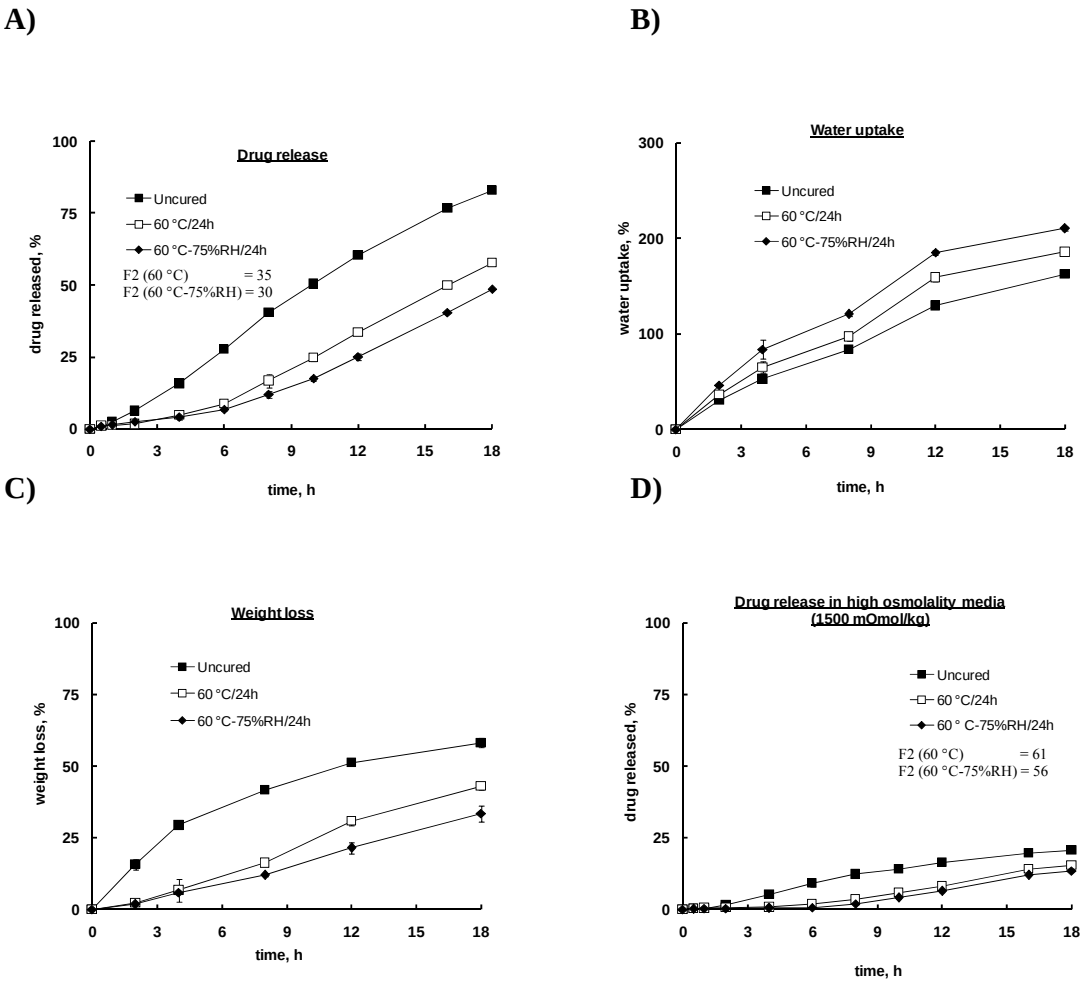


Figure 33: *Effect of curing on propranolol HCl (10% w/w) loaded sugar pellets coated with Eudragit® NE 30 D (talc 35% w/w), coating level 20% w/w, A) Drug release, B) Water uptake, C) Weight loss and D) Drug release in 1500 mOsmol/kg pH-2 medium.*

suppression of localized swelling of due to decreased osmotic pressure inside the uncured pellets (Figure 33D). This indicates that the difference in swelling behaviour of uncured and cured pellets was the main reason for the curing effect like the Kollicoat® SR 30 D coated pellets. In addition, an osmotic driven drug release mechanism was perdicted.

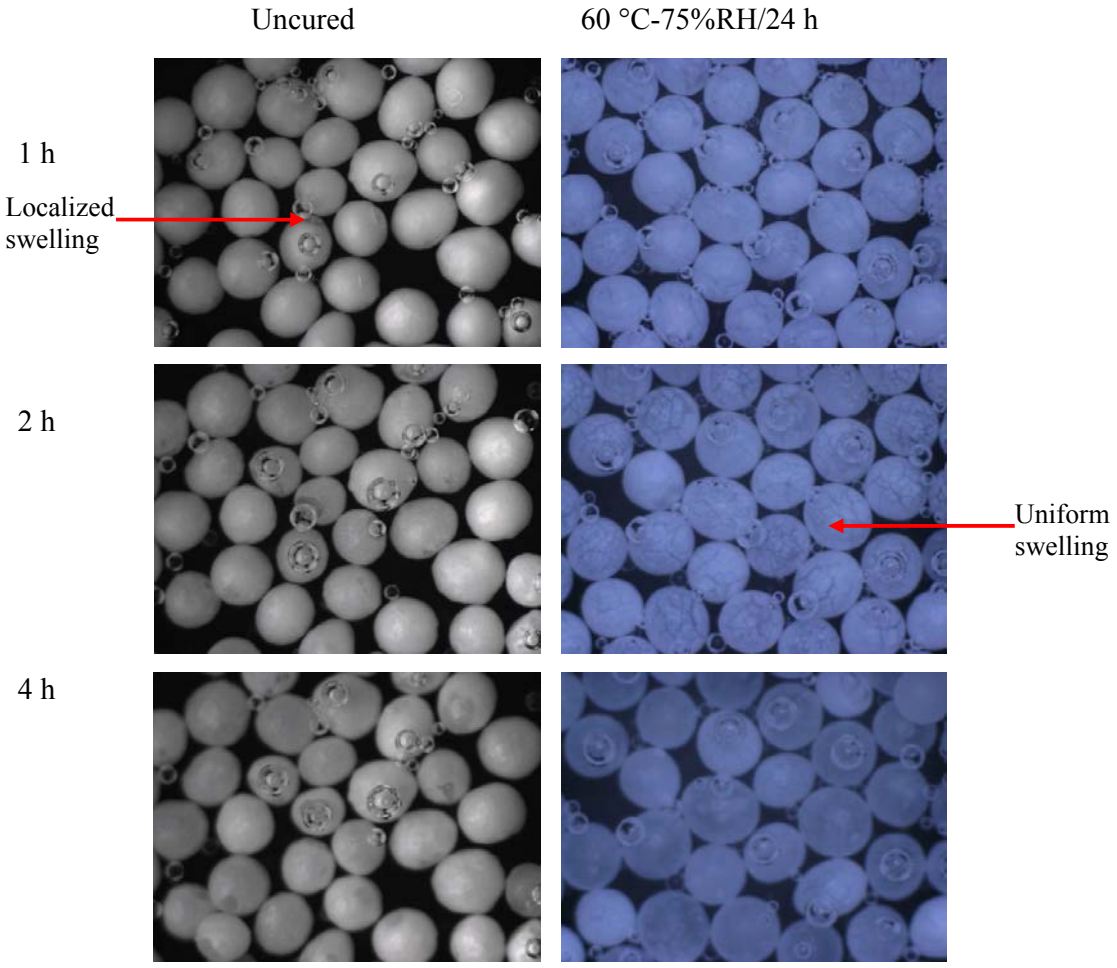


Figure 34: *Video monitoring of the uncured and cured propranolol HCl 10% w/w loaded sugar pellets coated with Eudragit® NE 30 D during dissolution, coating level 20%, (talc 35% w/w).*

3.4.2 Additional investigated aspects

Some additional aspects like effect of drug loading, increasing drug to binder and reducing the flexibility of coating by incorporating higher amount of talc were investigated. The results with description of curing effect and swelling behaviour are enlisted in Table 6.

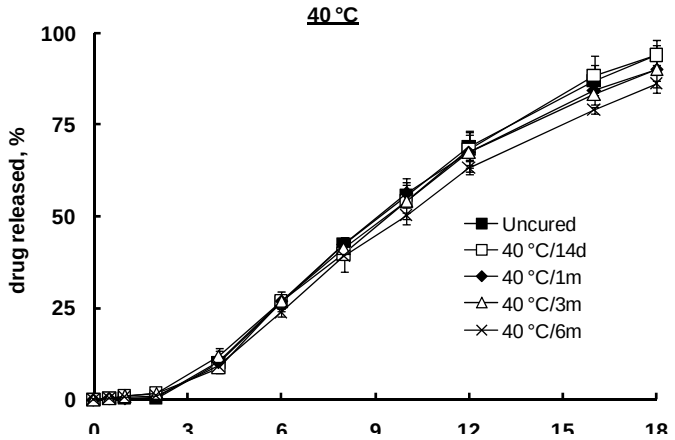
The results showed that no curing effect was seen with a low (2%) or with a high (30%) drug loading. In addition, the video monitoring during dissolution revealed the similar swelling behaviour of the uncured and cured pellets in both drug loadings like the Kollicoat® SR 30 D coated pellets.

Two approaches, i) increasing drug to binder ratio to resist decrease in adhesive force of the coating and ii) incorporating higher amount of talc (100%) to reduce the flexibility of the coatings, were successfully applied to eliminate the curing effect. Moreover, the long term storage of the coated pellets with talc 100% in the coating was carried out under stress conditions for 6 months and the drug release was found to be well stable (Figure 35).

Table 5 *Effect of drug loading, drug to binder ratio and higher amount of talc in coating, on the curing effect of propranolol HCl (10% w/w) loaded sugar pellets coated with Eudrgait® NE 30 D, coating level 20% w/w.*

Parameter	Curing	Description of experiments			
		Drug loading, %		Drug:binder ratio (3:1)	Talc 100% in coating
		2	30		
Curing effect, f_2 value	60 °C	no (73)	no (56)	no (57)	no (88)
	60 °C-75%RH	no (54)	no (51)	no (59)	no (93)
Swelling behaviour	Uncured	Uniform	Uniform	Local	Low uniform
	60 °C-75%RH	Extensive uniform	Extensive uniform	Low uniform	Low uniform

A)



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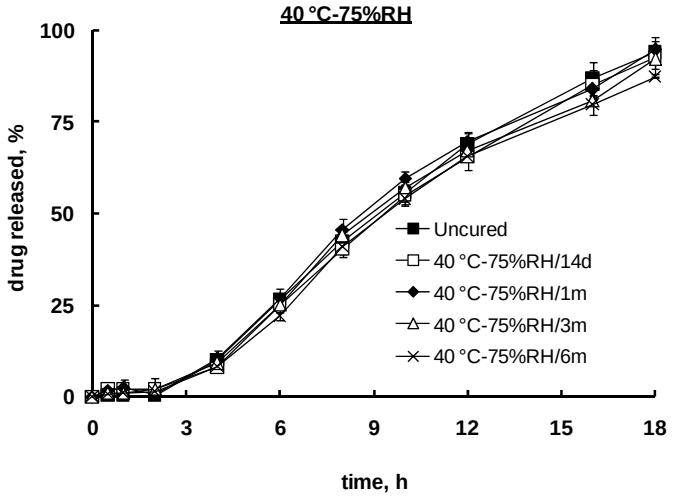


Figure 35: *Effect of long term storage under stress conditions on the stability of propranolol HCl (10% w/w) loaded sugar pellets coated with Eudragit® NE 30 D using talc 100% w/w, coating level 20% w/w, A) 40 °C and B) 40 °C-75%RH.*

3.4.3 Conclusions

The Eudragit® NE 30 D coated sugar pellets showed a strong curing effect by following the similar mechanism like the Kollicoat® SR 30 D coated pellets. The observed curing effect was successfully eliminated by adopting different approaches in accordance with the identified reasons. Importantly, the Eudragit® NE 30 D coated pellets without curing effect were storage stable under stress conditions till 6 months.

3.5 Evaluation of montmorillonites as anti-tacking agents

The objective of this part of work was to investigate anti-tacking properties of montmorillonites (MMTs) in comparison with talc, a conventionally used anti-tacking agent, using aqueous polymer dispersions. MMTs have a large surface area and a high aspect ratio; exhibit good adsorption ability, cation exchange capacity and drug carrying capability. MMTs are mostly used to enhance mechanical properties, reduce flammability and improve gas barrier properties in plastic and paper industry (Majumdara et al., 2003). MMTs have been used for different purposes in pharmaceutical field such as for the formation of drug-clay and polymer-clay intercalated nanocomposites to attain controlled release (Menga et al., 2009; Malhotra et al., 2006; Siew-Yoong and Milford, 2008; Joshi et al., 2010; Brostow et al., 2010; Pongjanyakul and Rongthong, 2010), and to small extent as a filler, glidant and lubricant (McGinity and Lach, 1975). However, no work so far has been done to investigate the anti-tacking properties of MMTs.

3.5.1 Stability of the mixed dispersions

The stability of aqueous polymer dispersions is often disturbed upon addition of additives. Addition of pigments to latex dispersions seldom affects their stability due to latex-pigment interactions by disturbing electrical double layer balance (Derjaguin et al., 1941; Verway et al., 1948; Hunter, 1989; Isrelachvili, 1991; Lyklema, 1995). Therefore, the stability of the polymer dispersions resulted by the addition of different concentrations (10%, 20% and 35% w/w) of the MMTs and talc was examined for 7 days. All polymer dispersions were found to be stable by the addition of talc. However, Eudragit® RS 30 D and Eudragit® RL 30 D were stable with both of used MMTs; Cloisite® Ca^{++} and Nanofill® 116. In contrast, Eudragit® NE 30 D and Eudragit® NM 30 D dispersions were stable with Nanofill® 116 and irreversible flocculation occurred with Cloisite® Ca^{++}, while Kollicoat® SR 30D was stable with Cloisite® Ca^{++} and not with Nanofill® 116. The instability could be caused by the change in pH and viscosity of the dispersions, surface charge of the colloidal particles and interaction of pigments with the polymeric particles (Nyamweya et al., 2001; Dangel et al., 2000; Garcia-Garcia et al., 2009; Ishikawa et al., 2005). The investigation of the exact reason for the unstable dispersions was beyond the scope of this study. Both instability and stability of the used polymer dispersions were observed independent of the MMTs concentrations. The stable dispersions were used for further experiments. The solid contents of stable dispersions with

35% addition of Nanofill® 116 were adjusted to 5% w/w due to its high swelling properties for further studies.

3.5.2 Wettability of the MMTs and talc

The uniform distribution of additives in aqueous polymer dispersion is largely dependent on their wettability. The hydrophilic substances have higher wettability and can be uniformly distributed in the formulations whereas hydrophobic substances exhibit the opposite behaviour due to their low wettability (Grundke et al., 2008). In order to check wettability, the contact angle on the surfaces of the MMTs and talc was measured using deionized water and the polymer dispersions (Table 6). Talc had the contact angle values over 100 with deioinzed water and the polymer dispersions which showed its strong hydrophobic characteristics. In contrary, the droplet on the surface of Cloisite® Ca^{++} spread very quickly and no value of contact angle was recorded whereas Nanofill 116 exhibited small values due to its high swelling properties. The lower contact values proved the higher wettability of the MMTs. The increase in wettability of the agar based nanocomposite films by adding Cloisite® Na^{+} has also been reported (Rhim, 2009).

Table 6 *Contact angles of the MMTs and talc using deionized water and different aqueous polymer dispersions.*

	Contact angle, θ° (n = 3)		
Polymer/water	**Talc**	Cloisite® Ca^{++}	Nanofill® 116
Deionized water	104 ± 2.1	0	22 ± 1.6
Kollicoat® SR 30 D	126 ± 1.5	0	24 ± 0.7
Eudragit® RS 30 D	110 ± 2.8	0	18 ± 3.1
Eudragit® NE 30 D	114 ± 0.9	0	19 ± 2.7

3.5.3 Tackiness of various polymers

Tackiness of various aqueous polymer dispersions, which generally cause sticking problem during coatings, was evaluated. Eudragit® NE 30 D, Eudragit® NM 30 D and Kollicoat® SR 30 D were selected as the flexible polymers, while Eudragit® RS 30 D and Eudragit® RL 30 D

were used as an example of the sticky brittle polymers. The obtained tackiness force was of the following order: Eudragit® NE 30 D ≥ Eudragit® NM 30 D > Eudragit® RS 30 D > Kollicoat® SR 30 D > Eudragit® RL 30 D (Figure 36). The films of Eudragit® NE 30 D and Eudragit® NM 30 D exhibited the maximum tackiness which could be due to their low glass transition temperature and high flexibility. Even though the product temperature is usually adjusted between 16–20 °C for this polymer, the agglomeration problem during coating cannot be overcome completely (Bodmeier and Paeratakul, 1994b; Wesseling et al., 1999). Interestingly, the films of Kollicoat® SR 30 D, another flexible polymer known to cause an agglomeration problem during coating, did not show higher tackiness like Eudragit® NE 30 D. This could be related to the presence of polyvinyl alcohol, a water soluble polymer, in Kollicoat® SR 30 D dispersion (Kollicoat® SR 30 D technical information, 2007). The films of Eudragit® RS 30 D and Eudragit® RL 30 D displayed tackiness behaviour almost similar to Kollicoat® SR 30 D. Although, often strong electrostatic interaction and agglomeration problem are evident with these polymers if use without anti-tacking agents. The lower tackiness with these polymers could be linked to their high glass transition temperature. The slightly lower tackiness of Eudragit® RL 30 D compared to Eudragit® RS 30 D could be possibly explained by the presence of more quaternary ammonium groups in the polymer (Wesseling et al., 1999).

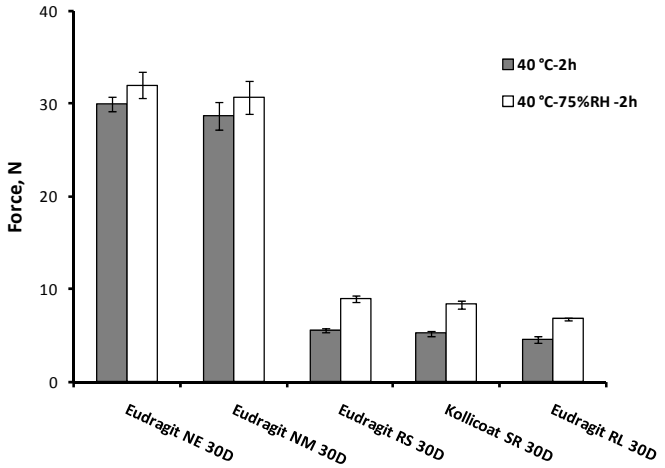


Figure :36 *Tackiness of films prepared from different aqueous polymer dispersions (Eudragit® RS & RL 30 D and Kollicoat® SR 30 D were plasticized with 20% w/w and 10% w/w TEC respectively, while Eudragit® NE & NM 30 D films were plasticizer free).*

In addition, the detachment force required to separate the polymeric films was increased after inducing tackiness at 40 °C-75% RH for 2 h. This could be due to the exposure of the films to

more humid conditions where water acted as a plasticizer and increased the flexibility of polymer particles and consequently increased tackiness.

3.5.4 Effect of the MMTs and talc on tackiness

The tackiness of the different polymeric films (Eudragit® NE 30 D, Kollicoat® SR 30D and Eudragit® RS 30 D) using various concentrations (10%, 20% and 35%) of the MMTs (Cloisite® Ca^{++} and Nanofill® 116) and talc are shown in Figure (37A-C). Interestingly, the MMTs reduced the tackiness of polymeric films more effectively than talc in all used concentrations and at both tackiness inducing conditions (40 °C-2 h and 40 °C-75%RH/2 h).

Eudragit® NE 30 D films with 20% of Nanofill® 116 had lower detachment force when compared with 20% and 35% of talc (Figure 37A). Also Eudragit® NM 30 D films had the same trend (data not shown). Similarly, the films of Kollicoat® SR 30 D with 20% of Cloisite® Ca^{++} required lower force to separate the films than those with 20% and 35% of talc (Figure 37B). The films of Eudragit® RS 30 D with 10% of cloisite® Ca^{++} and Nanofill® 116 exhibited a lower detachment force in comparison with 10%, 20% and 35% of talc. The Eudragit® RL 30 D films had the same trend (data not shown). The lower detachment force of films with the MMTs could be attributed to their uniform distribution in the polymer dispersions and then in casted films (Figure 38A-C). In comparison, talc was not uniformly distributed and a few talc free small patches were observed in the films (Figure 38A-C). The irregular distribution of talc might be related to its high hydrophobicity, which can be explained by the absence of Al and OH in the octahedral and basal surface of elementary sheets, respectively. On the other hand, the MMTs, being hydrophilic in nature, were homogenously dispersed in the formulations and as a result had a uniform and smooth distribution in the casted films. This led to a better covering of polymeric particles by the MMTs and eventually reduced the tackiness more effectively.

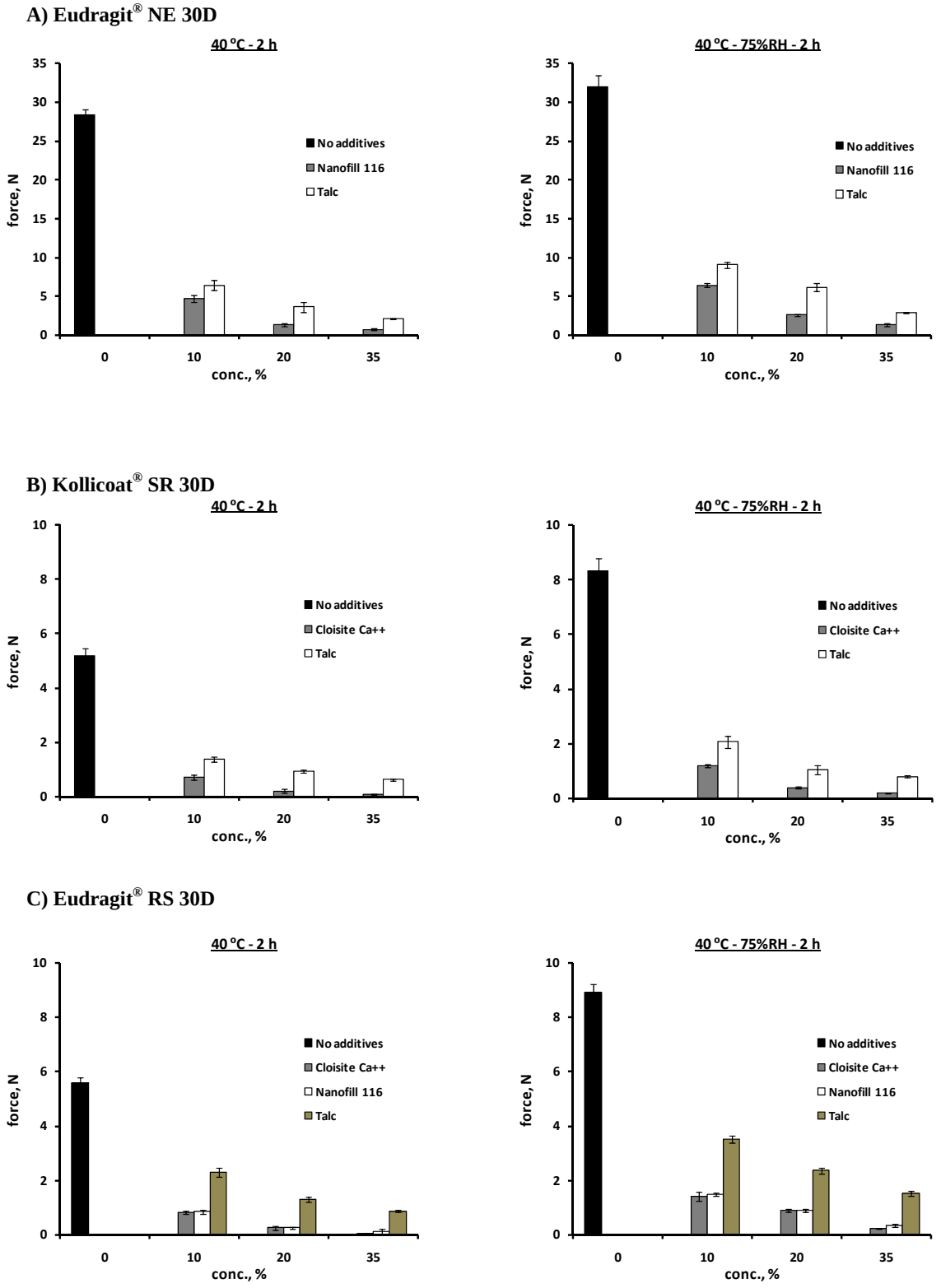
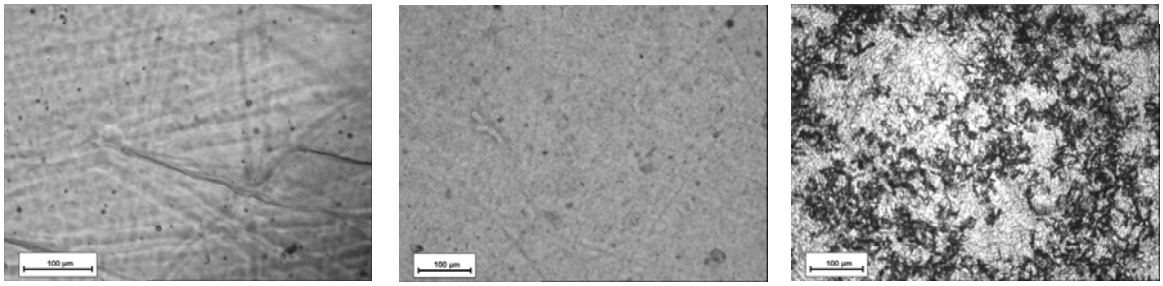


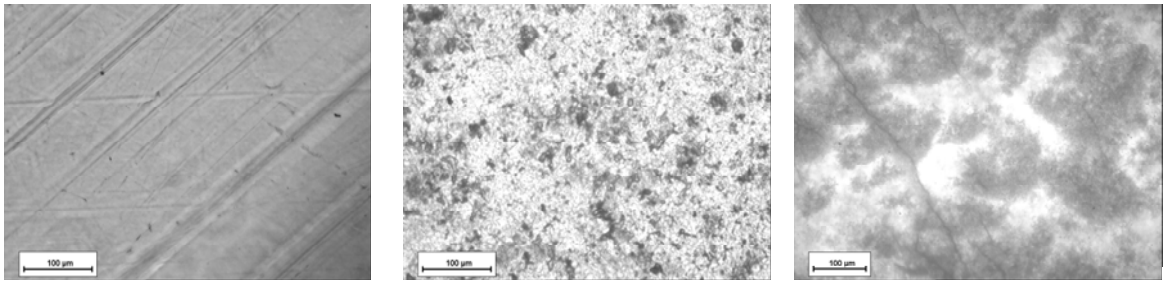
Figure 37: *Effect of different concentrations of the MMTs and talc on the tackiness of various polymeric films A) Eudragit® NE 30 D, B) Kollicoat® SR 30 D and C) Eudragit® RS 30 D.*

A) Eudragit® NE 30 D



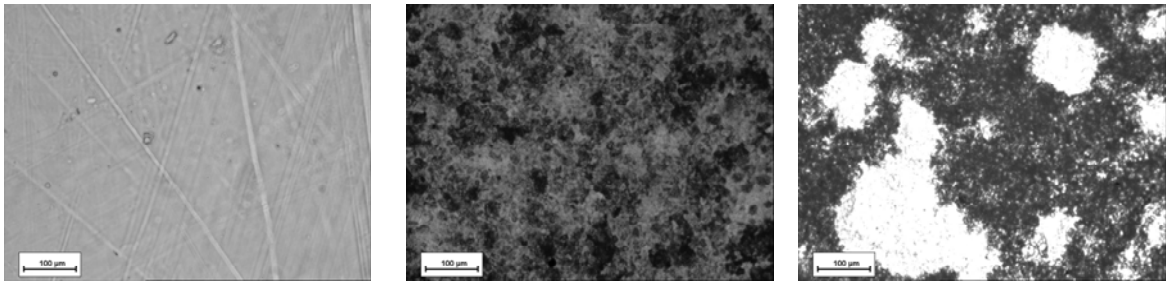
No additive **Nanofill® 116** **Talc**

B) Kollicoat® SR 30 D



No additive **Cloisite® Ca^{++}** **Talc**

C) Eudragit® RS 30 D



No additive **Cloisite® Ca^{++}** **Talc**

Figure 38: *Macroscopic images of the polymeric films containing 20% w/w of the MMTs and talc A) Eudragit® NE 30 D, B) Kollicoat® SR 30 D and C) Eudragit® RS 30 D.*

3.5.5 Effect of plasticizer concentration on tackiness

Higher amounts of plasticizers are added into coating formulations for many reasons, for instance, making the coatings flexible to avoid any damages during the compression of pellets, to reduce stability problems especially with brittle coatings and in some cases to withstand the mechanical agitation of gastrointestinal tract on thin coated dosage forms. Therefore, the effect of higher concentrations of plasticizer (TEC) on anti-tacking effect of the MMTs and talc was determined and the results are enlisted in Table 7. The tackiness of Kollicoat® SR 30 D and Eudragit® RS 30 D films was increased as a function of TEC concentration but the effect was more pronounced with Eudragit® RS 30 D films which could probably due to the sticky nature of the polymer.

Table 7 *Effect of plasticizer concentration on the tackiness of Kollicoat® SR 30 D and Eudragit® RS 30 D casted polymeric films.*

Polymer	Anti-tacking agent, %	Detachment force (N), M. V. ± S. D., n = 6			
		Lower plasticizer concentations		Higher plasticizer concentrations	
		40 °C /2h	40 °C - 75%RH /2h	40 °C /2h	40 °C - 75%RH /2h
Kollicoat® SR 30 D*	–	5.20 ± 0.27	8.32 ± 0.47	7.15 ± 0.48	10.54 ± 0.49
	Cloisite® Ca^{++}, 10	0.71 ± 0.10	1.21 ± 0.05	1.53 ± 0.26	2.28 ± 0.16
	Cloisite® Ca^{++}, 20	0.21 ± 0.06	0.40 ± 0.04	0.79 ± 0.06	1.21 ± 0.07
	Cloisite® Ca^{++}, 35	0.10 ± 0.01	0.20 ± 0.01	0.35 ± 0.05	0.63± 0.09
	Talc, 10	1.38 ± 0.01	2.07 ± 0.20	2.07 ± 0.20	2.29 ± 0.07
	Talc, 20	0.95 ± 0.05	1.05 ± 0.16	1.05 ± 0.16	1.92 ± 0.05
	Talc, 35	0.63 ± 0.04	0.79 ± 0.03	0.79 ± 0.03	1.05 ± 0.06
Eudragit® RS 30 D**	–	5.58 ± 0.22	8.93 ± 0.31	11.46 ± 0.70	15.69 ± 0.47
	Cloisite® Ca^{++}, 10	0.84 ± 0.06	1.42 ± 0.15	2.46 ± 0.32	3.98 ± 0.20
	Cloisite® Ca^{++}, 20	0.26 ± 0.03	0.91 ± 0.04	1.19 ± 0.16	1.96 ± 0.23
	Cloisite® Ca^{++}, 35	0.07 ± 0.01	0.23 ± 0.02	0.58 ± 0.05	1.09 ± 0.08
	Talc, 10	2.30 ± 0.15	3.52 ± 0.14	5.79 ± 0.10	8.31 ± 0.59
	Talc, 20	1.31 ± 0.09	2.36 ± 0.11	3.51 ± 0.07	5.46 ± 0.11
	Talc, 35	0.88 ± 0.08	1.53 ± 0.08	2.54 ± 0.18	4.03 ± 0.27

*Kollicoat® SR 30 D-TEC concentration increased from 10% to 20% w/w

**Eudragit® RS 30 D-TEC concentration increased from 20% to 30% w/w

The glass transition temperature (T_g) and minimum film formation temperature (MFT) decreases with an increase in TEC concentration and it correlates with the tackiness of the dried films (Wesseling et al., 1999). A correlation between hydrophilic plasticizers and the adhesion of polymeric film has also been reported (Felton and McGinity, 1997). However, the increased concentrations of TEC did not affect the anti-tacking properties of the MMTs and talc noticeably.

3.5.6 Effect on Tg of polymers

The DSC studies of the polymeric casted films were performed to see the effect of the MMTs and talc on the Tg of the polymers. The results showed that 10% addition of Cloisite® Ca^{++} induced a small increase in Tg of Kollicoat® SR 30 D which was gradually increased as a function of concentration whereas 35% addition of talc did not bring any change in Tg of Kollicoat® SR 30 D. In comparison, a pronounced increase in Tg of Eudragit® RS 30 D was observed by adding Cloisite® Ca^{++} For example, 10% addition of Cloisite® Ca^{++} increased the Tg of the Eudragit® RS 30 D from 20 to 25 ºC which was further raised to 33 ºC by increasing concentration to 35%. However, 35% addition of talc also increased the Tg of Eudragit® RS 30 D from. 20 to 25 ºC (Table 8). The increase in Tg could be related to multiple factors such as reduction of polymer free volume, interaction between the polar groups of the polymer and the MMTs, and physical stiffening resulting from the presence of the rigid antiplasticizer molecules adjascent to the polar group of the polymer (Jackson et al., 1967). The increase in Tg of the amylose by polymer-nanoclay interaction has been reported (Liua et al., 2011). The more increase in Tg of Eudragit® RS 30 D could be due to interaction of positively charged groups of Eudragit® RS 30 D with negatively charged ions on the surface of the MMTs.

Table 8 *Effect of the MMTs and talc on the Tg of Kollicoat® SR 30 D and Eudragit® RS 30 D.*

Polymer	Anti-tacking agent, %	Tg, °C
Kollicoat® SR 30 D*	–	23
	Cloisite® Ca^{++}, 10	24
	Cloisite® Ca^{++}, 20	25
	Cloisite® Ca^{++}, 35	27
	Talc, 35	24
Eudragit® RS 30 D**	–	20
	Cloisite® Ca^{++}, 10	25
	Cloisite® Ca^{++}, 20	28
	Cloisite® Ca^{++}, 35	33
	Talc, 35	25

*Kollicoat® SR 30 D plasticized with TEC 10% w/w

**Eudragit® RS 30 D plasticized with TEC 20% w/w

3.5.7 Coating processability of polymer dispersions

The coating processability of the different aqueous polymer dispersions with the addition of the MMTs was evaluated in order to check their practical advantage over talc. A good coating quality with high efficiency and short processing time has always been of a great importance for pharmaceutical industries. For this purpose, three different concentrations of the MMTs (10 %, 20% and 35%) were compared with 35% of talc. Cloisite® Ca^{++} was used with Kollicoat® SR 30 D and Eudragit® RS 30 D, while Nanofill® 116 was investigated with Eudragit® NE 30 D and Eudragit® RS 30 D.

The coating processability was analyzed on a small scale fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) equipped with a bottom spary (Wurster system) using 70 g of sugar pellets loaded with propranolol HCl 10% as cores. The performance of coating was rated into three zones of excellent, good and poor quality based on spray rate, processing time, flow of pellets, yield and nozzle clogging (Cervera et al., 2004).

The coating processability of Eudragit® NE 30 D is depicted in Figure 39A-D. The addition of Nanofill® 116 to Eudragit® NE 30 D formulations resulted in better coating processability in comparison with talc. A 10% addition of Nanofill® 116 provided a wider zone of excellent processability compared to 35% of talc (Figure 39A & D). However, by further increasing Nanofill® 116 concentrations to 20% and 35%, the zones of excellent and good processability were widened to a small extent. This can be explained becuase Eudragit® NE 30 D has a low glass transition temperature of - 8 ºC and to use a product temperature over 23 ºC is not possible.

The coating processability of Kollicoat® SR 30 D was improved effectively by the addition of different concentrations of Cloisite® Ca^{++} (Figure 40A-D). An addition of 10% Cloisite® Ca^{++} to coating formulation provided much broader zone of excellent processability in comparison with 35% of talc (Figure 40A & D). With the addition of 10% of Cloisite® Ca^{++}, a spray rate of up to 2.7 g/min was achieved without any signs of bed formation, nozzle clogging or sticking of pellets using a product temperature range of 28–36 ºC. Importantly, by further increasing the concentration of Cloisite® Ca^{++} to 20% and 35%, the zones of excellent and good processability were widened correspondingly. For example, a maximum spray rate of 3.3 g/min with good flowability of pellets could be achieved with 35% addition of Cloisite®

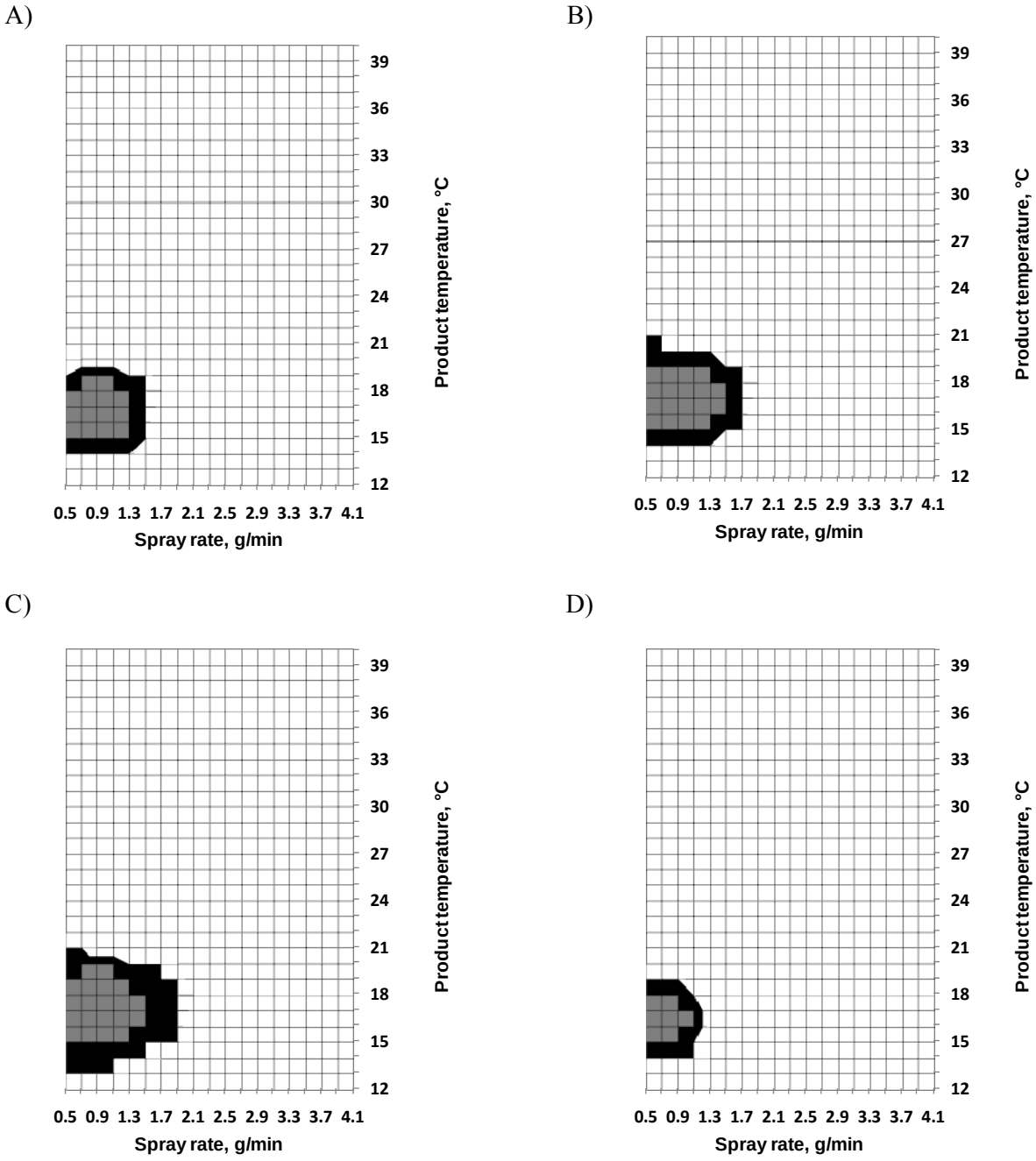


Figure 39: *Coating processability of Eudragit® NE 30 D formulations containing A) Nanofill® 116 10% w/w, B) Nanofill® 116 20% w/w, C) Nanofill® 116 35% w/w and D) Talc 35% w/w, (■) excellent, (■) good and (□) poor.*

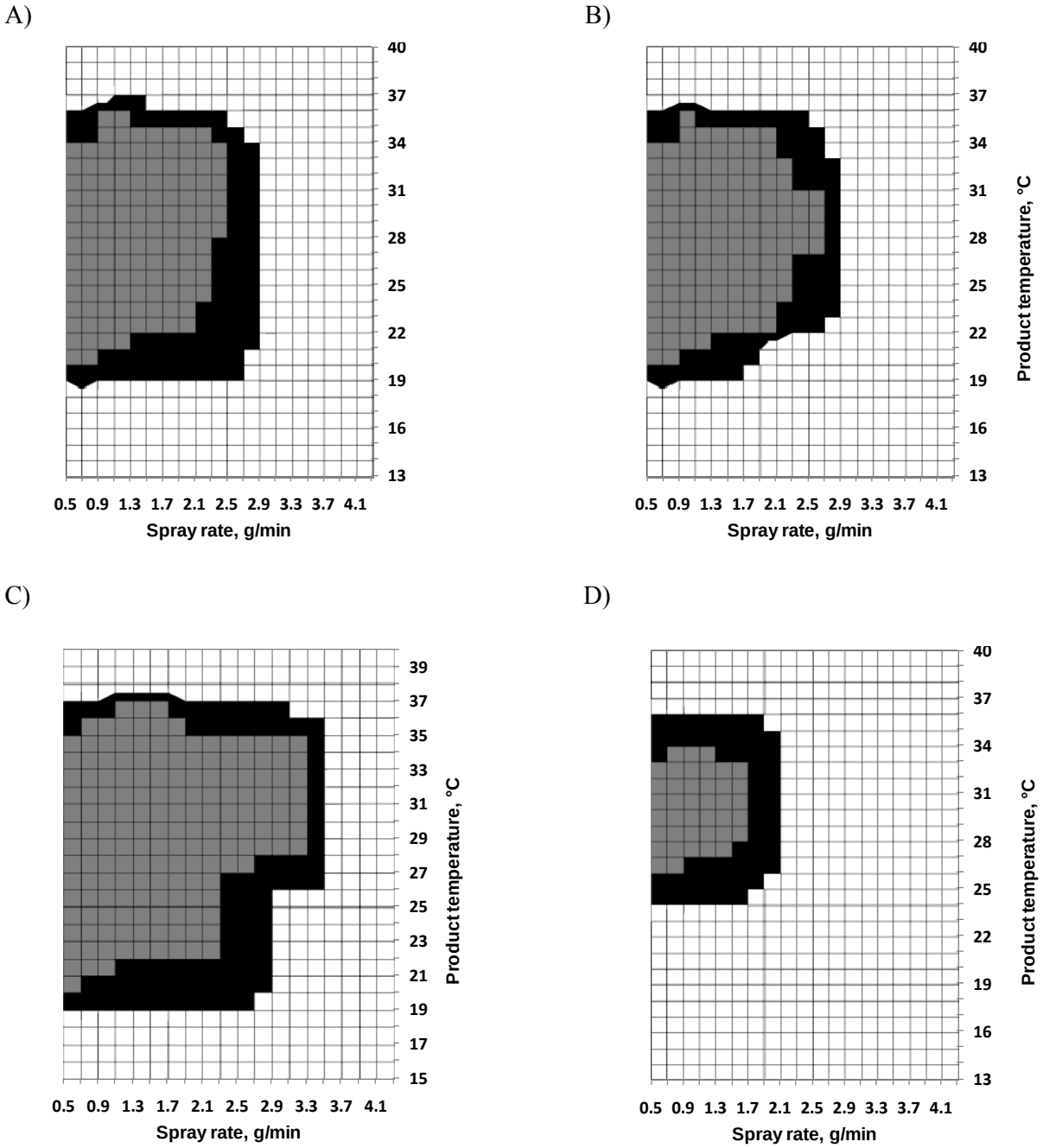


Figure 40: *Coating processability of Kollicoat® SR 30 D formulations containing A) Cloisite® Ca^{++} 10%, B) Cloisite® Ca^{++} 20%, C) Cloisite® Ca^{++} 35% and D) Talc 35%, (■) excellent, (■) good and (□) poor*

Ca^{++} which is almost twice as high as of 35% talc. Moreover, the number of pellet doubles after coating process was significantly lower with Cloisite® Ca^{++} coated formulations. In contrast, an addition of 35% talc could attain maximum 1.7 g/min of spray rate using a product temperature range of 28–32 ºC with a few times nozzle clogging.

The better coating processability of formulations with Nanofill® and Cloisite® Ca^{++}could be attributed to their smaller particle size and better wettability over talc that led to their stable uniform distribution in the coating formulations. However, the lower wettability of talc particles due to its high hydrophobicity could be the reason for unstable non-uniform distribution which resulted in low spray rate and nozzle clogging (Lin et al., 1994).

Eudragit® RS 30 D, a charged cationic polymer, is widely used for the controlled release coatings. The tendency of sticking during coating process and upon curing has been widely reported with this polymer (Maejima et al., 2000; Pearnchob and Bodmeier, 2003).

The coating processability of Eudragit® RS 30 D formulations using different concentrations of Cloisite® Ca^{++} (10%, 20% and 35%) and talc (35%) is shown in Figure 41A-D. The coating processability of Eudragit® RS 30 D formulations was improved to a large extent by the addition of Cloisite® Ca^{++} than talc. For example, a formulation with 10% addition of Cloisite® Ca^{++} achieved a maximum spray rate of 3.1 g/min with a higher product temperature range in comparison to 2.1 g/min of talc 35% with a lower product temperature range (Figure 41A & D). Moreover, the spray rate was further increased to 3.5 g/min and 3.9 g/min by increasing the concentration of Cloisite® Ca^{++} to 20% and 35%, respectively (Figure 41B & C). The improved coating processability of Eudragit® RS 30 D with the addition of Cloisite® Ca^{++}could also be linked to its stable and uniform distribution in the coating formulations. The extent of electrostatic interaction during the coating process was decreased with Cloisite® Ca^{++} formulations which might be due to the neutralization of positively charged $-NH_3$ groups of Eudragit® RS 30 D by negatively charged ion on the surface of Cloisite® Ca^{++}. The coating processability of Eudragit® RS 30 D using Nanofill® 116 was also effectively improved (data not shown).

The uniform distribution of the MMTs was confirmed from the SEM images. Figure 42A-B showed the SEM micrographs of cross section of the Eudragit® RS 30 D coated pellets with Cloisite® Ca^{++} and Nanofill® 116 and talc distribution in the coatings. The order of distribution was ranked as Nanofill® 116 > Cloisite® Ca^{++} > talc.

Another advantage of Cloisite® Ca^{++} addition to the coating formulation was the pale yellow appearance of the final coated pellets which could be beneficial to enhance the patient compliance. The quality of product and coating process could also be reflected by the colour of the product since it is an easily observable feature of the drug product (Chan et al., 2001).

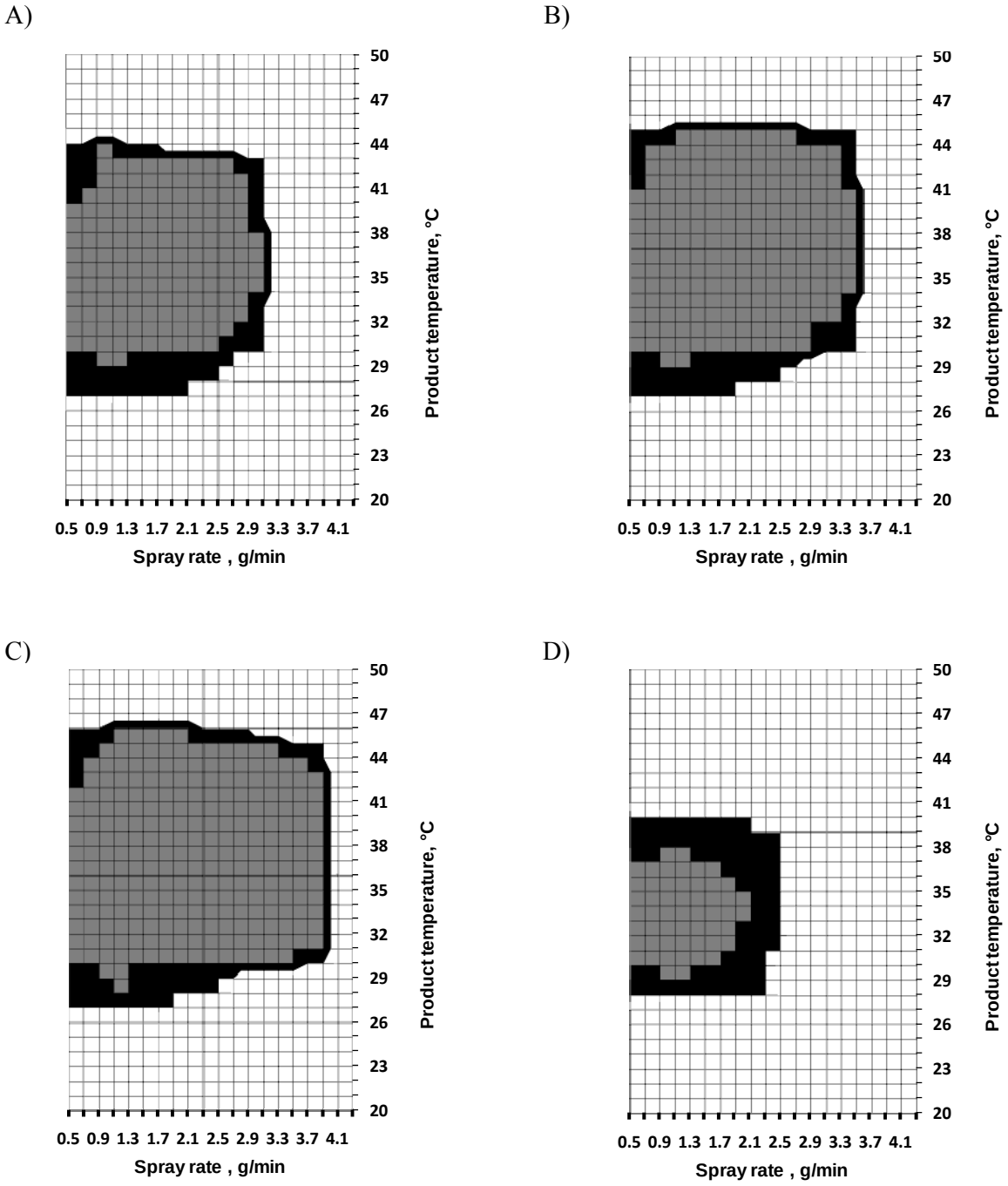


Figure 41: *Coating processability of Eudragit® RS 30 D formulations containing A) Cloisite Ca^{++} 10%, B) Cloisite Ca^{++} 20%, C) Cloisite Ca^{++} 35% and D) Talc 35%, (■) excellent, (■) good and (□) poor.*

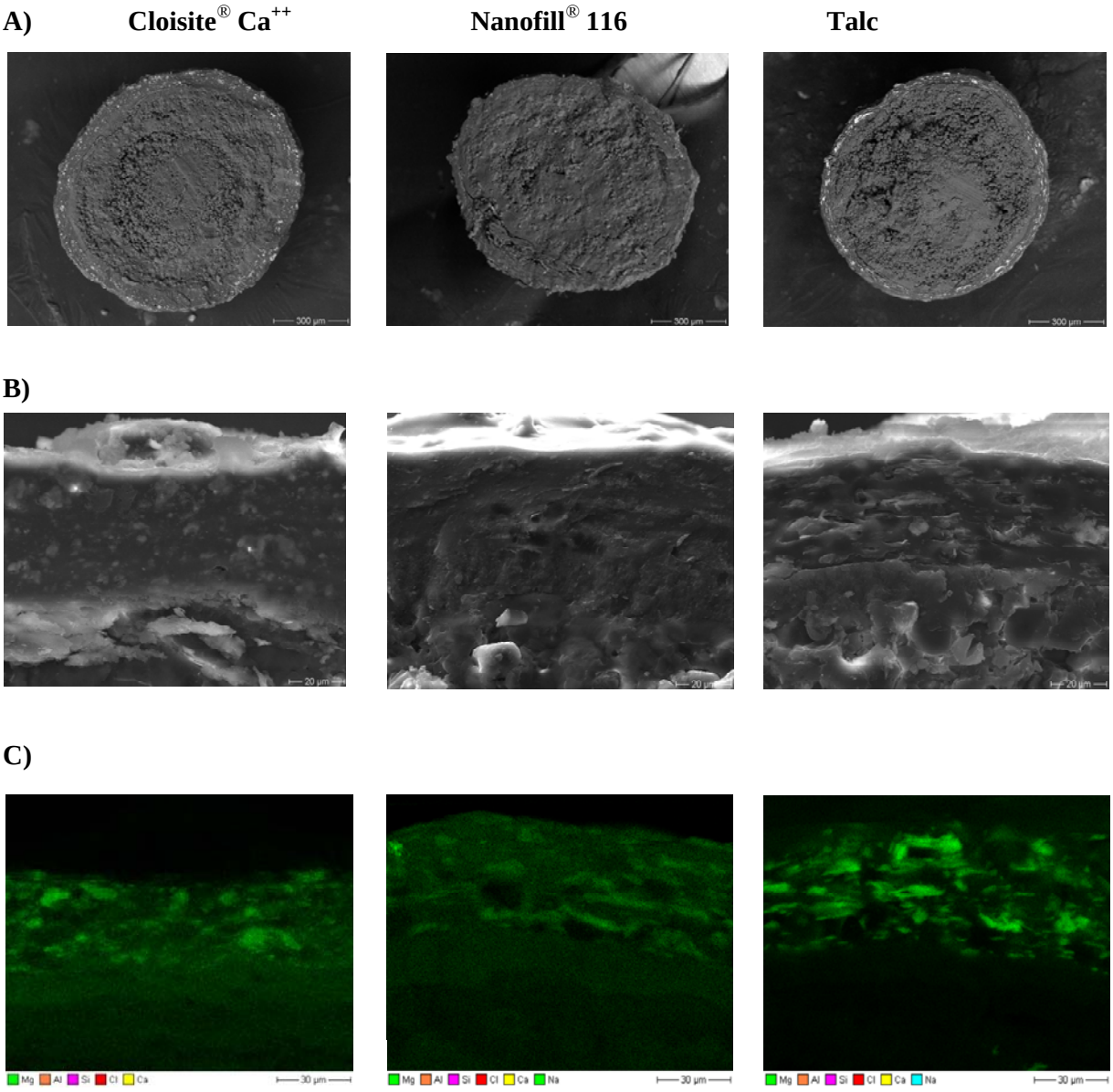


Figure 42: *SEM images of the cross section of pellets showing the distribution of the MMTs and talc (35% w/w) in Eudragit® RS 30 D coatings, TEC 20% w/w, coating level 20% w/w, A) cross-section of the whole pellets (lower magnification,) B) cross-section of one segment (higher magnification) and C) mapping of Mg.*

3.5.8 Tackiness of the coated pellets during curing

To evaluate the anti-tacking performance during curing, the coated pellets using different concentrations of the MMTs and talc were stored at different curing conditions without adding any external anti-tacking agent. The tackiness was characterized by % agglomeration (Table 9).

The coated pellets without adding anti-tacking agent in the coating formulations were irreversibly agglomerated during curing. In comparison, the Kollicoat® SR 30 D coated pellets with 10% addition of Cloisite® Ca^{++} did not stick at elevated temperature but showed 60% of agglomeration at elevated temperature/humidity which was reduced to 30% and 4% by increasing concentration to 20% and 35%, respectively. In contrary, the pellets with 35% addition of talc in the coating were completely agglomerated at elevated temperatures and humidity.

Table 9 *Effect of the MMTs and talc on the tackiness of coated pellets during curing at different temperature and humidity.*

Polymer	Anti-tacking agent, %	% agglomeration after 24 h				
		Curing / Storage				200 ml, pH-2
		40 °C	40 °C - 75%RH	60 °C	60 °C - 75%RH	37 ± 0.5 °C
Kollicoat® SR 30 D*	–	99.8	99.8	99.9	99.9	99.9
	Cloisite® Ca^{++}, 10	2.5	60.1	4.2	64.4	60.1
	Cloisite® Ca^{++}, 20	0.15	22.6	1.4	24.6	29.6
	Cloisite® Ca^{++}, 35	0.07	1.7	0.4	4.1	2.2
	Talc, 35	0.7	99.3	7.1	99.3	88.1
Eudragit® RS 30 D**	–	97.6	98.8	97.5	98.3	49.5
	Cloisite® Ca^{++}, 10	8.6	1.44	3.5	2.56	2.44
	Cloisite® Ca^{++}, 20	6.5	0.98	2.6	0.51	1.33
	Cloisite® Ca^{++}, 35	0.86	0.32	0.8	1.38	0.32
	Talc, 35	18.5	8.2	2.8	89.9	2.8
Eudragit® NE 30 D	–	99.8	99.9	99.9	99.9	99.9
	Nanofill® 116, 10	1.17	13.8	0.99	24.2	24.9
	Nanofill® 116, 20	0.98	6.8	0.6	7.9	5.55
	Nanofill® 116, 35	0.67	3.4	0.52	4.2	4.52
	Talc, 35	0.67	24.1	0.67	90.5	90.5

*Kollicoat® SR 30 D plasticized with 10% TEC

**Eudragit® RS 30 D plasticized with 20% TEC

The Eudragit® RS 30 D pellets with Cloisite® Ca^{++} in the coatings did not stick irrespective of concentration and curing conditions. However, the pellets with 35% of talc in the coating did

not agglomerate under low temperature and humidity conditions but had a 89 % of agglomeration at higher temperature and humidity. The Eudragit® NE 30 D coated pellets with 10% of and 20% of Nanofill® 116 showed about 24% and 7.9% of agglomeration, respectively, under elevated temperatures and humidities which was limited to 4.5% with 35% addition of Nanofill® 116. In comparison, the pellets with 35% talc in the coating did not stick at elevated temperatures but had a 90% agglomeration at elevated temperatures and humidities.

The difference in the agglomeration tendency of various polymers at different elevated temperatures and humidities could be related to their variable sensitivity towards the exposed conditions. A clear correlation was found between the tackiness of the films, coating processability and sticking of the pellets upon curing.

3.5.9 Mechanical properties of polymeric films

The type and the amount of the additives in the film can significantly affect the mechanical properties which in turn can have a big influence on the drug release mechanism from the coated drug product. Hence, the effect of different conentrations of the MMTs and talc on the mechanical properties of casted films in a dry state was evaluated (Table 10).

The Cloisite® Ca^{++} addition decreased the flexibility of the Kollicoat® SR 30 D films more effectively than talc while the puncture strength was less affected which is an indicative of better mechanical strength of films. For instance, a film with of 10% of Cloisite® Ca^{++} had less % elongation and more puncture strength when compared with 35% addition of talc. In contrast, the addition of Cloisite® Ca^{++} to Eudragit® RS 30 D films decreased both flexibility and puncture strength significantly more than talc which is suggestive of hard and brittle films. This could be due to interaction of positively charged $–NH_3$ groups of the polymer with negatively charged ions of the Cloisite® Ca^{++}. The decrease in tensile strength and elongation of poly-L-lactide composites in presence of Cloisite Ca^{++} has been reported (Rhim et al., 2009).

However, the interesting results were found with Eudragit® NE 30 D films. The addition of Nanofill® 116 reduced the flexibility of the films higher than talc. However, the puncture strength was increased as a function of Nanofill® 116 concentration which was even more than with the pure films. The increase in puncture strength occured by the stronger interfacial interaction through hydrogen or ionic bonds between polymer and intercalated layered silicate

with vast interfacial area (Alamsi et al., 2010). A similar behaviour of increase in puncture strength with increase in the clay content have been observed in various biopolymer-based nanocomposite films such as starch (Alamsi et al., 2010; Avella et al., 2005; Cyras et al., 2008; Chrissafis et al., 2007; Huang et al., 2006; Jong-Whan Rhim, 2009), chitosan (Casariego et al., 2009), and soy protein (Kumar et al., 2010b).

Table 10 *Effect of the MMTs and talc on the mechanical properties of different polymeric casted films in dry state (thickness = 33 –350 µm).*

Polymer	Anti-tacking agent, %	Mechanical properties, n = 9	
		Puncture Strength, N/mm^2	Elongation, %
		M. V. ± S. D.	M. V. ± S. D.
Kollicoat® SR 30 D*	–	17.7 ± 0.9	176.4 ± 1.9
	Cloisite® Ca^{++}, 10	13.4 ± 0.9	92.5 ± 1.4
	Cloisite® Ca^{++}, 20	13.1 ± 1.2	73.8 ± 0.1
	Cloisite® Ca^{++}, 35	12.6 ± 0.8	37.7 ± 0.1
	Talc, 10	12.7 ± 0.2	132.5 ± 0.8
	Talc, 20	11.9 ± 1.2	122.0 ± 0.1
	Talc, 35	11.6 ± 0.6	114.2 ± 0.2
Eudragit® RS 30 D**	–	10.7 ± 0.7	73.7 ± 0.2
	Cloisite® Ca^{++}, 10	3.9 ± 0.1	37.5 ± 0.2
	Cloisite® Ca^{++}, 20	0.7 ± 0.1	14.7 ± 0.2
	Cloisite® Ca^{++}, 35	0.6 ± 0.1	10.6 ± 0.1
	Talc, 10	9.7 ± 0.8	45.5 ± 0.2
	Talc, 20	8.2 ± 0.2	40.2 ± 0.4
	Talc, 35	6.7 ± 0.8	37.7 ± 0.1
Eudragit® NE 30 D	–	12.6 ± 0.6	431.1 ± 0.7
	Nanofill® 116, 10	15.3 ± 0.4	157.7 ± 0.2
	Nanofill® 116, 20	25.3 ± 0.5	73.9 ± 0.4
	Nanofill® 116, 35	26.2 ± 0.7	63.9 ± 0.9
	Talc, 10	8.4 ± 0.6	338.2 ± 0.5
	Talc, 20	7.9 ± 0.3	276.0 ± 0.1
	Talc, 35	7.2 ± 0.4	246.2 ± 0.1

*Kollicoat® SR 30 D plasticized with TEC 10%

**Eudragit® RS 30 D plasticized with TEC 20%

It can be concluded that the MMTs decreased the flexibility of polymers higher than talc. However, the MMTs reduced the puncture strength of the charged polymers (Eudragit® RS 30 D) more and less of the neutral polymers (Kollicoat® SR 30D, Eudragit® NE 30 D) when compared with talc. The pronounced reduction in the puncture strength of Eudragit® RS 30 D films could also be due to increase in Tg (Table 8).

3.5.10 Drug release from coated pellets

The drug release from the coated pellets was performed to compare the effect of the MMTs and talc on release rates. In addition, the pellets were cured to elucidate the effect of curing. Some of the drug release results are shown in Figure 43A-E comparing 35% addition of both MMTs and talc to coating formulations.

The drug release from Kollicoat® SR 30 D coated pellets shows that Cloisite® Ca^{++} addition did not bring unwanted change in release rates before and after curing (Figure 43A & B). Positively, the curing effect was eliminated at elevated temperature which could be due to reduction in the flexibility of the coatings (shown earlier). The elimination of curing effect of Kollicoat® SR 30 D coated pellets has been shown by decreasing the flexibility of coatings (Ahmed et al., 2008). Moreover, the 20% addition of Cloisite® Ca^{++} to coatings almost had the same results (data not shown).

In comparison with talc addition, the slightly faster drug release from Eudragit® RS 30 D coated pellets was observed with Cloisite® Ca^{++} (Figure 43C & D). This could be due to pronounced decrease in the flexibility of coatings by Cloisite® Ca^{++}. In addition, 10% and 20% addition of Cloisite® Ca^{++} almost had the same results (data not shown). The drug release was remained unaffected after curing from pellets having Cloisite® Ca^{++} or talc in the coatings.

Nanofill® 116 addition as well did not show unexpected effect on the drug release from Eudragit® NE 30 D coated pellets in comparison with talc (Figure 43E & F). However, likewise Kollicoat® SR 30 D, the curing effect was minimized due to the decrease in flexibility of the coatings.

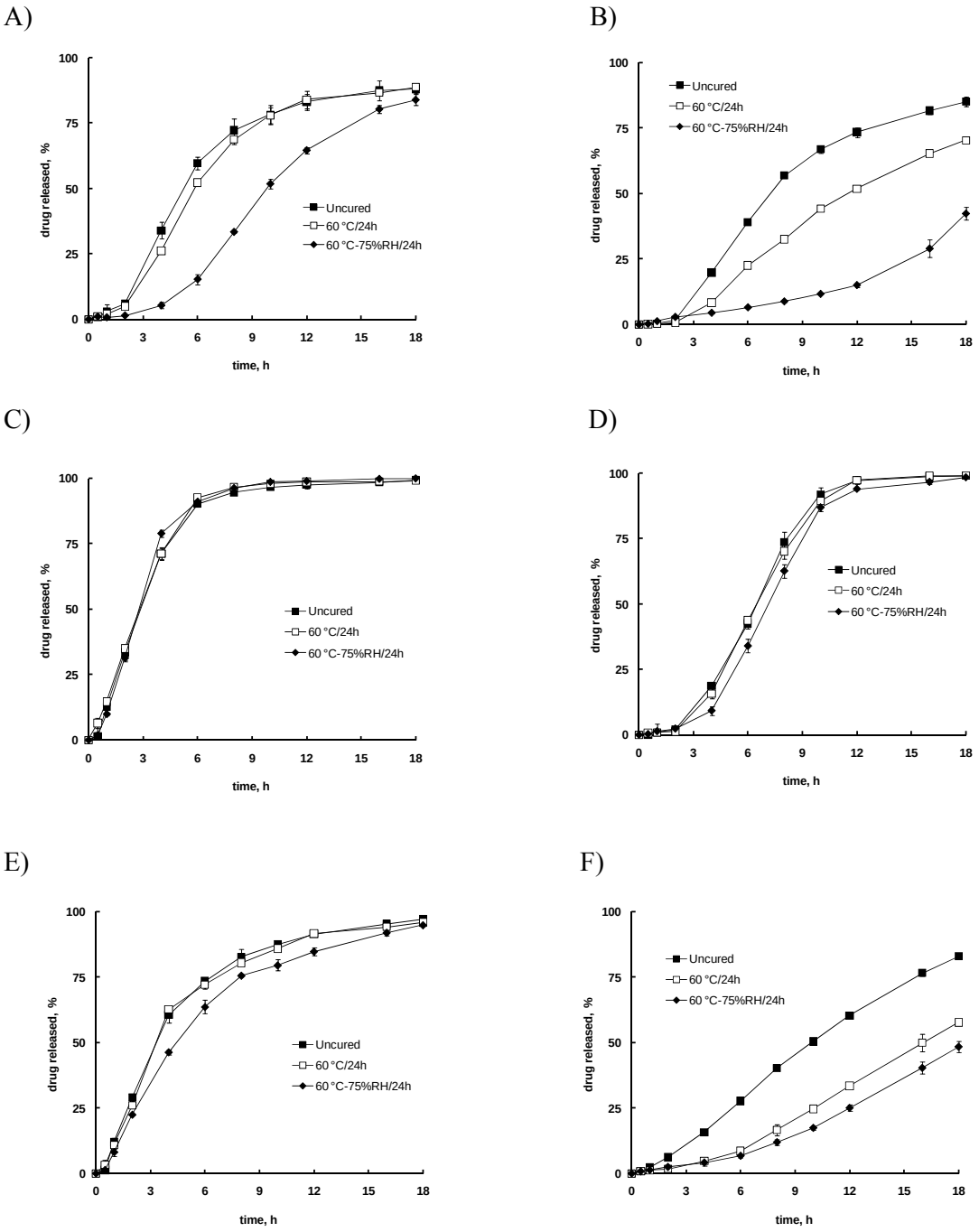


Figure 43: *Propranolol HCl release from pellets coated with different polymers using 35% w/w of the MMTs and talc, coating level 20% w/w, A) Kollicoat® RS 30 D-Cloisite® Ca^{++}, B) Kollicoat® RS 30 D-talc, C) Eudragit® RS 30 D-Cloisite® Ca^{++}, D) Eudragit® RS 30 D-talc, E) Eudragit® NE 30 D-Nanofill® 116 and D) Eudragit® NE 30 D-talc.*

3.5.11 MMTs as external anti-tacking agent

The performance of the MMTs as external anti-tacking agent was evaluated. In this regard, 1% addition of Cloisite® Ca^{++}, talc and Aerosil® to Eudragit® RS 30 D coated pellets were compared during curing at 60 °C. The agglomerated pellets after curing were separated by applying mechanical force which could damage the coating depending on the extent of sticking. The difference in damage was compared from release results of the uncured and cured pellets and thus related with anti-tacking effect.

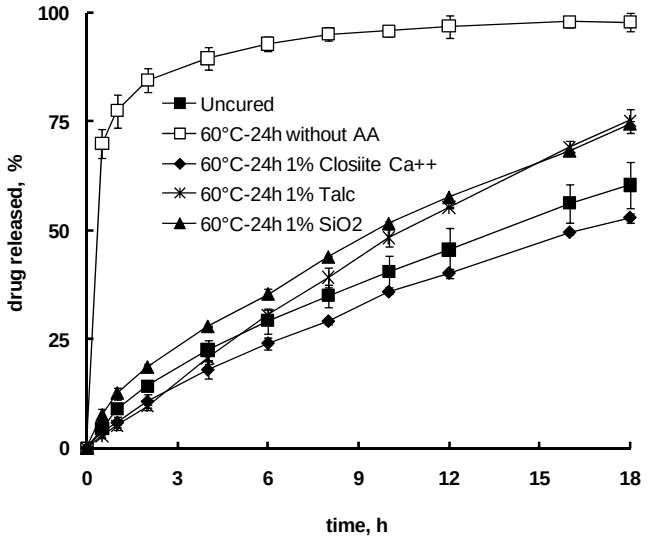


Figure 44: *Theophylline release Eudragit® RS 30 D coated pellets showing the anti-tacking effect of different anti-tacking agents during curing (TEC 20% w/w), coating level 20 % w/w.*

The pellets cured without adding anti-tacking agent were irreversibly sticked together and a strong mechanical force was applied to separate them. In comparison, the pellets cured using 1% of talc, Aerosil® and Cloisite® Ca^{++} showed partial reversible sticking of various extents. The pellets were separated by applying a mild mechanical force.

Theophylline release from the uncured pellets followed almost zero order patterns due to its low solubility. However, the pellets cured without anti-tacking agent revealed a very fast release profile with 80% release in 1 h (Figure 44). This was due to the breaking of coating during separation of the pellets, which was seen in macroscopic pictures after the release

(Figure 45B). In contrast, the pellets cured using 1% of talc and aerosil showed a small increase in release profile which is an indication of tiny cracks formed in coatings while separating the pellets (Figure 45C & D). However, the drug release from pellets cured using Cloisite® Ca^{++} 1% exhibited a small decrease and no visible cracks were observed in coatings from the macroscopic picture after release. This indicates that pellets cured with Cloisite® Ca^{++} had less sticking and a gentle mechanical force was enough to separate them. As a result, the coating was not damaged and the drug release decreased due to better film formation upon curing.

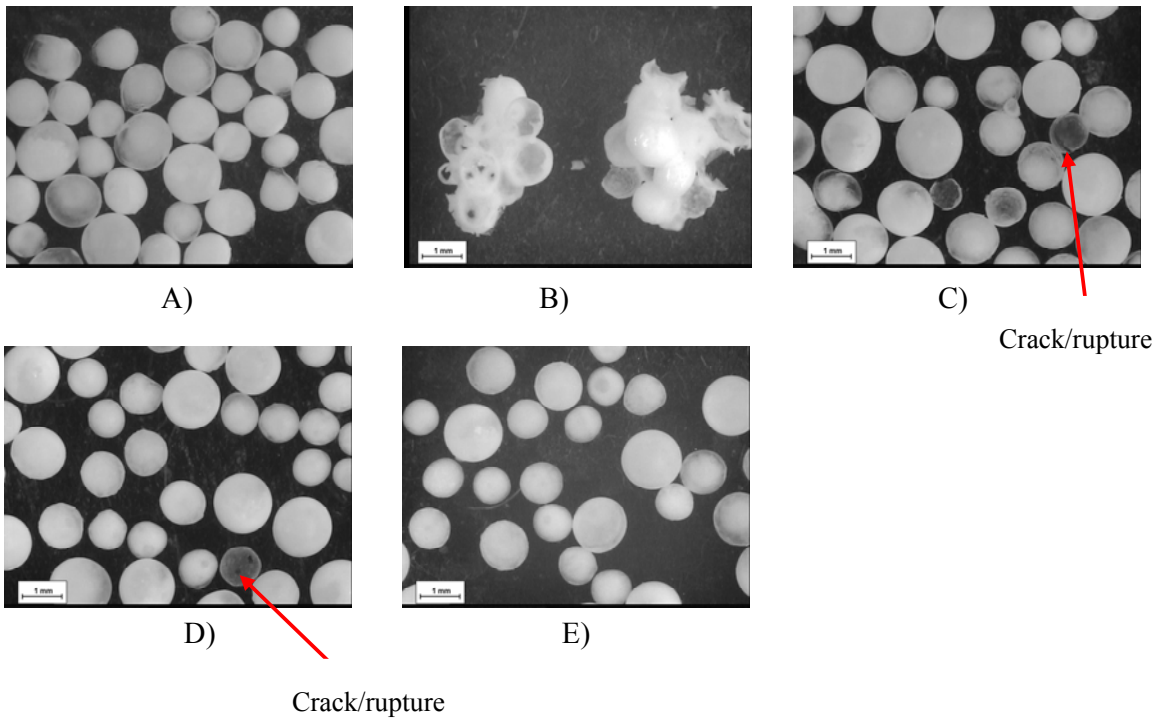


***Figure 45**: Macroscopic pictures of the Eudragit® RS 30 D coated pellets after release (TEC 20% w/w), coating level 20% w/w, A) uncured, B) 60 °C/24 h cured without anti-tacking agent, C) 60 °C/24 h cured using 1% w/w of aerosil, D) 60 °C/24 h cured in presence of 1% w/w of talc and E) 60 °C/24 h cured in presence of 1% w/w of Cloisite® Ca^{++}.*

3.5.12 Conclusions

Two MMTs, Cloisite® Ca^{++} and Nanofill® 116, were found to be the promising anti-tacking agents for aqueous polymer coatings. The MMTs in lower concentrations reduced the tackiness of casted polymeric films more effectively comparing with a higher concentration of talc. Practically, the MMTs improved the coating processability of different aqueous polymer dispersions to a large extent. In addition, the MMTs exhibited better anti-tacking properties during curing of coated pellets. The MMTs affected the mechanical properties varyingly depending on the nature of polymer (charged vs. neutral) but did not bring any unexpected change on the drug release from coated pellets before and after curing. Positively, in some case, the elimination of curing effect was observed due to decrease in flexibility of the coatings.

4 Summary

Curing mechanism of flexible aqueous polymer coatings

The main objective of this part of work was to investigate and understand the curing mechanism of Kollicoat® SR 30 D coated pellets. In this regard, effect of starter cores, drug solubility, drug loading, adhesion of coating to core and flexibility of coating on curing was evaluated in detail.

A strong curing effect (change in drug release) was observed with propranolol HCl loaded sugar pellets coated with Kollicoat® SR 30 D within a drug loading range of 10%-20% at elevated temperature (60 °C) and elevated temperature/humidity (60 °C-75%RH). The curing effect was more pronounced at 60 °C-75%RH. Importantly, a complete film formation from Kollicoat® SR 30 D coatings was confirmed by unchanged properties (water uptake, weight loss, mechanical properties in wet state and permeability) of free films after curing. Thus, the observed curing effect could not be explained by well-known hydroplasticization or further coalescence of polymeric particles. However, a significant difference between water uptake and swelling of uncured and cured pellets was observed during dissolution. The curing effect was explained by a completely different swelling behaviour of uncured and pellets cured at 60 °C-75%RH observed from video monitoring during dissolution. This is described in the following two scenarios:

First scenario (observed for uncured pellets): Upon medium penetration into pellets, coating detached from the drug layer only locally at "weak point". Dissolution of the sugar core resulted in a rapid arising of osmotic pressure directed towards the coating only at that "weak point" (localized swelling). Because of high flexibility, coating elongated at this point extensively (approx. 300% as estimated from the pictures) until rupturing by exceeding the elongation limit of the coating. After rupturing flexible coating collapsed, therefore pellets after drug release appeared moderately swollen. Drug release occurred through visible macro cracks formed after rupturing of coatings and followed a typical sigmoidal release pattern.

Second scenario (observed for pellets cured at 60 °C-75 %RH): Swelling of the pellets occurred uniformly along the drug layer/coating interface due to decrease in the adhesive force of coatings upon curing. In this case, osmotic pressure was directed towards the whole inner surface of the coating resulting in a maximal extension of up to 150 % without visible rupturing (extensive uniform swelling). Drug release occurred slowly after a certain lag time necessary for the thinning of the coating and the formation of non-visible micro pores. Coating extended until equilibrium of inner/outer liquids and did not collapse. Therefore, pellets appeared extremely swollen (5 times) after release.

In case of pellets cured at 60 °C, some of the pellets exhibited a localized swelling while the others followed a low uniform, thus had a release profile faster than those cured at 60 °C-75%RH but slower than uncured pellets.

Importantly, the presence of a curing effect was only observed when uncured and cured pellets followed 1st and 2nd scenario (completely different swelling behaviour), respectively. No curing effect was observed either in low (2%-5%) or in high (30%-50%) loadings of propranolol HCl. In these cases, the video monitoring revealed that both uncured and cured pellets followed 2nd scenario during dissolution. This could be explained as follow: 2%-5% drug loading formed a thin layer which was rapidly dissolved upon medium penetration whereas the thicker 30%-50% layer delayed the penetration of medium. As a result, medium reached to the cores equally from all sides. Hence, uncured and cured pellets followed the 2nd scenario (uniform swelling) and eventually showed no curing effect.

The curing effect of Kollicoat® SR 30 D coated pellets was found to be strongly dependent on drug solubility. Likewise propranolol HCl, a strong curing effect was seen by following the above mentioned mechanism with a poorly soluble drug (carbamazepine) and a drug with intermediate solubility (theophylline) within a drug loading range of 10%-20%, but not for 2%-5% and for 30%-50% drug loadings. In comparison, freely soluble drugs (tramadol HCl and metoprolol tartrate) did not show curing effect irrespective of drug loading. Clearly, uncured and cured pellets of these drugs exhibited an extensive uniform swelling by following the 2nd scenario which could be due to rapid dissolving of drug layer caused by their higher solubilities.

Osmotically inactive MCC cores did not show curing effect irrespective of drug solubility and drug loading. Like the sugar pellets, water uptake and swelling of MCC coated pellets did not change significantly upon curing.

The curing effect of Kollicoat® SR 30 D coated pellets was successfully eliminated by adopting different approaches in accordance with the identified reasons i) a seal coating of sugar cores to suppress their osmotic activity ii) an approach to hinder a decrease in adhesion of coating upon curing by increasing drug to binder ratio (3:1) or by applying a 10% sub coating of HPMC iii) incorporating a higher amount of talc (100%) to make coatings brittle or using small sized hydrophilic titanium dioxide and iv) making the coatings porous by adding pore-formers.

The Kollicoat® SR 30 D coated pellets were well storage stable under stress conditions for 12 months.

In addition, Eudragit® NE 30 D coated sugar pellets showed a strong curing effect by following similar mechanism like Kollicoat® SR 30 D pellets.

Montmorillonites as anti-tacking agents

The objective of this part of work was to investigate and evaluate the anti-tacking effect of two naturally occurring montmorillonites (MMTs), marketed as Cloisite® Ca^{++} and Nanofill® 116, in comparison with talc, a conventionally used anti-tacking agent, using different aqueous polymer dispersions. In this regard, stability of mixed dispersions, tackiness and mechanical properties of casted films and coating processability of different polymer dispersions was determined using different concentrations of MMTs (10%, 20% and 35%) in comparison with 35 % of talc.

Eudragit® NE/NM 30 D were not stable upon Cloisite® Ca^{++} addition whereas Kollicoat® SR 30 D was not stable upon Nanofill® 116 addition. In comparison, Eudragit® RL/RS 30 D were well stable with both MMTs. The exact reason for the instability of the dispersions was beyond the scope of the present study. The stable dispersions were used for the further studies.

The MMTs reduced the tackiness of casted polymeric films significantly more than talc. Clearly, an addition of 10% MMTs to the polymer dispersions resulted in a lower detachment force to separate tacky films than with 35% of talc. This was explained by a more homogenous distribution of MMTs in polymer films due to their smaller particle size and higher hydrophilicity. As a result, polymeric particles were covered better by MMTs and tackiness was effectively decreased. In contrary, talc was not homogenously distributed due to its higher hydrophobicity and a few talc free patches in the films were observed which

resulted in less effective reduction of tackiness. An increase in plasticizer concentration did not affect significantly anti-tacking properties of the MMTs.

The coating processability (spray rate and yield) of different aqueous polymer dispersions was effectively improved with lower concentrations of MMTs than with a higher concentration of talc. As an example, Eudragit® RS 30 D formulations with 10% addition of Cloisite® Ca^{++} could achieve a maximum spray rate of 3.1 g/min in comparison to 2.1 g/min with 35% addition of talc, which was increased to 3.5 g/min by further increasing the concentration to 20%. Moreover, broader ranges of product temperatures could be used during coatings with MMTs containing formulations in comparison with talc. This was attributed to an increase in the polymer Tg by addition of MMTs confirmed by DSC studies. In addition, MMTs reduced the tackiness of coated pellets significantly better than talc during curing.

Furthermore, MMTs decreased the flexibility of polymers more than talc. However, reduction in puncture strength of charged polymers (Eudragit® RS/RL 30 D) by MMTs was more pronounced than for neutral polymers (Kollicoat® SR 30D and Eudragit® NE/NM 30 D) in comparison with talc. This could be due to the interaction between the positively charged groups of Eudragit® RS/RL 30 D and the negatively charged groups on the surface of MMTs. Clearly, MMTs addition to the coating formulations did not bring unwanted changes in drug release from coated pellets. In some cases, the elimination of curing effect could be linked to decrease in the flexibility of coatings.

5 Zusammenfassung

Curing Mechanismus von flexiblen wässrigen Überzügen

Das Hauptziel dieses Teils der Arbeit war den Curing-Mechanismus von mit Kollicoat® SR 30 D überzogenen Pellets zu untersuchen und zu verstehen. Im Hinblick darauf wurde im Detail der Effekt des Starterkerns, der Wirkstofflöslichkeit, Wirkstoffbeladung, Adhäsion des Überzuges an den Kern und die Flexibilität des Überzugs auf das Curing bewertet.

Die Wirkstofffreisetzung von Kollicoat® SR 30 D überzogenen mit Propranolol HCl beschichteten Zuckerkernen wurde durch das Curing innerhalb einer Wirkstoffbeladung von 10-20% gesenkt und dieser Effekt war am stärksten ausgeprägt bei 60°C-75% RH (erhöhte Temperatur/ Feuchtigkeit). Eine komplette Filmausbildung des Kollicoat® SR 30 D Überzugs konnte anhand von unveränderten Eigenschaften des freien Filmes nach dem Curing (Wasseraufnahmefähigkeit, Gewichtsverlust, mechanische Eigenschaften im nassen Zustand und Permeabilität) bestätigt werden. Folglich konnte der beobachtete Curing-Effekt nicht erklärt werden mit dem bereits bekannten hydroplasticization oder einer weitergehenden Koaleszenz der Polymerpartikel. Es konnte allerdings ein signifikanter Unterschied zwischen der Wasseraufnahmefähigkeit und dem Schwellen von nicht nachbehandelten und nachbehandelten Pellets beobachtet werden. Der signifikante Unterschied in der Freisetzungsrate (Curing-Effekt) von nicht nachbehandelten und nachbehandelten Pellets wurde basierend auf Videoaufnahmen während der Auflösung anhand der zwei folgenden Szenarien erklärt:

Erstes Szenario (beobachtet bei nicht nachbehandelten Pellets): Bei der Penetration des Mediums in die Pellets löste sich der Überzug von der Wirkstoffschicht nur stellenweise an „Schwachstellen“ ab. Die Auflösung des Zuckerkernes resultierte in einer schnellen Erhöhung des osmotischen Druckes gegen den Überzug nur an den „Schwachstellen“ (lokalisiertes

Schwellen). Aufgrund der hohen Flexibilität dehnte sich der Überzug an diesen Stellen stark (annähernd 300% wie aus den Bildern geschlossen werden kann) bis zum Reißen durch Überschreiten des Dehnungslimits des Überzugs. Nach dem Reißen kollabiert der flexible Überzug, daher erscheinen die Pellets nach der Wirkstofffreisetzung moderate geschwollen. Die Wirkstofffreisetzung erfolgte nur durch die sichtbaren Makrorisse, gebildet durch das Reißen des Überzugs, und folgte einem typischen sigmoidalen Freisetzungsprofil.

Zweites Szenario (beobachtet für nachbehandelte Pellets bei 60°C-75% RH): Das Schwellen der Pellets erfolgte gleichmäßig entlang der Wirkstoffschicht/Überzugs-Grenzfläche aufgrund einer Erniedrigung der adhäsiven Kräfte des Überzugs durch das Curing. In diesem Fall war der osmotische Druck gegen die gesamte innere Oberfläche des Überzugs gerichtet und resultierte in einer maximalen Ausdehnung von bis zu 150% ohne sichtbare Risse (starkes, einheitliches Schwellen). Die Wirkstofffreisetzung erfolgte nach einer gewissen Verzögerungszeit, die nötig war zum Verdünnen des Überzugs und der Ausbildung nicht sichtbarer Mikroporen. Der Überzug dehnte sich aus bis zu einem Gleichgewicht zwischen innerer/äußerer Flüssigkeit und kollabierte nicht. Daher erschienen die Pellets nach der Freisetzung extrem geschwollen (5 mal).

Im Falle der bei 60°C nachbehandelten Pellets wiesen einige lokalisiertes Schwellen auf, während die anderen ein geringes einheitliches aufwiesen. Demzufolge hatten sie ein schnelleres Freisetzungsprofil als diejenigen, die bei 60°C-75% RH nachbehandelt wurden aber langsamer als die nicht nachbehandelten Pellets.

Wichtig anzumerken ist, dass der Curing-Effekt nur auftrat, wenn die nicht nachbehandelten und nachbehandelten Pellets dem ersten und zweiten Szenario folgten (komplett unterschiedliches Schwellungsverhalten). Kein Curing-Effekt war zu beobachten bei niedriger (2-5%) oder hoher (30-50%) Beladung mit Propranolol HCl. In diesen Fällen zeigten die Videoaufnahmen, dass beide , nicht nachbehandelte und nachbehandelte Pellets, dem zweiten Szenario während der Auflösung folgten. Das könnte wie folgt erklärt werden: die Wirkstoffbeladung von 2-5% bildete nur eine dünne Schicht, die sich schnell auflöste bei der Mediumpenetration, wohingegen die dickere 30-50% Schicht die Penetration des Medium

verlangsamte. Infolgedessen erreichte das Medium die Kerne gleichmäßig von allen Seiten. Daher folgten nicht nachbehandelte und nachbehandelte Pellets dem zweiten Szenario (gleichmäßiges Schwellen) und zeigten eventuell keinen Curing-Effekt.

Der Curing-Effekt von Kollicoat® SR 30 D überzogenen Pellets zeigte sich als stark abhängig von der Wirkstofflöslichkeit. Gleichermaßen wie bei Propranolol HCl, konnte mit einem schwerlöslichen Wirkstoff (Carbamazepin) und einem Wirkstoff mittlerer Löslichkeit (Theophyllin) innerhalb einer Wirkstoffbeladung von 10-20%, aber nicht für 2-5% und 30-50%, ein starker Curing-Effekt, dem oben genannten Mechanismus entsprechend, beobachtet werden. Im Vergleich dazu, zeigten Wirkstoffe mit sehr hoher Löslichkeit (Tramadol HCl und Metoprololtartrat) keinen Curing-Effekt über den gesamten untersuchten Wirkstoffbeladungsbereich. Nicht nachbehandelte und nachbehandelte Pellets dieser Wirkstoffe wiesen eindeutig ein starkes, dem zweiten Szenario folgend ein einheitliches Schwellen auf, was durch das schnelle Auflösen der Wirkstoffschicht aufgrund der hohen Löslichkeit verursacht sein könnte.

Osmotisch unaktive MCC-Kerne zeigten keinerlei Curing-Effekt unabhängig von der Wirkstofflöslichkeit und Wirkstoffbeladung. Ähnlich wie bei den Zuckerpellets änderte sich die Wasseraufnahmefähigkeit sowie das Schwellen bei den überzogenen MCC-Pellets nicht wesentlich.

Der Curing-Effekt von Kollicoat® SR 30 D überzogenen Pellets wurde erfolgreich beseitigt durch verschiedene Ansätze entsprechend der vorher erkannte kritischen Gründe i) ein Schutzüberzug des Zuckerkerns um die osmotische Aktivität zu unterdrücken ii) einen Ansatz die Herabsetzung der Adhäsion durch das Curing zu verhindern, indem das Verhältnis von Wirkstoff zu Bindemittel erhöht wurde (3:1) oder durch Aufbringen eines 10%igen Unterüberzugs aus HPMC iii) Einarbeitung einer größeren Menge Talk (100%) um den Überzug spröde zu machen oder durch das Ersetzen von Talk mit einem anderen hydrophilen Antiklebmittel mit kleiner Partikelgröße (TiO_2) und iv) den Überzug porös machen durch Zusatz von Porenformern.

Die mit Kollicoat® SR 30 D überzogenen Pellets waren unter Stressbedingungen für 12 Monate gut lagerstabil.

Außerdem wurde mit einem anderen flexiblen Polymer ebenfalls ein starker Curing-Effekt beobachtet; Eudragit® NE 30 D überzogene Zuckerpellets folgten beinahe dem selben Mechanismus.

Montmorillonite als Antiklebmittel

Ziel dieses Teils der Arbeit war es den Antiklebeffekt von zwei natürlich vorkommenden Montmorilloniten (MMTs), vermarktet als Cloisite® Ca^{++} und Nanofill® 116, zu untersuchen und im Vergleich zu Talk als konventionelles Antiklebmittel in verschiedenen wäßrigen Polymerdispersionen zu bewerten. Im Hinblick darauf wurden die Stabilität, Verarbeitungsfähigkeit des Überzugs aus gemischten Polymerdispersionen, Klebrigkeit und mechanische Eigenschaften der gegossenen Polymerfilme und Wirkstofffreisetzung der überzogenen Pellets unter Verwendung verschiedener MMT-Konzentrationen (10%, 20% und 30%) bestimmt und mit Talk (35%) verglichen.

Eudragit® NE/NM 30 D war instabil bei Zusatz von Cloisite® Ca^{++}, wohingegen Kollicoat® SR 30 D instabil bei Zusatz von Nanofill® 116 war. Im Vergleich dazu war Eudragit® NE/NM 30 D gut stabil mit beiden MMTs. Der genaue Grund für die Instabilität der Dispersionen ging über den Rahmen der hier vorgestellten Studie hinaus. Die stabilen Dispersionen wurden für die weitergehenden Untersuchungen benutzt.

Die MMTs reduzierten die Klebrigkeit der gegossenen Polymerfilme signifikant stärker als Talk. Ein Zusatz von 10% MMTs zu den Polymerdispersionen resultierte eindeutig in einer geringeren Ablösekraft zum Trennen der klebrigen Filme als mit 35% Talk. Das erklärt sich durch die homogenere Verteilung der MMTs in den Polymerfilmen begründet in ihrer kleineren Partikelgröße und höheren Hydrophilie. Daraus resultierend sind die Polymerpartikel besser durch die MMTs bedeckt und die Klebrigkeit ist effektiv verringert. Im Gegensatz hierzu war Talk nicht homogen verteilt wegen seiner höheren Hydrophobie und es wurden sogar einige wenige talklose Stellen innerhalb der Filme beobachtet, was zu einer

weniger effektiven Reduktion der Klebrigkeit führte. Eine Erhöhung der Weichmacherkonzentration hatte einen geringen Effekt auf den Antiklebeffekt der MMTs.

Wichtig anzumerken ist, dass die Verarbeitungsfähigkeit der Überzüge (Sprührate und –ergiebigkeit) der verschiedenen wässrigen Polymerdispersionen mit kleineren MMT-Konzentrationen viel besser war als mit hohen Konzentrationen von Talk. Als Beispiel hierfür: Formulierungen mit Eudragit® RS 30 D unter Zusatz von 10% Cloisite® Ca^{++} hatten ein Maximum der Sprührate bei 3,1 g/min im Vergleich zu 2,1 g/min bei einem Zusatz von 35% Talk, das konnte erhöht werden auf 3,5 g/min durch die Erhöhung der Cloisite® Ca^{++}-Konzentration auf 20%. Außerdem konnte während dem Coating mit MMT-enthaltenden Formulierungen ein breiterer Bereich an Produkttemperatur verwendet werden. Das rührt von der Erhöhung der Polymer-Tg durch Zusatz von MMTs und wurde mit DSC-Untersuchungen bestätigt. MMTs reduzierten auch die Klebrigkeit der überzogenen Pellets während der Nachbehandlung signifikant besser als Talk.

Zudem senkten MMTs die Flexibilität aller benutzten Polymere stärker als Talk. Jedoch war die Verringerung der Spannungsfestigkeit geladener Polymere (Eudragit® RS/RL 30 D) durch MMTs ausgeprägter als bei den neutralen Polymeren (Kollicoat® SR 30 D und Eudragit® NE/NM 30 D), wenn man sie beide mit Talk vergleicht. Das könnte an der Wechselwirkung der positiv geladenen Gruppen von Eudragit® RS/RL 30 D und der negativ geladenen Gruppen auf der Oberfläche der MMTs liegen. Der Zusatz von MMTs zur Überzugsformulierung beeinflusste eindeutig nicht die Wirkstofffreisetzung aus den überzogenen Pellets. In einigen Fällen konnte die Eliminierung des Curing-Effekts mit der verringerten Flexibilität der Überzüge in Verbindung gebracht werden.

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7 Publications

Research articles

Dashevsky, A., Ahmed, A.R., Mota, J., **Irfan, M**., Kolter, K., Bodmeier, R., Effect of water-soluble polymers on the physical stability of aqueous polymeric dispersions and their implications on the drug release from coated pellets. Drug Dev. Ind. Pharm. 36, 152-160, 2010.

Irfan, M., Ahmed, A.R., Dashevsky, A., Kolter, K., Bodmeier, R., A new insight of curing mechanism of flexible aqueous polymer coatings. (under preparation)

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Poster presentations

Ahmed, A.R., **Irfan, M.,** Dashevsky, A., Kolter, K., Bodmeier, R., 2008. Elimination of curing effect of coatings with the aqueous dispersion Kollicoat® SR 30 D. Annual AAPS Meeting, Atlanta, GA, USA.

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Irfan, M., Ahmed, A.R., Dashevsky, A., Kolter, K., Bodmeier, R., 2010. Curing and aging phenomena of polyvinyl acetate (Kollicoat® SR 30 D) coatings. Biannual Meeting of the GDCh-Division of "Macromolecular Chemistry" and Polydays. Berlin-Dahlem, Germany.

Irfan, M., Ahmed, A.R., Dashevsky, A., Kolter, K., Bodmeier, R., Effect of starter core, drug solubility and loading on curing and aging phenomena of polyvinyl acetate (Kollicoat® SR 30 D) coatings (abstract accepted for Annual AAPS Meeting 2011, Washington DC, USA).

8 Curriculum Vitae

For reasons of data protection, the Curriculum Vitae is not included in the online version.