ORAL CONTROLLED RELEASE LIQUID DOSAGE FORMS (RECONSTITUTABLE POWDER) BY ION EXCHANGE RESINS

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To my parents and family,

with love and gratitude

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List of abbreviations

API	Active pharmaceutical ingredient
IER	Ion exchange resin
c.l.	Coating level
DBS	Dibutyl sebacate
d.l.	Drug loading
DSC	Differential scanning calorimetry
DRC	Drug-resin complex
DVB	Divinyl benzene
EC	Ethyl cellulose
GIT	Gastro intestinal tract
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
IPA	Isopropanol
K-SR	Kollicoat® SR 30 D
MCC	Microcrystalline cellulose
MFT	Minimum film forming temperature
NP	Nonpareils (sucrose starter cores)
PBS	Phosphate buffer saline
PEG	Polyethylene glycol
PPL	Propranolol HCl
PVA	Polyvinylalcohol
PVP	Polyvinylpyrrolidone
PXRD	Powder X-ray diffraction
SD	Standard deviation
SLS	Sodium lauryl sulfate
TBC	Tributyl citrate
TEC	Triethyl citrate
AERs	Anion exchange resins

1 Introduction

1. Introduction

1.1 Background

Ion exchange resins are cross-linked synthetic high molecular weight solid polymers. They are insoluble not only in water but also in organic solvents. They were discovered in the mid-20th century as a part of drug delivery system, when they were first time used in oral suspensions (Chaudhry et al., 1956). Their size varies from 0.05 - 1 mm in diameter, they usually exist as beads, white or yellowish, fabricated from an organic polymer substrate. The exchange of ions takes place with simultaneous releasing of other ions, thus the process is called ion exchange (Bilandi et al., 2014). In the ion exchange process, ions of similar charges are exchanged between liquid (solution) and solid (resin). It is a reversible process and undergoes an equilibration between ionic sites of the exchange resin and the ions of the solution (Martin, 1955). The research over the last few years has revealed that IERs are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking. An ion exchange resin is exhibited like small beads with a diameter between 0.3 - 2 mm. It is usually white or yellowish and fabricated from an organic polymer substrate backbone (Srikanth et al., 2010).

1.2 Structure of Ion Exchange Resins

Notwithstanding their insolubility, the resins have ionizable ionic sites (hydrophilic functional groups) in their structures. These ionic groups have specific pKa values which can carry acidic and basic drugs (Jenke, 1989). The polymer backbone is usually made of Polystyrene, which is cross-linked to a moiety of divinyl benzene (DVB) with side chains of ionic functional groups generating the pores between cross-linked chains (Figure 1, 2). The pores are of very small size, only few angstrom (A°). The hydrated ion exchange resins have the pore size of 1-2 nm (10-20A°) (Bilandi et al., 2014). The ion exchange resins having macro porous nature, in addition to their small gel pores, they also have macrospores with a size of about 20 to 100 nm (200 to 1000 A°). The interlinked chains of the resins give the polymer more stability and a tri-dimensional structure. The higher the amount of cross linking, the more rigid is the polymer structure. The cross links are evenly distributed along the matrix of the ion exchange resins (Bilandi et al., 2014). The Ion exchange process is always a reversible process of ionic change between a liquid phase and a solid phase, without change in conformation or properties of the latter (Anand et al., 2001).

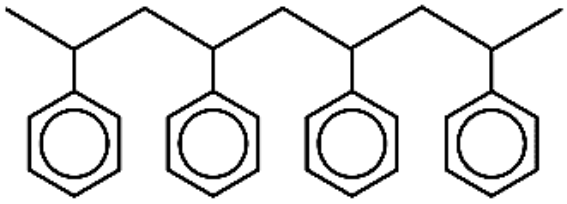

Figure 1. A small fraction of a polystyrene chain.

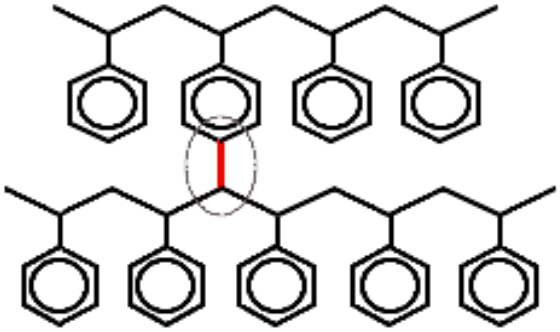

Figure 2. Schematic presentation of the general structure of an ion exchange resin cross linked with divinyl benzene (DVB) adapted from (Bilandi et al., 2014).

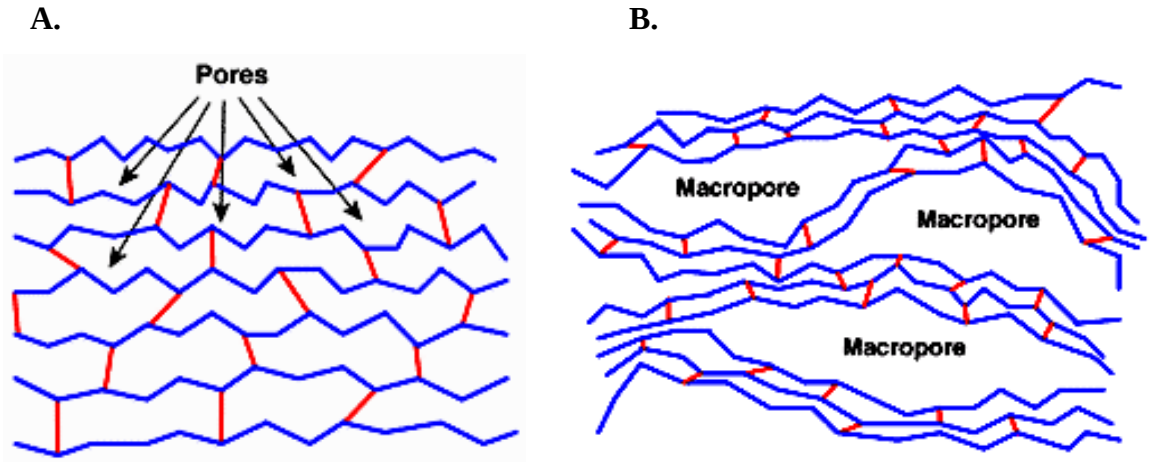

Figure 3. Schematic presentation of ion exchange resin (A) gel structure with pores; (B) macro porous structure (François., 2015).

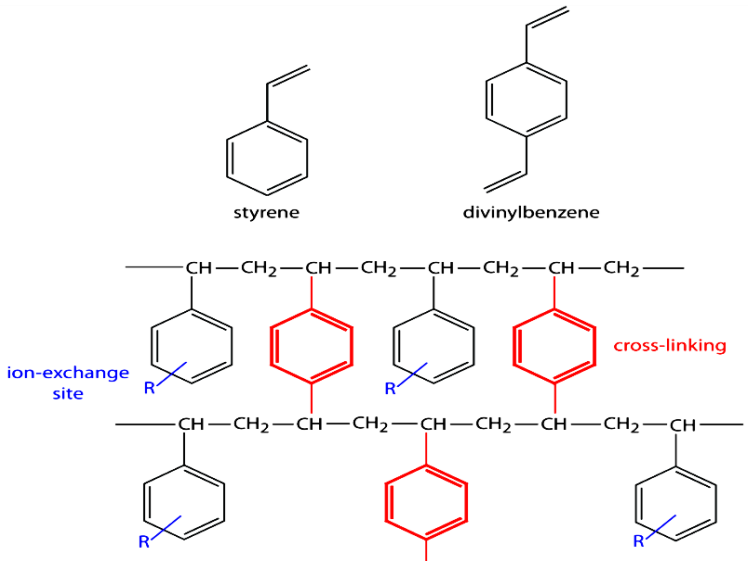

Figure 4. Schematic presentation of the general structure of an ion exchange resin adapted from (Srikanth et al., 2010).

Several steps are involved in the manufacturing of ion exchange resins, out of which the following two steps are most critical (Sawaya et al., 1987).

- Polymerization of the ion exchange resin matrix
- Functionalization (attachment of functional groups to the resins matrix)

The process of polymerization is normally carried out in a suspension medium. It is done with stirred reactors (batch polymerization) or special "jetting" equipment. The manufactured polymers are small spherical beads 200 to 500 µm in diameter (Helfferich, 1962). The uniform bead sizes are produced by jetting process, whereas Gaussian distributed particle size beads are manufactured by the batch polymerization process. These beads swell to a size of 300 to 1200 µm on subsequent hydration steps. The drug resin complexation converts the drug to amorphous form leading to improved drug dissolution (Becker, 1959).

1.3 Types of Ion Exchange Resins

There are various kinds of ion exchange resins. Mostly resins that are used for commercial purpose are usually made of polystyrene sulfonate backbone (François de Dardel et al., 2008). They are classified as follows (Figure 5).

1.3.1 Strong acid cation exchange resin

These types of resins have a chemical behavior like a strong acid. They are highly ionized in their acid form as well as in their salt form. Usually, this type of resin contains a sulfonic acid group ($R\text{-}SO_3^-H^+$) which exchanges a H^+ and a sulfonic salt ($R\text{-}SO_3^-Na^+$) which exchanges a Na^+. Such type of resins can convert to a metal salt to its corresponding acid. The most important fact about these resins, their exchange capacity is independent of the pH of the medium. The pKa values of these resins is below 1. They are ionizable at all physiological pH of the body (Srikanth et al., 2010).

1.3.2 Weak acid cation exchange resin

Weak acid cation exchange resins, like weak acids, show a pH-dependent ionization and thus possess limited activity below a pH of 5. Their functional group is usually a COOH, exchanging H^+ in acidic environments. They are usually used for taste masking in the pharmaceutical field. The pKa value of these ion exchange resins is around 4 – 5, which makes them more ionizable in pH higher than their pKa (Srikanth et al., 2010). The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, capacity of ion exchange resin depends in part on the solution pH. A typical weak acid resin has limited capacity below a pH of 6.0, making it unsuitable for deionizing acidic metal finishing waste water.

1.3.3 Strong base anion exchange resin

These resins have usually a quaternary ammonium group (NH_4^+) in their structure and exchange mainly OH^- and Cl^- ions. Like the strong acid cation exchange resins, they are ionizable at all pH ranges of GIT and thus suitable for sustained release drug delivery system. The strong base anion exchange resins (AERs) have a pKa value of 14 which makes them ionizable at all physiological pH conditions (Helfferich, 1962).

1.3.4 Weak base anion exchange resin

The dissociation of weak base anion exchange resins is highly influenced by pH of the medium. These resins have a pKa value of 8 - 10. The common functional groups include polyalkyl amine chains, which may be primary or secondary amines.

Weak base resins are like weak acid resins. Hence, weak base resins exhibit minimum exchange capacity above a pH of 7.0.

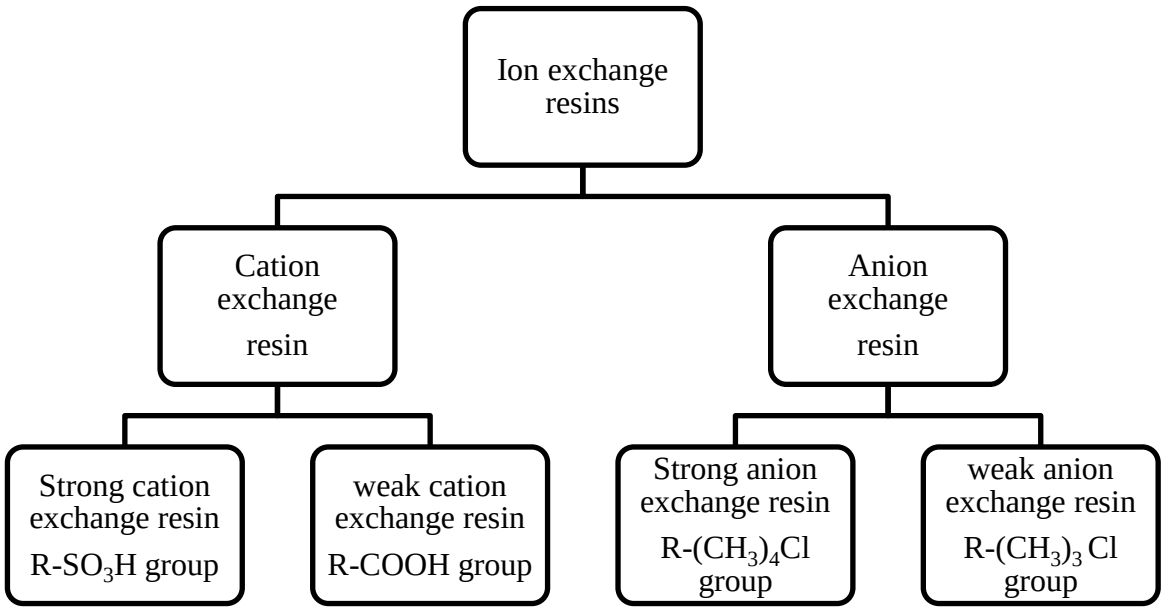

Figure 5. Different types of ion exchange resins.

1.4 Physicochemical Properties of Ion Exchange Resins

IERs have specific properties like ion exchange capacity, acid base strength, particle size, porosity and swelling. The release characteristics of drug from resinates usually depend on these properties. Drug resinates are generally prepared with purified resins and appropriate drugs.

1.4.1 Cross linkage

The amount of crosslinking depends on the proportions of different monomers used in the polymerization step. The practical ranges are between 4 % to 16 % (Boyd et al., 1947). Resins with very low crosslinking tend to be wet and change dimensions markedly depending on the type of ion they possess. Mostly, all properties of ion exchange resins based on their cross-linking of poly styrene chains in their matrix (Akerman et al., 1999). Low amount of cross-linking is characterized by large amount of moisture, high degree of permeability, high equilibrium rate and less incidence of physical stability.

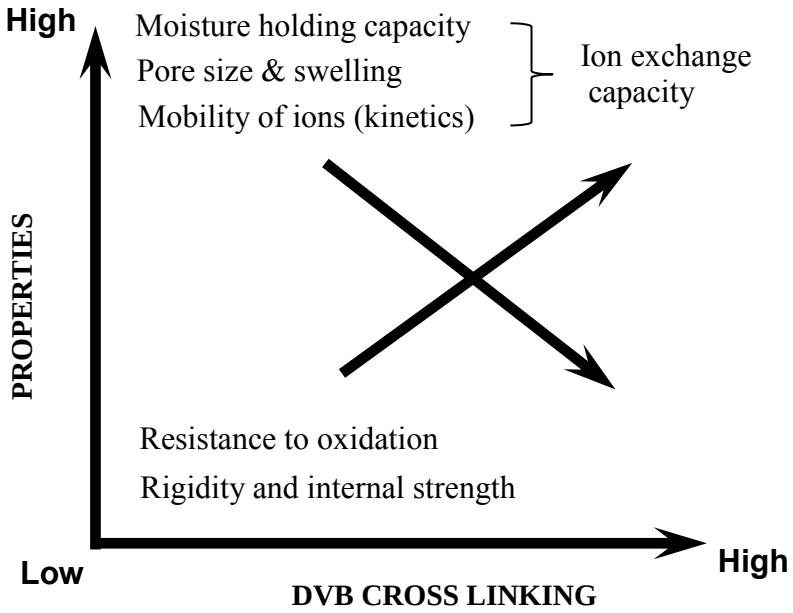

Figure 6. Schematic presentation of different properties, co-related with DVB cross linking of ion exchange resin.

1.4.2 Ion Exchange Capacity

The capacity of an ion exchange resin is the total number of equivalents available for exchange per unit weight or unit volume of resin. The capacity may be expressed in terms of milliequivalents (meq) per dry/wet gram of resin or milliequivalents per milliliter. The situation is reversed, when a wet volume basis is used to measure the capacity on a resin. Although fewer functional groups are introduced into a highly crosslinked resin, these groups are spaced closer together on a volume basis because the volume of water is reduced by the additional crosslinking. Thus, the capacity on a wet volume basis increases as cross-linking increased (Akerman et al., 1998).

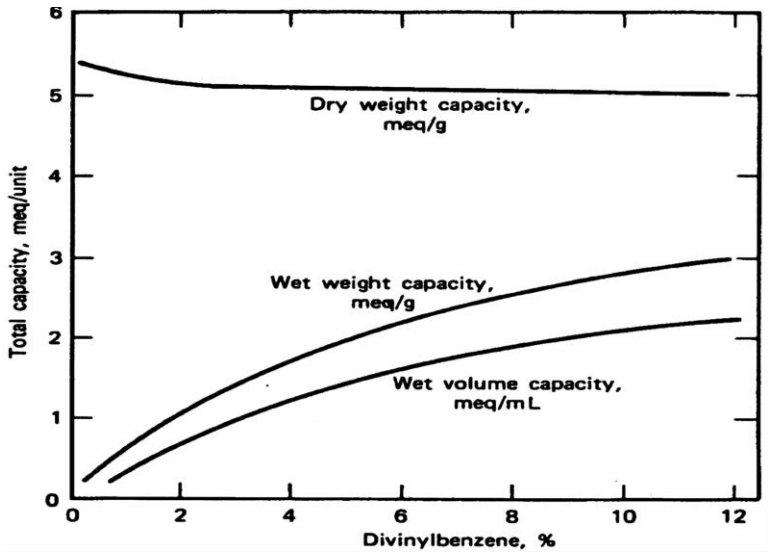

Figure 7. A co-relation shown between DVB cross linking and total ion exchange capacity of ion exchange resins.

1.4.3 Swelling/expansion of ion exchange Resins

When water comes in contact with the hydrophilic ionic sites of the resin, it forms solvation shells leading to uncoiling of resin matrix which leads to swelling of ion exchange resins. The swelling of the ion exchange resin depends on % DVB cross-linking. The degree of swelling is inversely proportional to the cross-linking (Boyd et al., 1947).

1.4.4 Moisture contents of ion exchange resins

The moisture holding property of ion exchange resins changes with the extent of cross-linking of the resin. For instance, sulfonic acid groups attract water, and this water is tenaciously held inside each resin particle. The quaternary ammonium groups of strong anion exchange resins also act in the similar way (Boyd et al., 1947).

1.4.5 Particle size of ion exchange resin

The size of the resin is of key importance, it is controlled during the polymerization step of their manufacturing of ion exchange resins. The ASTM sieves are used to achieve size uniformity.

Particle size also decides, which method is appropriate for drug loading on them. It is important to describe that for fine particle size of irregularly shape (powder) resin. The batch process is always preferred, the column process is used for bigger spherical form resins (Borodkin et al., 1979).

1.4.6 Equilibration rate

Reactions of ion exchange resins are always equilibrium based. The bigger ion takes more time to diffuse into the resin with the same extent cross-linking of their polymer chains. The DVB cross linking has a definite influence on the time required for an ion to reach equilibrium. An ion exchange resin with a high degree of cross-linking offers, more hindrance to the diffusion of various ions through it. Hence, the time required to reach equilibrium is much longer. In general, the larger the ion or molecule diffusing into an ion exchange resin, or the more highly cross-linked the polymer, the longer will be the time required to reach equilibrium conditions (Jenke et al., 1989).

1.4.7 Flow rate

Ion exchange processes are usually carried out in columns with the resin resting on a suitable support. Liquids may be processed either up-flow or down-flow through such columns. The spherical particles of ion exchange resin resist the flowing of a liquid through or around them. The smaller the particle size, the greater will be its resistance against which a liquid flow. This resistance goes up very rapidly when particles smaller than 100 mesh are employed (Yuan et al., 2014).

1.5 Uses of Ion Exchange Resins

1.5.1 Pharmaceutical use of ion exchange resins

The drug delivery from the IERs depends on the ionic surroundings but are less susceptible to other conditions such as the enzymatic degradation, temperature or the site of absorption. Considering this, IERs have been shown as important delivery systems especially for the gastrointestinal tract (GIT) but also for the topical pathway, nasal, iontophoretic and for taste masking (Guo et al, 2009). There are many advantages of using IER as drug delivery systems,

such as their low running cost, their inert nature, uniform size, spherical shape, equilibrium driven process of loading and also reproducible dissolution profiles (Jeonget al., 2008).

1.5.2 Taste Masking

A great number of drugs have an unpleasant taste, making the formulation of such drugs is a big challenge. This represents a crucial parameter regarding patient compliance and marketing acceptability of these formulation. At the salivary pH of 6.5, the resinates are not soluble and thus, maintaining the original complex and not allowing the drug to be dissociated and bitter tasted (Lumy et al., 1991). Moreover, lower concentration of ions in the saliva compared to the stomach, ensures minimum drug release in the mouth. There are already some formulations with IERs as taste masking agents. For example, pseudoephedrine can be successfully masked using the polymethacrylic acid IER (Amberlite® CG-50). Nicorette is a chewing gum for smoking cessation, contains nicotine ionically complexed to an IER, providing a slow elution/release from the resin particles for an extended activity of nicotine. It is important to select the appropriate resin with low cross-linking in their matrix structures for taste masking (Yoshida et al., 2013).

1.5.3 Sustained/extended release

IERs play one of the major roles in sustained/controlled release of drugs due to their drug retention properties and prevent dose dumping. The physical properties of ion exchange resins also make this system advantageous for sustained release, as the drug always liberated in a uniform and continuous way with help of counter ions (Anand 2001). The biphetamine is used as an anti-obesity agent and for behavioral control in children. It contains amphetamine and dextroamphetamine ionically complexed with a strong acid CER containing sulfonic groups (Guo et al., 2009). Another example of sustained release formulation, where IERs are used is the complex of pseudoephedrine with Amberlite® IRP 69 (Kelleher et al., 1991).

1.5.4 Site specific drug delivery systems

Delivering the drug to site specific locations can have many of advantages in therapeutics. The accumulation of drug in the desired place, assuring a minimum effective concentration, reducing systemic toxicity. It is an important advantage in cytotoxic drugs and some antibiotics and reducing

the first pass effect of some drugs. This area has a great potential for ion exchange resins, being rarely investigated in this regard (Whitehead, et al., 1998, Anand 2001).

1.5.5 Gastric drug delivery systems

Some drugs, such as metformin, furosemide, cyclosporine, allopurinol and ciprofloxacin are mainly absorbed in the upper gastrointestinal tract. To increase the time, floating gastric formulations have been developed. In these formulations, the drug is complexed with the resin, with a bicarbonate matrix. As it reaches stomach, the resin exchanges bicarbonate with hydrogen ions from the gastric acid, thus releasing carbon dioxide. Since the gas is trapped inside the outer membrane, and the particle floats (Sharma et al., 2014). Some anion exchange resins also possess mucoadhesive properties due to electrostatic interaction with the mucosal epithelium. The use of bioadhesive capacity makes it possible to design new gastroretentive formulations. Microparticles with mucoadhesive properties of coated resinates containing cholestyramine increases the drug permanence in the stomach and the rate of absorption (Umamaheshwari et al., 2003). This property can also enhance the delivery of tetracyclines to the gastric sites with Helicobacter Pylori and enhanced the therapeutic effect in the gastric ulcer treatment (Irwin et al., 1990).

1.5.6 Nasal/Ophthalmic drug delivery system

There are some studies describing the nasal drug delivery, especially of proteins. In one study, a formulation of nicotine was delivered through the nasal pathway (Illum, 1999). The critical condition for nasal drug delivery with IER, its ion exchange capacity, which needs to be higher than 0.2 meq/L (Kelleher et al., 1991). Currently, formulations for ophthalmic drug release, e.g. Betoptic S, (sterile ophthalmic suspension containing 0.25% Betoxalol HCl) bound to a strong acid cation resin. In the eye, the resin exchanges the drug with the sodium ions present in tears. The formulation is used for the treatment of glaucoma (Guo et al., 2009).

1.5.7 Stability improvement

The ionic drugs form the complexes with ion exchange resins, the resinates have a better stability than the drug alone as used in formulations of vitamin B12 (Srikanth et al., 2010). The vitamin plays a major role in the cellular division process and used for the treatment of patients with

intrinsic factor deficiency. The conventional formulations of vitamin B12 have a shelf-life of only 3 months. The formulations with IERs not only increased the stability of this drug but also extending the shelf-life up to 2 years (Fazal et al., 2012; B.E et al., 1958). This formulation is widely used today. Another good example of improved stability with IER formulations is nicotine, which discolors in the presence of oxygen and light. New formulations containing nicotine loaded resinates, to protect the drug from chemical and physical degradation process and extending its stability (Hite et al., 2013).

1.5.8 Treatment of cancer

The formulation of cytotoxic drugs complexed with IER is an innovative and interesting approach in cancer specific targeted delivery. The tumor tissues are usually more acidic pH 6 or 6.5 than normal healthy tissues pH 7.4 (Yoshida et al., 2013). This pH difference is due to the disrupted cellular metabolism of tumor tissues, since tumor cells grow faster, being consumed high levels of glucose and producing lactic acid (Zhou et al., 2011). The drugs, such as doxorubicin have an ionic nature to make complex with resins and form resinates (Joneset al., 1989).

1.6 Coating of drug-resin complex (DRC)

In order to protect the incorporated API, against light, oxygen, moisture, and degradation by gastric juice, pharmaceutical dosage forms are coated. Additionally, coatings are applied onto the dosage forms to enhance appearance, promote identification or to mask the taste and odor of bitter/ obnoxious drugs. For different release profiles, if the release mechanisms has to be adapted, a suitable coating is selected, for instance, enteric coating, colon targeting, pulsatile release, extended release or fast dissolving coatings. To achieve the desired release profile, different polymers which are characterized by different solubility and swelling properties in water, gastric and intestinal fluids, are screened (Grunnerson and Bruno, 1990).

1.6.1 Coating Equipment and different types of coating

1.6.2 Fluidized bed coater

For coating of smaller cores, such as pellets, granules and powders, fluidized bed equipment is used. The three widely used methods for fluidized bed coating are top, bottom (Wurster) and

tangential (rotary granulator) spray methods (Jones, 1994; Deasy, 1991). A typical description of a fluidized bed coater with top and bottom spray nozzles (Figure 8). As compared to the Wurster and tangential process, the top spray process is less efficient and productive (Mehta et al,1986). It is also less effective for drug layering than rotary equipment. In all these methods water or organic liquids are used as solvent or dispersion medium, which is removed by drying during the coating process.

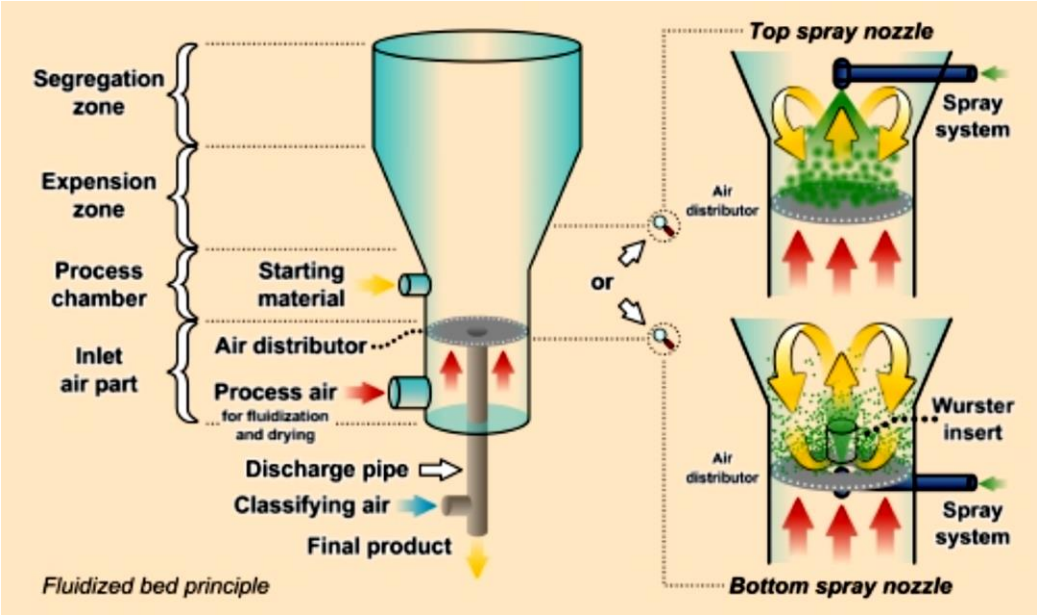

Figure 8. A fluidized bed coater with top and Wurster bottom spray nozzles.

1.6.3 Aqueous dispersion coating

Polymeric coating materials for extended release are insoluble in water and commercially available as aqueous colloidal dispersion. They are classified as true latexes or pseudo latexes depending on manufacturing method employed. In aqueous dispersion systems, water acts as carrier for the polymer particles. A complete film formation is due to the deformation of polymer molecules into each other on removal of water from the formulation (Osterwald, 1985; Sun et al., 1999).

1.6.4 Organic coating

For water insoluble polymers, organic solvents are preferred over aqueous polymer dispersion coatings. Most commonly used solvents are alcohols like ethanol and isopropanol. For polymers having structural units can form hydrogen bonds. The water is the best co-solvent 3-5% water is added to the mixture of ethanol-acetone to dissolve polymethacrylate copolymers (Lehmann et al., 1989). The high viscosity of polymeric solutions is an important aspect for the organic coatings. Which in turn depends on the affinity of the solvent to the polymer and the molecular weight of polymers. The spreading of polymer chains occurs when the solvent has a high affinity for the polymer chain of highly viscous polymer solutions. On the contrary, when the affinity of the solvent for polymer is low, some polymer chains aggregate and shrink which leads to low viscosity. That is why mixtures of solvents can provide better dissolution properties for the polymer along with an appropriate solution viscosity. In organic coatings, solvent is evaporated, and a continuous film is formed throughout the surface of the substrate. During the coating of polymers from organic solution the film is formed at room temperature irrespective of the Tg of the polymer. The most important phase in the film formation is the gel formation. Solvents which do not produce gel lead to the formation of poor films characterized by poor transparency in the dry state (Spitael and Kinget, 1980). It has been noted that sprayed films show more porosity compared to casted films. The droplet-like structure created during spraying, remains apparent in the final film structure (Spitael and Kinget, 1977).

A mixed solvent system, contains a good solvent of high evaporation rate under the said coating conditions. It is sometimes very useful in the mechanism of film formation. The film forming processes are as follows. Firstly, a droplet of polymer solution reaches the core surface and spread when the polymer solution has a sufficiently low viscosity. Secondly, the more volatile solvent quickly evaporates. 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).

Table 1. Comparison between aqueous dispersion coating and organic coating

aqueous coating	organic coating
▪ Economical, as water is used as solvent ▪ No risk of environmental hazards ▪ High solid contents with low viscosity could be applicable	▪ Expensive due to use of organic solvents ▪ High risk of environmental hazards ▪ High solid contents difficult to coat

1.6.5 Polymers for coating

1.6.5.1 Ethyl cellulose

Ethyl cellulose (EC), a cellulose derivative substituted with ethoxy groups, is an insoluble, non-swellable polymer and by itself is impermeable to water. Its monographs exist in the European, Japanese and United States Pharmacopoeia (Rekhi and Jambhekar, 1995).

It is used for moisture protection, taste masking and controlled drug release formulations. It is hydrophobic in nature. It is semi-synthetic polymer manufactured from cellulose and transferred with sodium hydroxide to alkali cellulose. Owing to its insoluble nature in gastro-intestinal tract and neutral side chains, it provides pH independent drug release (Siepmann et al., 2007). As it is non-toxic, non-irritant and non-allergic, it is widely used in oral drug delivery system as film former. Its permeability is very low approximately one tenth of cellulose acetate. (Bindschaedler et al.,1983).

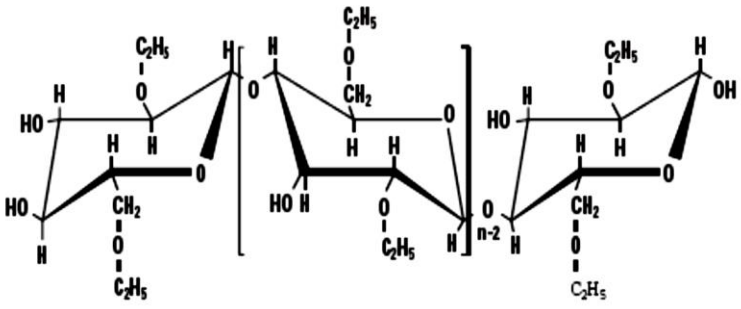

Figure 9. Chemical structure of ethyl cellulose.

1.6.5.2 Polyvinyl acetate

An aqueous polymer dispersion produced by an emulsion polymerization process was developed and available with 30% solid contents. It is abbreviated as Kollicoat® SR 30D. It consists of 27% polyvinyl acetate, 2.7% polyvinyl pyrrolidone (PVP) as a pore former, and 0.3% sodium laurylsulfate (Kollicoat® SR 30 D). The dispersion is used for taste masking purpose of pH independent extended release formulations (Dashvesky et al., 1999; Kolter and Ruchatz, 1999). With mixing of other polymers, it is used for target specific films, for instance, colon targeting (Rock et al., 2000). It has MFT 18 ºC in plasticized state and give brittle film in dry state. Different plasticizers are added to improve mechanical properties of the coating and the final MFT is based on the concentration and type of plasticizer.

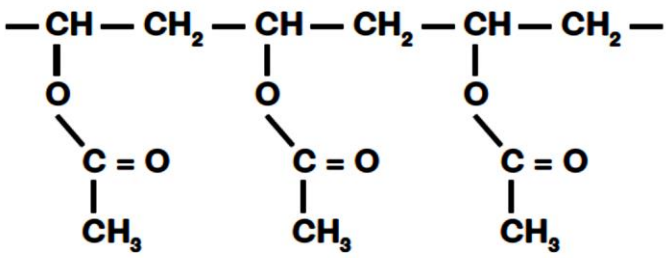

Figure 10. Chemical structure of Polyvinyl acetate.

1.6.5.3 Acrylates

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

1.6.5.4 Eudragit® NE 30D

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 commonly used for wet granulation, transdermal formulation or buccal

patches and extended release film coating. Soft and flexible films are formed at room temperature without the need of plasticizer. Anti-tacking agents are used to reduce the stickiness of the formulation.

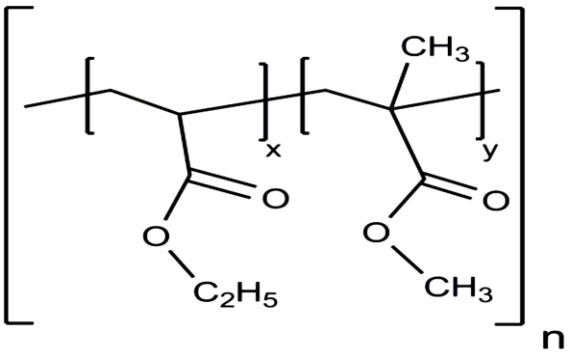

Figure 11. Chemical structure of Eudragit® NE.

1.6.5.5 Eudragit® RS/RL 30D

The 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% of total dispersion. The colloidal polymer particles are stabilized by the positively charged quaternary ammonium groups. Which have chloride ions as counter ions. Since Eudragit® RL 30 D contains double number of ionized functional group. It is more hydrophilic and has a higher tendency to swell in water than Eudragit® RS 30 D (Product broucher technical information). The drug release can be controlled from coated dosage forms by manipulating the film thickness and by the mixing various proportions of Eudragit® RL 30 D and RS 30 D, which in turn determines the film permeability.

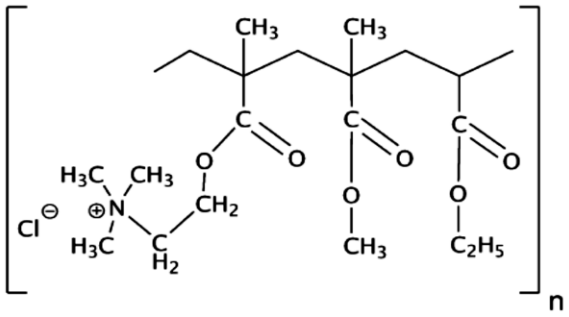

Figure 12. Chemical structure of Eudragit® RS/RL.

1.6.5.6 Eudragit® L 30D-55

The Eudragit® L 30 D-55 is the aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The ratio of the free carboxyl groups to the ester groups is approx. 1:1. The monomers are randomly distributed along the copolymer chain. Based on SEC method, average molar mass (Mw) of Eudragit® L 30 D-55 is approx. 320,000 g/mol. It is milky-white liquid of low viscosity with a faint characteristic odour. The dispersion is miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part of Eudragit® L 30 D-55 with 5 parts of acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol. Initially, the polymer is precipitated, then dissolves again in the excess of organic solvent. A clear or slightly cloudy liquid is obtained by mixing 1 part of Eudragit® L 30 D-55 with 2 parts of 1 N sodium hydroxide (Product broucher technical information).

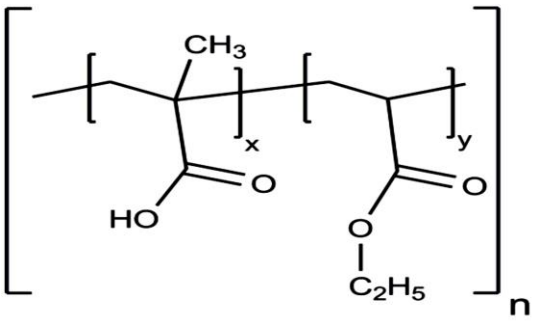

Figure 13. Chemical structure of Eudragit® L30D-55.

1.7 Mechanism of film formation

Film formation from aqueous polymeric dispersions is completely different from the conventional organic solution coatings, where the polymer solution undergoes a gel transition upon solvent evaporation to form the final film. For aqueous dispersions, this process is more complex. 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 forming temperature (MFT) of the polymer (Lehmann, 1994; Keshikawa and Nakagami, 1994). At temperature above MFT, coalescence of latex particles takes place. The addition of plasticizers is required to achieve MFT above the coating temperature for the aqueous polymer dispersions (Bodmeier et al., 1997). The flexibility and toughness of the resulting films is improved by addition of plasticizer. The plasticizer also softens the dispersed polymer particles and facilitate their deformation and final coalescence (Harris and Ghebre-Sellassie, 1997). The mechanism of latex film formation, 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. The film formation from aqueous dispersions can be explained in three main phases. A description of film formation mechanism from aqueous polymer dispersion is elaborated below (Figure 14).

Phase1: Water evaporation and particle concentration

It is longest of all three phases. It persists until polymer reaches approximately 60-70% volume fraction. At first, polymer particles freely move with Brownian motion, elastically rebounding and colliding with one another. The latex surface and solid contents become concentrated by the evaporation of water from the latex surface. The tendency of polymer particles to move around ceases when they come into close contact with one another.

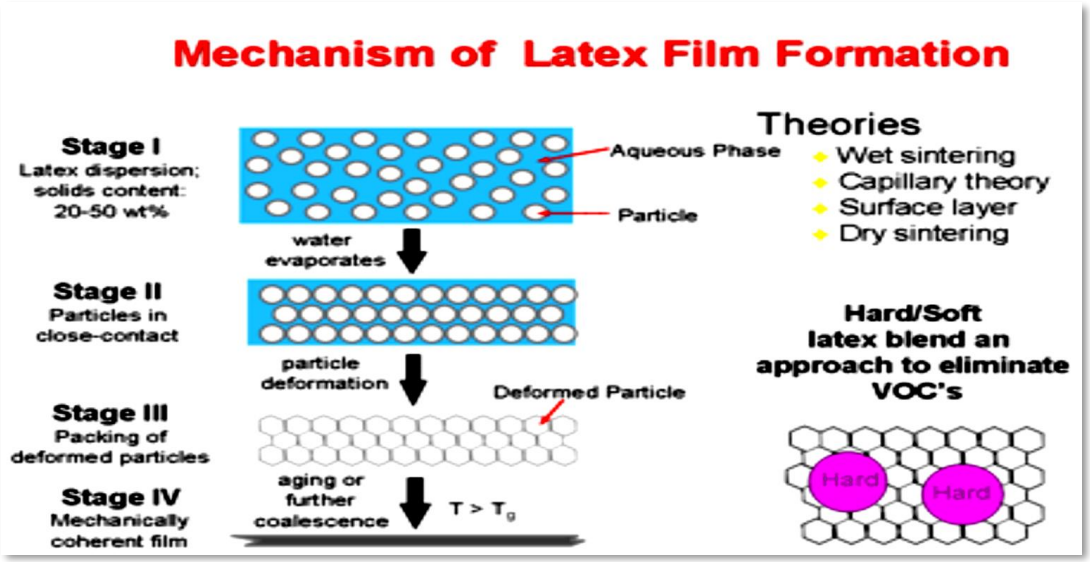

Figure 14. Mechanism of film formation from aqueous colloidal polymer dispersion.

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. 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. This packing is 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 rate of evaporation finally slows down the water leaves the film initially via inter-particle channels and then by diffusion through the fused polymer skin. During this phase, soft latex gains mechanical properties on getting more homogenous. As polymer chain interfusion takes place, a process variously termed as maturation, autohesion, or further gradual coalescence and particle interface tend to become less distinct. The film finally gets its drastic properties during this phase due to polymer chain

entanglements. In 1958, Voyutskii proposed a theory stating 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 (Harris and Ghebre-Sellassie, 1997).

1.8 Solution/suspension layering

Its spraying of different layers of drug or drug resin complex, or on starter core with help of binders in form of solution/suspension. The composition of core usually of some inert material like granules of drug itself or mixture of starch and sucrose or microcrystalline cellulose. In this process the drug-resin complex is dispersed in a binder solution and then layered on MCC/NP core in a fluidized bed coater. As the droplets of drug-resin complex touches the surface of the core, they solidify and forms solid bridges between core and initial drug-resin layer. By this technique, successive layers of drug-resin complex are achieved with additional layer of ions (Christensen and Bertelsen, 1997).

Various technologies are used for solution/suspension layering. Fluidized bed technology is most commonly used technology for layering. In this technology, the drug-resin complex or simple drug is sprayed from the top, from the bottom (using Wurster insert) or tangentially (Jones, 1994). Because of the unorganized fluidization patterns and the unavoidable spray drying, top spray mode is considered as less effective in film coating and drug layering, than bottom or tangential modes (Mehta et al., 1986; Iyer et al., 1993).

The Wurster process is preferable for suspension and solution layering, because of its ability to apply high quality films/layers after the palletization operation. This technique enables layering of 100-150% w/w solids based on the starting/initial core weight (Ghebre-Sellassie, 1989).

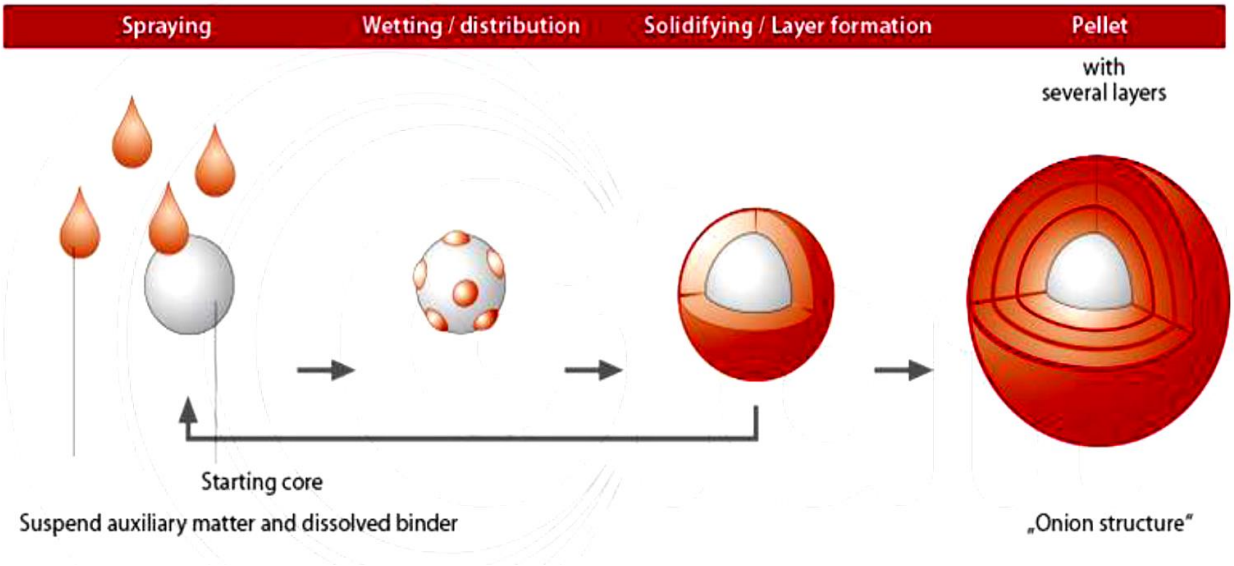

Figure 15. Schematic presentation of suspension/solution layering technique (Glatt GmbH, 2013).

1.9 Additives

For several reasons, different types of excipients are used in aqueous polymeric dispersions, most common being plasticizers, pore formers and anti-taking agents. These excipients strongly influence the 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.

1.9.1 Pore formers

To adjust the drug release of extended release coatings, pore formers are added into formulations. The pore formers which are most commonly used are sugars (sucrose, lactose, sorbitol), salts (sodium chloride, calcium phosphate) and hydrophilic polymers (polyethylene glycol, polyvinylpyrolidone and HPMC) or surfactants (sodium lauryl sulfate) (Muhammad et al., 1992; Li et al., 1990; Erdmann et al., 2000). These pore formers during dissolution leach out from coating polymer and enhance permeability of the membrane. The concentration of the pore former can control the release kinetics of ethyl cellulose coatings and different polysorbates used as additives (Samani, 1999). The drug release from aqua coat 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 aqua coat coatings was stabilized under stress conditions by adding pore formers (Siepmann et al., 2007; Siepmann et al., 2008; Muschert et al., 2009).

1.9.2 Plasticizers

Plasticizers give flexibility to the hard and brittle polymers. These are organic solvents having high boiling points. They act by reducing cohesive intermolecular forces within the polymer chain, thus changing polymer properties. For example, plasticizers cause increase in elongation, flexibility and reduction in the glass transition temperature and tensile strength of the polymer. The purpose of plasticizer to reduce the minimum film forming temperature (MFT) below the coating temperature (Bindschaedler et al., 1983). The plasticizer diffuses into polymer particles and promotes the particle deformation and coalescence to form a smooth film. The plasticizer should be compatible with the polymeric particles for good plasticization effect. Incompatible plasticizers cause the coagulation of aqueous polymer dispersions. Mostly, these phenomena occur with ethyl acrylate/methacrylic acid copolymer formulations (Kollicoat® MAE 30 D) (Flöβer et al., 2000; Dangel et al., 2000). Thus, selection of appropriate plasticizer must be made carefully. The plasticizer could have an anti-plasticizer effect if taken in lower concentration than the appropriate concentration required for optimum plasticization in the coating solution (Guo,1994; Guo et al.,1999).

1.9.3 Anti-taking agents

Anti-tacking/separating agents and pigments are commonly added to aqueous polymer formulations to reduce agglomeration or sticking of coated particles during the coating process. Glyceryl monostearate (GMS), magnesium stearate, titanium dioxide and talc are most commonly used anti-tacking agents in aqueous film coatings. Talc as an anti-tacking agent known to have a sedimentation tendency and causing the blockade of the nozzles during coating process. Therefore, during coating process dispersion must be kept under continuous stirring. The amount of pigments in the aqueous coating dispersion must be optimized without exceeding the maximum carrying capacity of the polymer or critical pigment volume concentration (CPVC). The anti-tacking agents have strong impact on final film properties such as 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). Pigments have a high binding capacity with polymer dispersions. In order to avoid sticking during polymer dispersion coatings talc up to 200%, based on dry polymer mass could be incorporated into the coating formulation of Eudragit® RL/RS 30 D. Which was already plasticized with 30% w/w TEC based on polymer mass (Maejima and

McGinity, 2001). Glyceryl monostearate (GMS) is used in lower concentration. It is shown to have a ten-times higher anti-tacking effectiveness than talc. The addition of talc and GMS reduce the flexibility of coated polymer during the coating process. When the granules swelled in the release medium an orange peeling effect of film coating was observed (Wan and Lai, 1993). During coating process, fine particles have a higher tendency of agglomeration. This could be reduced by adding NaCl to an aqueous spray solution of hydroxyl propyl cellulose (Fukumori, 1993). It was proposed that with reduction of viscosity of the spraying/coating solution, suppression of agglomeration could be achieved (Yuasa, 1997).

To promote further gradual coalescence of the film, coated dosage forms are stored at elevated temperatures. This process is known as curing. It can also be defined as the input of energy into the film-coated system after the desired film coating level is applied (Hamed and Sakr, 2003). Curing of film-coated dosage forms is an important step in the film formation from aqueous polymer latexes. During coating process, curing takes place to a certain extent. However, this is 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).

1.10 Storage Stability

The objective of long term stability is to provide information, how quality of drug substance or drug product changes under the influence of environmental factors such as temperature, humidity, and light, and to further establish a re-test period for the drug substance or drug product or a shelf life for the drug product under recommended storage conditions (European medicine Agency; ICH guidelines). For registration of new chemical entities, a long term stability data is required. Generally, a drug substance must be evaluated under storage conditions (with appropriate tolerances) with its thermal stability, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen must be enough to cover shipment for subsequent use and storage. International committee on harmonization (ICH) recommends different storage conditions, 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, intermediate and accelerated long term stability conditions respectively. Contradictory results were reported in

literature of coated dosage forms regarding long term stability storage. The release of lipophilic drug ibuprofen was increased after storage (Bodmeier and Paeratakul, 1994). The release of theophylline was decreased after storage (Yuen et al., 1993; Goodhart et al., 1984; Bando and McGinity 2006). The stability was carried out of optimized formulation. The formulation was stored in amber coloured bottle after reconstitution at 2°C-8°C till one week. Further it could be evaluated for other physical characteristics as well.

The numerous factors are the cause of change in release profile over long term storage. For example, inadequate amount of plasticizer in the coating formulation results in the change of polymer films over storage. In such cases longer curing times are required to achieve the stable film and release profile. The decrease in theophylline release from coated pellets with Eudragit® RS 30D containing 10% or 20% triethylcitrate (TEC) depending on dry weight of polymer concentration in the formulation (Amighi and Moes, 1996). Another reason could be the physical instabilities in the coating that leads to cracks and chipping of the coating. In addition, the researchers have concluded these problems could lead to increase in water contents of the films rather than a decrease water contents (Chowhan et al., 1982). The faster drug release in case of Aquacoat® ECD coatings was due to the formation of micro-ruptures in the film during storage (Wesseling and Bodmeier, 2001).

The increased in compaction of polymer structure and decrease in the free volume of the film due to gradual coalescence with the ageing progresses was also reported, as one reason for unstable release profile (Guo et al., 1993). This is due to the 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. The decrease of drug release under high humidity was due the gradual coalescence as a result of decreased permeability for water and drug in the formulation (Amighi and Moes, 1997, Bajdik et al., 2003).

The storage at 40 °C and 75% RH of Kollicoat® SR 30 D coated pellets also resulted in the decreased drug release due to continuous film formation (Shao et al., 2002). In contrary, an increased lag time without any significant change in release profile was observed with Kollicoat® SR 30 D coated pellets upon one-month storage at 40 °C/75% RH (Ensslin et al., 2008). The addition of talc up to 200% in the formulation of Eudragit® RS 30 D coated pellets provides a

stable release profile. In fact, the polymeric particles were embedded in the skeleton of talc around the pellets, which led to an inhomogeneous film formation. The smoothness of film was further decreased due to the densification of polymeric particles on curing. The drug release was taken place through pores without any change (Maejima and McGinity, 2001; Ahmed et al, 2008).

1.11 Oral liquid-controlled release formulations

Oral liquid-controlled release formulations have always been a challenge to the formulation scientists due to their stability concerns. When high dose of the drug required in the formulation. The formulation becomes challenging both for the manufacturer and for the patients, where flexible dose of drug required in pediatric and geriatric patients. Oral liquid-controlled release is specifically designed for geriatric and pediatric patients. They may be developed to take into consideration the diseased condition of the patient such as esophagitis where flexible dose of the drug required. As breaking of tablet lead to affect its release profile. These formulations are designed to meet the targets, where the drug product is facing stability concerns in aqueous form/state. It is possible to formulate liquid product/formulation, having sustained/controlled action by suspending the coated drug-resin particles into the suitable liquid media. The suspending medium has no action on coated granules. These formulations of drug-resin complex is always of suspension type due to insoluble nature of resinates. Suspensions are biphasic dosage systems in which the solid phase is suspended in a liquid phase. To produce a controlled release liquid dosage forms from ion exchange resins, the drug is ionically complexed with resin and coated with suitable/appropriate polymer, which controls the drug release. It is formulated as suspension using HPMC E5 as a suspending agent. In an attempt of sustained-release drug delivery systems, the microparticles have got much attention because of uniform distribution of coated particles in the GI tract. Which ultimately brings the uniform absorption and decrease risk of local effects on the GI tract.

1.12 Commercial products of ion exchange resins

Ion exchange resins were used for different range of dosage forms, for example from solid to liquids. Different ion exchange resins were selected for the current work by keeping in view their nature, as basic drugs complexed with cation exchange resins and acidic drugs could be associated

with anion exchange reins and both drugs simultaneously carried with amphoteric resin. The commercial products of ion exchange resins are as under.

Table 2. List of commercial products of ion exchange resins

Drug	Brand Name	Dosage form	Dose for adults
Cholestyramine	Questran® (Mead Johnson)	powder	1 packet TID or QID before meals
Colestipole HCl	Colestid (Upjohn)	granules	15-30g/day in divided Doses BID to QID
Na Polystyrene	Kayexalate (Breon)	powder	Orally;15g QID
Phentermine	Ionamin® (Pennwalt)	capsule	15-30mg daily before breakfast
Hydrocodone	Tussionex®	Suspension	1 teaspoonful(capsule
Phenyltoloxamine	(Pennwalt)	Tablet, capsule	or tablet) every 12 h
Dextromethorphan	Delsym® (Pennwalt)	liquid	2 teaspoonful BID
Betoxalol	Betoptic®	Eye drops	2-4 drops in the night

Table 3. List of selected cationic and anionic exchange resins

Name of I.E resins	Shape	Moisture Contents (%)	Swelling (%)	I.E. Capacity (meq/g)	DVB (%)	Particle Size (µm)	Ionisable counter ion
Amberlite® IRP 69	powder	10.42±0.3	46.0 ±1.4	2.8 - 3.4	4 - 16	45-150	$R\text{-}SO_3^-Na^+$
Amberlite® IR 69F	beads	40.16±0.1	57.0 ±2.5	2.9 - 4.4	7.2	300-1100	$R\text{-}SO_3^-H^+$
Purolite® C100MRNS	powder	10.95±0.2	46.0 ±1.2	2.8 - 3.4	8	45-150	$R\text{-}SO_3^-Na^+$
Purolite® C100CaMRNS	Powder	1.95±0.2	46.0±12	2.8 - 3.4	8	45-150	$R\text{-}SO_3^-Ca^{+2}$
Purolite® WCA100	beads	57.0±2.5	30±1.56	0.9 - 0.9	--	240-280	$R\text{-}COO^-Na^+$ $RN^+(CH_3)_3OH$
Purolite® C108DR	powder	10±2.56	35±1.56	--	8	45-150	COOH
Purolite® A430MR	powder	12±3.45	55±2.56	1.8-2.2	8	45-150	$RN^+(CH_3)_3Cl^-$
Duolite™ AP143/1093	powder	10±2.55	50±2.56	1.8-2.2	8	45-150	$RN^+(CH_3)_3Cl^-$

Table 4. List of cationic and anionic model drugs

Name of drug	Melting point	Solubility mg/ml	Log P	Molecular weight	pKa	Nature of drug
Propranolol HCl	96	220	3.48	296	9.03	basic/cationic
Diltiazem HCl	212	950	2.70	450.97	8.06	basic/cationic
Tramadol HCl	300	970	2.4	190	9.41	basic/cationic
Ibuprofen	77-78	0.03	3.5	206.28	4.43	acidic/anionic
Diclofenac sodium	156-158	5.26	4.26	318.42	4.2	acidic/anionic

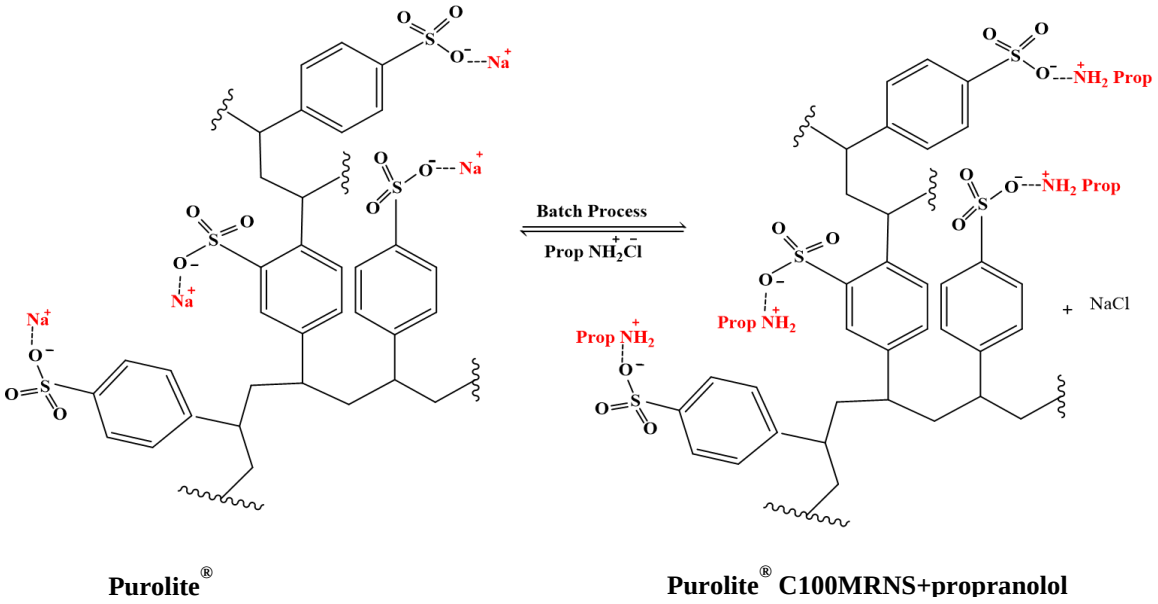

Figure 16. A schematic presentation of reversible reaction/process between cation exchange resin and the propranolol HCl (cationic drug).

1.13 Challenges

Oral controlled release liquid formulations in reconstitutable powder form are not easy to formulate. They are having following challenges.

1.13.1 Tackiness

Making bond of measurable strength, when come in contact with another material is called as tackiness. Tack is 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. Additionally, the extent of deformity of polymer chain and Vander Wall forces has a huge impact on tack strength. Autohesion 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 tackiness problems more likely to happens with small particles size substrates and when coated with Eudragit® RS 30D and Eudragit® RL 30D,

Eudragit® NE 30D or Eudragit® NM 30D and Kollicoat® SR 30D owning to tackiness of polymeric films (Voyutskii, 1971).

This leads to a massive problem of handling the coated substrate caused by sticking to each other and with the walls of the Wurster and chamber. In some worse cases, a stoppage of process was caused by irreversible agglomeration of small size coated substrates or due to 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 had to be established between sufficiently high product temperatures and non-agglomeration (Wesseling et al., 1999). In order to control tackiness during coating process several anti tacking agents were used for instance, talc, magnesium stearate and glycerol monostearate GMS. The talc and magnesium stearate were used in higher concentrations (50-100% with respect to dry weight of polymer) whereas, glycerol monostearate GMS was used in lower concentration 10-20%. The USP defines powders fineness as follows.

Table 5. USP defined range of fineness of powders

Descriptive term	Mesh opening size (µm)	Mesh size Number
Very coarse	≥1000	2-10
Coarse	355-1000	20-40
Moderately coarse	180-355	40-80
Fine	125-180	80-120
Very fine	90-125	120-200

Table 6. pH and ionic composition of different gastric and biological fluids. (Adapted from Thairs et al., 1998)

Fluid	pH	Na^+ (meq/L)	K^+ (meq/L)	Cl^- (meq/L)	HCO_3^- (meq/L)
Saliva	6-7	30	20	30	15
Gastric	1-3.5	(50 - 90)	10	110	0
Bile	7.8	140	5	105	40
Pancreatic fluid	8–8.3	140	5	60	90
Small Intestinal fluid	7.5-8	120	5	110	35
Large Intestinal fluid	5.5-7	130	10	95	20
Plasma	7.4	140	5	100	30
Interstitial fluid		150	5	110	30
Intracellular fluid		10	160	115	30

1.13.2 Incomplete release of drug from drug-resin complex (resinates)

As release of drug always takes place from the ionic sites of resin by dissociation of drug from the resin with help of counter ions in the release medium. But release of drug was incomplete as reported in literature. To get the complete drug release in the release medium was to be simulated with certain specific amount of NaCl and KCl. The role of divinyl benzene (DVB) cross linking inside the resin matrix was also to be considered so as to have its effect on drug release.

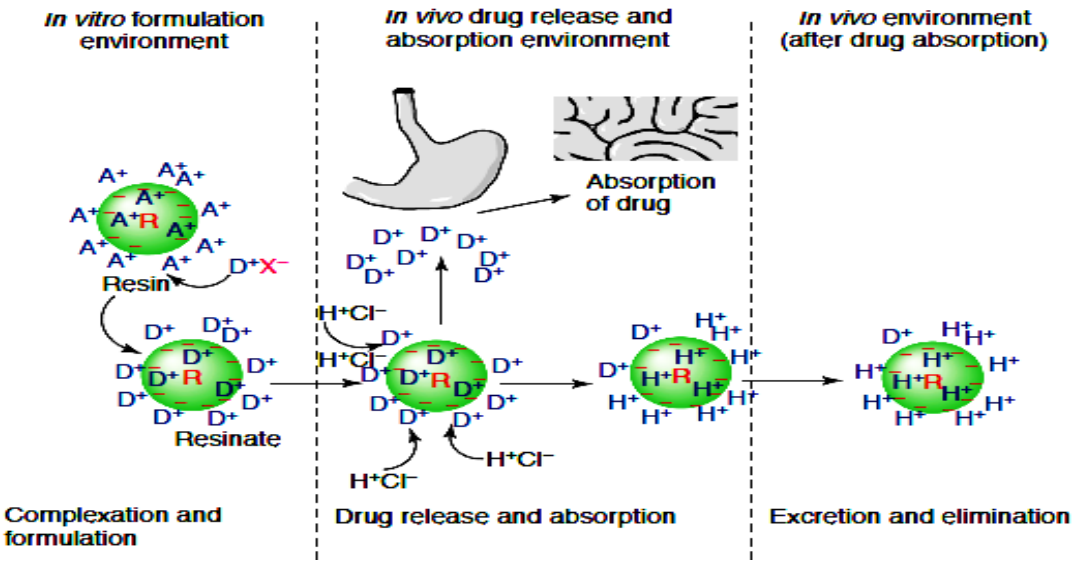

Figure 17. Schematic presentation of mechanism of drug loading and release in the stomach with IER. Adapted from (Anand et al., 2001).

1.13.3 Drug leaching/ drug retention by IERs

During the stability of the formulation, the drug leaching has to be considered in the suspending medium after reconstitution. The drug leaching depends on nature of the drug, pore size of ion exchange resin and nature of the counter ions which participate in the dissociation of drug from drug-resin complex. It was linear relationship between pore size, nature of drug-resin complex (resinates). The ion exchange resins having very good ability loading the drug on their ionic sites but also shows very good drug retention properties. After reconstitution the optimized formulation was tested for dissolution to evaluate its release profile, pH, viscosity, surface tension, sedimentation volume, degree of flocculation and ease of dispersibility.

1.14 Research Objectives

The present research work was focused on oral liquid formulations made of reconstituted powder with the aim of controlled drug release. The work was divided into the following four main studies:

i) Evaluation of cation exchange resin Purolite® C100MRNS for controlled release formulations by investigating formulation and process parameters and stability of formulations before and after reconstitution.

ii) Evaluation of Amberlite® IR69F for enteric drug delivery system by investigating the formulation and process parameters.

iii) Evaluation of Purolite® C100CaMRNS for drug combination delivery system with an aim of complete drug release for both drugs and investigating the formulation and process parameters.

iv) To enhance the robustness of reservoir system (pellets) by preventing diffusion of drug into coated polymer by layering of drug-resin complex on NP core and to evaluate drug-resin complex to enhance solubility of Ibuprofen.

2 Materials and Methods

2 Materials and Methods

2.1 Materials

Model Drugs

Propranolol HCl (K-W Pfannenschmidt GmbH, Hamburg, Germany), diltiazem HCl (PCAS Division Seloc France, Limay, France), ibuprofen (BASF SE, Ludwigshafen, Germany), tramadol HCl (Heumann pharma GmbH, Germany).

Ion Exchange Resins

Sodium polystyrene sulfonate (Amberlite™ IRP 69 Rohm and Haas France S.A.S), cholestyramine (Duolite™ AP143/1093 Rohm and Haas France S.A.S), Amberlite™ IR69F (Rohm and Haas France S.A.S), sodium polystyrene sulfonate (Purolite® C100MRNS Purolite Ltd, Wales, UK), Purolite® C100CaMRNS (Purolite Ltd, Wales, UK), cholestyramine (Purolite® A430MR, Purolite Ltd, Wales, UK), Purolite® WCA100 (Purolite Ltd, Wales, UK), Purolite® C108DR (Purolite Ltd, Wales, UK).

Polymers

Hydroxypropyl methylcellulose (Methocel™ E5, Methocel® K15M Premium CR, Methocel® K4M Premium CR and Methocel® K100LV Premium CR, Colorcon, Orpington, UK), polyvinylpyrrolidone (PVP) (Kollidon® 30, BASF SE, Ludwigshafen, Germany), ethyl cellulose (EC, Ethocel ™ Standard 45 c.P premium, Ethocel ™ Standard 100 c.P premium, (Colorcon, Dartford Kent, UK), ethyl acrylate and methyl methacrylate copolymer aqueous dispersion (Eudragit® NE 30 D, Evonik Industries AG, Darmstadt, Germany), polyvinyl acetate aqueous dispersion (Kollicoat® SR 30 D, BASF SE, Ludwigshafen, Germany), methacrylic acid and ethyl acrylate copolymer, powder and an aqueous dispersion (Eudragit® L 100-55, Eudragit® L 30 D-55, Evonik Industries AG, Darmstadt, Germany), ethylcellulose aqueous dispersion (Aquacoat® ECD, FMC BioPolymers, Cork, Ireland), ethyl acrylate and methyl methacrylate copolymer with a low content of a methacrylic acid ester with quaternary ammonium groups, aqueous dispersion (Eudragit® RS 100, Eudragit® RS 30 D, Evonik Industries AG, Darmstadt, Germany).

Other excipients

Triethyl citrate (TEC) (Citroflex® 2; Morflex, Greensboro, NC, USA), tributyl citrate (BASF SE, Ludwigshafen, Germany), Polyoxyethylene sorbitan monooleate (Tween® 80, Sigma-Aldrich Chemie GmbH, Steinheim, Germany), sodium lauryl sulfate (Carl Roth GmbH + Co.KG, Karlsruhe, Germany), Isopropanol, ethanol 96%, water. Inert sugar spheres, sieved size 710-850 μm (Suglets®, NP Pharm S.A.S., Bazainville, France), magnesium stearate (Herwe Chemisch-technische rezeugnisse, Sinsheim Dühren, Germany), fumed silica (Aerosil® 200, Evonik Industries AG, Darmstadt, Germany), talc (Luzenac pharma, Europe, Toulouse, France), magnesium stearate (Caelo, Caeasar & Loretz GmbH, Hilden, Germany), sodium chloride (NaCl) (Roth GmbH & Co. KG., Karlsruhe, Germany).

2.2 Methods

2.2.1 Purification of ion exchange resins

10 g of ion exchange resin was stirred with 200 ml of ethanol and washed with 200 ml of milli-Q® water, then stirred with 200 ml of methanol and again washed with enough milli-Q® water. Finally, the pre-washed resins were treated with 200 ml of NaOH to re-activate the Na^+ ions on its ionic sites. The resin was washed three times with milli-Q® water until the pH of filtrate turned neutral.

2.2.2 Moisture content of ion exchange resins

Moisture content was determined by loss on drying (LOD) by heating the sample at 103ºC for 3 to 5 minutes (HB43-S Halogen Mettler Toledo Germany). The 1.0 g of powder sample was placed on the aluminium pan and the lid was closed.

2.2.3 Swelling of ion exchange resins

The swelling of resins was measured using a 10 ml graduated measuring cylinder. A specified amount of resins was taken into the cylinder and volume was noted as (volume dry). The water was added into the cylinder and wet volume was noted after a vigorous shaking and allowed it to settle for half an hour. The % swelling of ion exchange resins was calculated by following formula.

$$\%\, Swelling\ = \frac{(Volume\ wet - Volume\ dry)}{Volume\ dry} \times\ 100$$

2.2.4 Particle size measurement

2.2.4.1 Powder laser diffraction

Particle size distribution of resins and resinates was measured by powder laser diffraction (Sympatec particle size analyzer Helos BF Germany). The 2.0 g of powder sample was added into the Powder Laser Diffraction at trigger condition, (STD trigger) with disperser RODOS STD disperser with particle size range 0.5/4.5-175 μm and 0.5/4.5-875 μm. The particle size distribution was obtained in X10, X50 and X90.

2.2.4.2 Liquid laser diffraction

Particle size distribution of formulation after reconstitution was determined by laser diffractometry (LD) (Mastersizer 2000, Malvern Instruments, UK). The index of refraction for both, Purolite® C100MRNS and Purolite® A430MR used was 1.59, and the absorption index was 0.001. The sample was added to the dispersion unit containing water with obscuration range 4-6%, and then the LD measurement was performed immediately at 1750 rpm stirring speed. The LD data obtained by average of 3 measurements was evaluated using the volume distribution diameters (D50%, D90% and D99%) which shows the percentage of particles having a diameter equal or lower than the said value.

2.2.4.3 Light Microscopy

Light microscopy was performed using Leica Wild M3Z (Leica Microsystems (Schweiz) AG, Heerbrugg, Switzerland). The used magnification was 20x10 fold. Each sample was observed 3 times. Drug-resin complexes were suspended in liquid paraffin and the crystallinity of the drug and drug-resin complex was examined under polarized light.

2.2.5 Reduction of particle size of resinates

Particle size of resinates was reduced either in dry state by mortar and pestle or in wet state by wet milling with HPMC E5 as binder in the formulation by the dyno mill (Retsch MM 2000 small ball mill, Retsch GmbH, Haan, Germany) using glass beads. The sample to glass bead ratio was 3:1 (v/v), the total sample volume 600 ml. Each run of the machine took 5-8 minutes to complete the cycle. The particle size of the sample was reduced by increasing the number of cycles or changing

the beads for operation. After milling, the ion exchange resins were dried in an oven at 60°C and finally sieved in a vibratory sieve shaker (Analysette 3 PRO, Fritsch GmbH, Idar-Oberstein, Germany) using sieves of 45, 75, 106, 160 μm pore size at an amplitude of 0.8 mm for 2 minutes. The size fractions <45, 75-106, 106-160 μm were used for the further drug loading studies. The particle size of powders and microsuspensions was analysed according to section 2.2.4.

2.2.6 Drug loading on resin/preparation of drug-resin complex (DRC)

2.2.6.1 Batch method

The batch process was a quick, simple to perform drug loading method on ion exchange resins. Furthermore, it was the only process suitable for very fine size of ion exchange resin particles. This method was performed with Amberlite® IR 69F (Rohm and Hass France), Amberlite® IRP 69 (Rohm and Hass), Purolite® C100MRNS (Purolite Ltd, Wales, UK) and the model drugs propranolol HCl, tramadol HCl and diltiazem HCl (Sigma Aldrich, USA). All the flasks containing the drug solution were stirred with resin suspension for 24 hours at 300 RPM at 23ºC as mentioned in Table 6. Finally, the samples were diluted and filtered using a syringe filter with 0.2 μm pore size (Acrodisc® SOTAX syringe filters with GHP membrane, Pall Corporation, USA). The drug association efficiency was determined indirectly through the drug contents in the supernatants using a UV spectrophotometer (HP 8483, Agilent Technologies at 289 nm). To determine the drug loading from drug-resin complex (w/w), a direct method was used. The drug-resin complex was dissociated with 2N NaCl/KCl solution and the drug content was measured with a UV-spectrophotometer (HP 8483, Agilent Technologies) at 289 nm after filtration through 0.2 μm syringe filters (Acrodisc® SOTAX syringe filters with GHP membrane, Pall Corporation, USA). The drug association efficiency and drug loading were calculated according to the following equations.

$$\%\ Drug\ association\ efficiency\ w/w = \frac{amount\ of\ drug\ associated\ (mg)}{amount\ of\ drug\ used\ (mg)} \times 100$$

$$\%\ Drug\ loading\ w/w = \frac{amount\ of\ drug\ eluted\ (mg)}{amount\ of\ drug\ resin\ complex(mg)} \times 100$$

Table 7. Summary of the formulations prepared with different drug and resin ratios w/w at 300 RPM for different range of temperature

Ratio Drug:Resin	Resin (mg)	Propranolol HCl (mg)	Milli-Q® water (ml)	Temperature (ºC)	Particle size (µm)	pH of loading solution
1:1	100	100	25	23	106-150	2.0
2:1	100	200	-	23	106-150	5.9-6.5
2:1	100	200	-	40	106-150	2.0
2:1	100	200	-	50	45-75	2.0
2:1	100	200	-	60	45-75	4.0
3:1	100	300	-	23	45-75	4.0
4:1	100	400	-	23	75-106	4.0
1:2	200	100	-	23	75-106	6.0
1:3	300	100	-	23	75-106	6.0

2.2.6.2 Column method

The column process was a feasible loading method for resins with a particle size of more than 500 µm. It involved passing a drug solution through a column packed with the IER until the effluent concentration was the same as the eluent concentration.

2.2.7 Effect of temperature, pH and particle size on drug loading

For the evaluation of the effect of temperature on the drug loading process, 3 flasks containing suspensions according to Table 6 with a 1:2 resin to drug ratio (w/w) were stirred for 24 hours in a hot water bath set at 40 ± 5 ºC, 50 ± 5 ºC and 60 ± 5 ºC using a heating/stirring plate. (Variomag Monotherm, H+P Labortechnik AG, Germany). The temperature was checked using an electronic Heat-Probe Thermometer (Wahl Thermistor 700M, Palmerwahl, USA). In the end, all samples were diluted and filtered through a 0.2 µm syringe filter (Acrodisc® SOTAX syringe filters with GHP membrane, Pall Corporation, USA).

The influence of pH (2-8) and different particle size of resin (45-75µm, 75-106 µm, 106-160 µm) on the drug loading was investigated. The different flasks were prepared containing 25 ml of Milli-Q® water and different ratios of drug to resin (Table 6). All flasks were stirred for 24 hours, at 300 RPM and 23 ºC. Finally, samples were diluted, filtered using a 0.2 µm syringe filter (Acrodisc® SOTAX syringe filters with GHP membrane, Pall Corporation, USA) and the drug content was measured UV-spectrophotometrically.

2.2.8 Conductivity studies and change in pH

The change in conductivity and pH of the loading medium before and after the batch process of drug loading was measured by a pH-meter (Metrohm 827 pH Lab, Metrohm AG, Germany) and conductivity meter (inoLab wtw Metrohm, Germany).

2.2.9 Vacuum filtration and drying of resinates

Vacuum filtration was performed after completion of the batch process. The resinates were dried overnight in the oven at 60 ºC and stored in the desiccator for further processing of granulation, coating and particle size distribution.

2.2.10 Characterization of drug-resin complex (resinates)

2.2.10.1 Powder x-ray diffraction (PXRD)

X-ray diffractometry for resin, drug, drug resin physical mixture and drug-resin complex was performed using a powder x-ray diffractometer (PW2273/20 copper anode, Analytical B.V., Almelo, The Netherlands; PW 1830 x-ray generator, PW 1710 diffraction control unit and PW 1820 vertical goniometer, Philips Industrial and Electroacoustic Systems Division, Almelo, The Netherlands). The data collection and machine control was done externally (ADM version 3.5, A. Wassermann Röntgenanalytik-Meßsysteme-Software, Kempten, Germany). The collected raw data was taken into CSV files and evaluated using Microsoft Excel 2013. Samples were put on a sample holder and mounted into the diffractometer. Spectra were collected at angles from 4° to 40° using a step size of 0.02° and a collection time of one second per data point.

2.2.10.2 Fourier transforms infra-red spectroscopy (FTIR)

FTIR spectroscopy measurement was performed with an Excalibur 3100 FTIR spectrophotometer (Varian Inc., Palo Alto, USA). The spectra from drug, drug resin physical mixture and drug- resin complexes and resin alone were obtained in the scan range of 600 to 4,000 cm^{-1} at a resolution of 4 cm^{-1} and average of 32 scans, using a horizontal ATR accessory with a single reflection diamond crystal (Pike Miracle, Pike Technologies, Madison, USA) and Varian software (Resolution Pro 4.0). Scans were taken every 2 minutes over 30 minutes using the Resolutions Pro Software (Version 4.0, Varian Inc., Palo Alto, CA, USA). Data were exported to Microsoft Excel for further evaluation.

2.2.11 Wet granulation of resinates

To improve the flowability of resinates during coating process, the resinates were wet granulated with different binders at different ratios (Table. 8). After granulation, they were sieved and the particle size fraction between 160-250µm was selected for the further coating process.

2.2.12 Coating of drug-resin complex (resinates)

The coating of resinates was performed in a fluidized bed coater (Mini-Glatt, Wurster insert, Glatt GmbH, Binzen, Germany). For each batch process, 50-55 g of granulated resinates were used. The coating processability was evaluated based on spray rate, product temperature, nozzle blockage, the flow of resinates particles, agglomeration tendency and yield. Additionally, the coated resinates were cured at 40 °C and 60 °C and 40°C/75% RH for 12 hours in aluminium pans in an oven. After curing, the powder was equilibrated in a desiccator for 24 hours before further use.

Table 8. Summary of concentration of different binders and granulation fluid during wet granulation of resinates

Formulation		**Binders**				**Granulation Fluid**	
Formulation code	Resinates % w/w	HPMC E5 % w/w	Kollidon® 30 % w/w	Ethocel™ % w/w	Eudragit® NE 40D % w/w	Ethanol: H_2O	IPA: H_2O w/w
F1	85	15	--	--	--	88:12	--
F2	85	--	15	--	--	88:12	--
F3	85	--	--	15	--	88:12	--
F4	70	15	--	15	--	88:12	--
F5	70	15	--	15	--	--	88:12
F6	85	--	--	--	15	--	88:12
F7	70	--	--	15	15	--	88:12

2.2.12.1 Eudragit® NE 30D

The aqueous dispersion of Eudragit® NE 30D, was plasticized with TEC 10% w/w (based on dry polymer mass) and the anti-tacking agent talc (35%-50% w/w based on dry polymer mass) was dispersed in HPMC E5 5% w/w and 5% Tween® 80 based on dry polymer mass). The HPMC E5 was heated up to 55°C in 1/3 of the water, the rest 2/3 water was added to form the clear solution of HPMC E5. The talc was added into clear solution of HPMC E5, with the dropwise addition of Tween® 80. The final solid contents were adjusted to 15% w/w with milli-Q® water. The coating was performed in a fluidized bed coater (Glatt GPCG-1, Glatt GmbH, Binzen, Germany) to obtain coating level of 20-25% w/w (based on dry polymer mass and total weight gain). The coating parameters were as follows: batch size = 50 g, inlet temperature = 28-30 °C, product temperature = 18-20 °C ±2 °C, air flow = 72 m3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 0.8-1 g/min, final drying at 20-25 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with coated resinates to avoid sticking during storage.

2.2.12.2 Aquacoat® 30D and Surelease®

Aquacoat® 30D was plasticised with TEC 25% w/w (based on dry polymer mass) and talc 35%-50% w/w (based on dry polymer mass) was added as anti-tacking agents to the polymer dispersion. Surelease® was used without plasticizer but with talc 35% w/w (based on dry polymer mass) which was added as anti-tacking and the final coating formulation was adjusted to 15% w/w solid contents with milli-Q® water. The coating was performed in a fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) to achieve a coating level of 15-20% w/w (based on total weight gain). The coating parameters were as follows: batch size = 45 g, inlet temperature = 60-62 °C, product temperature = 35±2 °C, air flow = 0.2 m3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 1-2 g/min, final drying at 30 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with resinates to avoid sticking during storage of the formulation.

2.2.12.3 Kollicoat® SR 30D

The aqueous dispersions of Kollicoat® RS 30D, was plasticized with TEC, 5% and talc 35%-50% w/w (based on dry polymer mass) was added as anti-tacking agents into polymer dispersion and the final solid contents were adjusted to 15% w/w with Milli-Q® water. The coating was performed in a fluidized bed coater (Mini-Glatt 4, Glatt GmbH, Binzen, Germany) to achieve coating level of 15-20% w/w (based on dry polymer mass or total weight gain). The coating parameters were as follow: batch size = 45 g, inlet temperature = 28 °C, product temperature = 18-20±2 °C, air flow = 0.2 m3/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 resinates to avoid sticking during storage of the formulation.

2.2.12.4 Eudragit® RS 30D and Eudragit® RL 30D

The aqueous dispersions of Eudragit® RS 30D and Eudragit® RL 30D, were plasticized with TEC 20% w/w (based on dry polymer mass) and talc 30% w/w (based on dry polymer mass) was added as anti-tacking agent to avoid sticking/tackiness of resinates during the coating process. The final formulation with 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 and total weight gain). The coating parameters were as follow: batch size = 50 g, inlet temperature = 55-60 °C, product temperature = 30 ±2 °C, air flow = 72 m3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 0.8-1 g/min, final drying at 30-35 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with coated resinates to avoid sticking during storage.

2.2.12.5 Eudragit® L 30D-55

The aqueous dispersion of Eudragit® L30D-55, was plasticized with TEC 10% w/w (based on dry polymer mass) and talc 35%-50% w/w (based on dry polymer mass) was added as anti-tacking agent to avoid sticking of resinates 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 (based on dry polymer mass and total weight gain). The coating parameters were as follows: batch size = 55 g, inlet temperature = 45-50 °C, product temperature = 25-30 °C, air flow = 0.2 m^3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 0.8-1 g/min, final drying at 30-35 °C for 10 min. After coating, 0.5% (w/w) of colloidal silica (Aerosil® 200) was mixed with coated resinates to avoid sticking during storage.

2.2.13 Diluent granules for reconstitution

The diluent granules for reconstitution were prepared with HPMC E5, HPMC E 50 LV and HPMC K15M with help of water and dried at room temperature for 24 hours. The desired size of granules 500-800 µm were collected by sieving process. The % quantity of polymer granules were added to coated resinates. It was selected on the basis of sufficient viscosity achieved upon reconstitution.

Table 9. Summary of concentration of granules used for reconstitution of formulation

Name of stabilizer	Reconstituted granules (g)	Coated resinates (g)	Ratio used	Water used (ml)
HPMC E5	3	7	1:2.3	50
HPMC E50 LV	2	8	1:4	50
HPMC K15 M	1	9	1:9	50

2.2.14 Stability studies

The long-term storage stability of coated powder of both extended release and enteric release were evaluated. For this purpose, coated powder was put in petri dishes and stored in an incubation chamber at isothermal stress conditions of 40°C and 75 % relative humidity (RH) and 25 ºC and 60% relative humidity (RH) for 12 weeks (3 months). Samples were taken after 1, 4, 8, 12 weeks (n=3) according to the ICH guideline Q1A (R2) "Stability Testing of New Drug Substances and Products" three batches for each formulation: (i) formulation with reconstitutable diluent granules and (ii) formulation without reconstitutable diluent granules were selected.

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2.2.15 Leaching of drug in suspending vehicle

The leaching of drug was evaluated at room temperature with three different types of vehicles to form final suspending media. Milli-Q® water, 5mM and 10mM NaCl with conductivity (658 ± 10.65 µS/cm) and 5mM and 10mM KCl with conductivity (585.85 ± 10.45 µS/cm).

2.2.16 Medium uptake and weight loss

400 mg accurately weighed coated resinate powder (n=3) was submerged in 900 ml 6.8 pH sodium phosphate buffer at 37 °C in a USP II paddle apparatus (Vankel VK 300, Vankel Industries, Edison, NJ, USA). It was set at 100 RPM, at predetermined time points, the coated particles were filtered and weighed (wet weight). The wet particles were then dried in an oven at 60 °C for 12 hours and additionally in a desiccator for 48 hours prior weighing (dry weight). The water uptake and weight loss were calculated as follows.

$$\%\, Water\ uptake\ = \frac{(wet\ weight - \ dry\ weight)}{dry\ weight} \times 100$$

$$\%\, Water\ loss\ = \frac{(initial\ weight - \ dry\ weight)}{initial\ weight} \times 100$$

2.2.17 Determination of pore size inside ion exchange resin particles

The pore size, pore volume and surface area of resin before and after drug loading was measured using the Quantachrome e4000 (NOVA 4000e surface area and pore size analyser GmbH &Co Germany). The resin amount, 2.0 g samples were filled into calibrated sample cells and degassed overnight. After degassing, samples were again taken into sample cells for analysis.

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2.2.18 Preparation of pellets from drug-resin complex

2.2.18.1 Layering of DRC (drug-resin complex) on NP core

The drug-resin complex of ibuprofen and purolite® A430MR was layered onto non-pareil (NP) cores (710-850 µm). The resinate layering suspension (20% w/w solid contents) was prepared in an isopropanol: water (88:12) mixture using HPMC E5 (20% w/w based on drug-resin complex mass) as binder. The layering of both drug and drug-resin complex was performed in a fluidized bed coater (Aeromatic Strea-I, Binzen, Germany) to a weight gain of 10% and 20% (based on initial weight of cores). The process parameters were as follows: batch size = 60 g, inlet temperature = 50 °C, product temperature = 30 ± 2 °C air flow = 0.2 m3/h, nozzle diameter = 0.5 mm, spray pressure = 0.9 bar, spray rate = 2-3 g/min, final drying at 40 °C for 15 minutes.

2.2.19 Dissolution studies

The drug release from uncoated and coated resinates was investigated in an USP II paddle apparatus (VK 7000, Vankel Industries, Edison, NJ, USA) at 50-150 rpm using 900 ml of 0.1 N HCl or sodium phosphate buffer pH 6.8 at 37°C with an optional addition of 0.25% w/v SLS, 5, 10, 100, 300 mM of NaCl and KCl were used to adjust the ionic strength and the osmolality of the release medium up to 600 mosmol/kg. At predetermined time points, samples were withdrawn, and the drug amount was quantified UV-spectrophotometrically (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at the following wavelengths: propranolol HCl: 289 nm, diltiazem HCl: 235 nm, tramadol HCl: 271, ibuprofen: 224 nm, diclofenac sodium: 276 nm, naproxen sodium: 262 nm, ranitidine HCl: 313 nm.

2.2.20 Video monitoring during drug release

The video monitoring of pellets during and after drug release was performed using a light macroscope (Inteq® informationtechnik, GmbH, Berlin, Germany) supplied with an image analysing software (IQ Easy measure®, Inteq® informationtechnik, GmbH, Berlin, Germany). It was to observe the morphology and possible rupturing/cracking and swelling of the coating layer during and after drug release.

3 Results and Discussion

3.1 Development of controlled release drug delivery system using Purolite® C100MRNS (cation exchange resin)

Ion exchange resins are high molecular weight polymers, which are insoluble in water and organic solvents. They have cationic or anionic ionisable functional groups in their structures to carry basic or acidic drugs in form of complexes called resinates. When the dose of the drug is high, tablets are difficult to be swallowed in patients having some disease such as dysphagia or esophagitis. Hence development of liquid controlled release dosage forms with flexible dosing is recommended. So, loading the drug on an ion exchange resin is an option however the drug release from uncoated resinates was rapid and incomplete. To control their rapid release, drugs were coated with water insoluble, swellable polymer such as Eudragit® NE 30D. Drug leaching in water was also considered because water is used to reconstitute powder for liquid dosage forms.

3.1.1 Drug loading

Drug loading was almost 55% w/w and it was remained unchanged for different particle size ranges (71-106 µm, 45-71 µm and 45-150 µm). When both drug and resin were stirred together in the batch process, maximum 38% drug was loaded in the first hour. It was increased up to 55% till 24 hours (Figure 18). Ionic sites of the ion exchange resin (Purolite® C100MRNS) became exposed and got readily available for drug association or complexation (Borodkin, 1993).

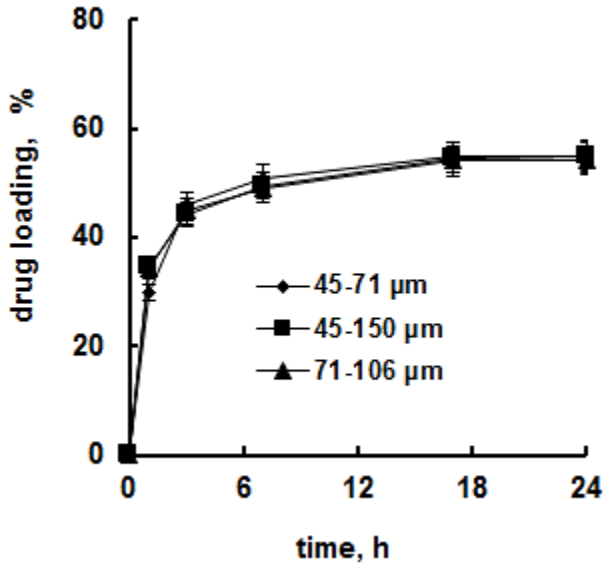

Figure 18. Effect of Purolite® C100MRNS particle size on propranolol HCl loading (n = 3).

During single batch process, for maximum drug loading of 53.62 ± 2.30 %, total used ion exchange capacity of Purolite® C100MRNS was 2.5 meq/g, when drug and resin were taken in the ratio 2:1 w/w. The total 1% drug was adsorbed/attached hydrophobically on the surface of the resin. For this range of drug loading, association efficiency was 57.99 ± 5.2%, which was further decreased up to 36.89 ± 2.93 % for 3:1 w/w drug and resin ratio. This sharp decrease in association efficiency was probably due to the total increased drug concentration in the system (Guo et al., 2009). The maximum used ion exchange capacity of Purolite® C100MRNS was 2.9 meq/g, when drug loading was 80.03 ± 0.66 % in fourth batch process (quadruple). On the other hand, 1.5 meq/g ion exchange capacity of the resin was utilized when drug and resin were used in a ratio of 2:3 w/w. The drug loading was reduced to 39.76 ± 0.05 %. It was might be due to the increased number of ionic sites of resin in the system (Pongjanyakul et al., 2005) (Table 10).

Table 10. Effect of process time and drug: resin (Purolite® C100MRNS) ratio on the association efficiency and the drug loading

No.	Batch process	Drug (mg)	Resin (mg)	Drug: resin	Association efficiency, %	Drug loading		Attached hydroph-obically %
						% w/w (±SD)	meq/g	
1	Single	100	100	1:1	97.01±1.75	49.23±0.45	1.6	0
2		200	100	2:1	57.99±5.2	53.62±2.30	2.5	1
3		300	100	3:1	36.89±2.93	52.48±2.00	2.5	1
4		400	100	4:1	24.67±2.04	49.61±2.06	2.5	1
5		200	200	1:1	98.26±1.95	49.56±0.10	1.6	0.5
6		200	300	2:3	99.03±2.13	39.76±0.05	1.5	1
7		100	200	1:2	99.05±0.41	33.12±0.09	1.3	1
8		100	300	1:3	99.35±0.03	24.87±0.07	0.9	1
9	Double	*379[2]	100		53.99±5.21	68.94±1.62	2.6	0
10	Triple	*482[9]	100		46.03±1.58	75.85±0.97	2.9	1
11	Quadru-ple	*530[10]	100		43.31±0.45	80.03±0.66	2.9	1

* Superscript number means continued the respective batch

The drug loading remained constant both for pH and stirring speed of loading medium. When different pH (2-8) and stirring speed (150-700 rpm) of loading medium was investigated. Both drug and resin remained ionized during this pH and rpm range and drug is complexed with ionic sites in the resin. It was due to the strong nature of the functional group R-$SO^-_3Na^+$ of resin and drug Prop- NH^+ Cl^- (Motycka, et al., 1979) (Figure 19A, B).

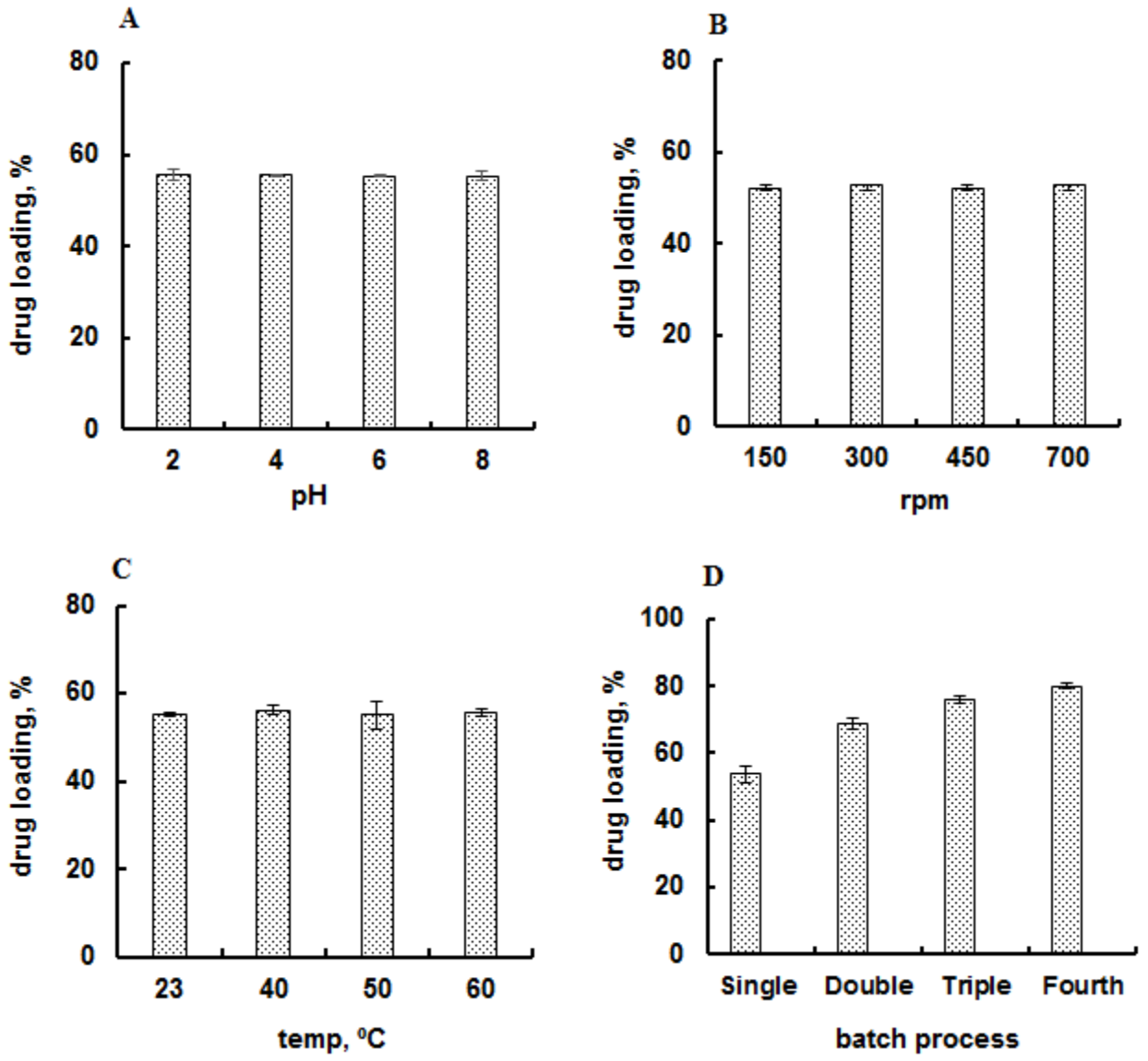

Figure 19. Effect of A) pH at 23 ºC and 300 rpm, B) stirring speed at pH 6 and 23 ºC and C) temperature at pH 6 and 300 rpm and D) sequential batch process on drug loading at pH 6, 23 ºC and 300 rpm (n = 3).

In (Figure 19C) there was no significant increase in drug loading with temperature for an investigation range of 23-60 ºC. It could be due to the ionization of ionic sites of both Purolite® C100MRNS and propranolol HCl. Whereas, drug loading was increased up to 80.03 ± 0.66 % w/w by sequential batch process. It could be due to removal of already exchanged ions in the single batch process. If these ions remained in the system, they might compete again for the ionic sites in the resin and reduced the drug loading. Therefore, during sequential batch process ions got separated by filtration process. This additional step of filtration led to an increase of almost 22% w/w extra drug loading on Purolite® C100MRNS by fourth batch process (Figure 19 D).

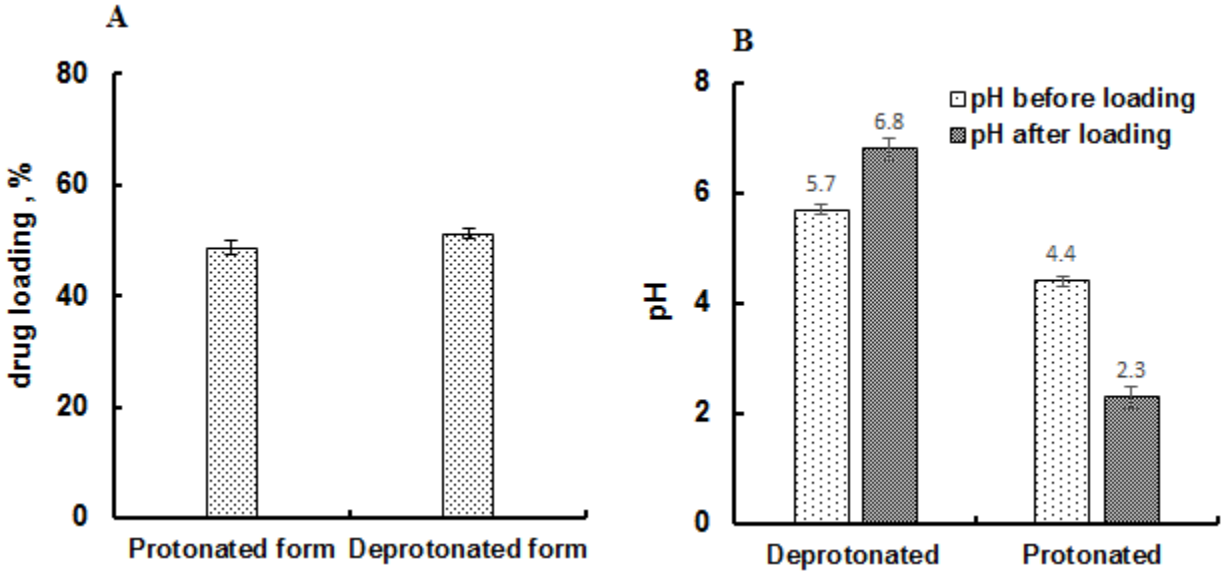

Figure 20. A) Effect of A) protonated and deprotonated forms of Purolite®C100MRNS on the drug loading and B) drug loading on the pH of the loading medium (n = 3).

There was total 3% decrease in drug loading when Purolite® C100MRNS had H^+ ion as counter ion and in protonated state than deprotonated state. It was due to the higher charge density of H^+ ions than Na^+ ions. In the deprotonated state, pH was increased from 5.7 before drug loading to 6.8 after drug loading. This was probably due to the formation of NaCl in loading media during exchange of drug with Na^+ ions of Purolite® C100MRNS (Helfferich, 1962). Whereas, in case of H^+ as counter ion or protonated state, pH decreased from 4.4 to 2.3. The increased acidity might

be due to the formation of acid HCl in the loading media when H^+ ions were exchanged with propranolol ions during drug loading process (Figure 20A,B).

3.1.2 Characterization of resinates

The shifting of stretching frequency of SO_3^{-1} group of resin from 1176.57 cm^{-1}, 1041.55 cm^{-1}, 1010.35 cm^{-1} to the 1170.78 cm^{-1}, 1033.84 cm^{-1}, 1004.94 cm^{-1} in drug-resin complex respectively and broadening of peaks shows the formation of drug-resin complex between –Prop-N^+H Cl^- and R- SO_3^{-1} group of resin (Borges et al., 2005; Li et al., 2007). Drug spectrum showed prominent absorption bands at 1500.03 and 1000.69 cm^{-1}, corresponding to the NH^+ stretching vibration in the amine group of the drug, disappeared (or shifted) in the resinate. In addition, new absorption bands emerged around 750.89 cm^{-1} and 900 cm^{-1} in the resinate spectra. In comparison with certain absorption bands around this wavelength position, the distinct increase in intensity of the new absorption bands in the resinate spectra indicated, they were not usual absorption bands associated with either resin or pure drug. The formation of new ionic bonds between propranolol HCl and Purolite® C100MRNS would be expected, in emergence of additional absorption bands or alterations in wavenumber position in resinates. The ionic association was referred to as a salt bridge, like hydrogen-bonding effect, the degree of the ionic interaction, closely related to the donating and accepting ability of an ion pair. It ultimately affected the NH^+ stretching. As the ionic association increases, the NH^+ stretching of propranolol decreased and subsequently shifted to a lower frequency and vice versa.

With 75% w/w drug loading the shifting and broadening of peaks was bit conspicuous as compared to drug-resin complex made by single batch process, where drug loading was 17% low. In triple batch process maximum ionic sites of resin were almost fully occupied with propranolol than single batch process, where some ionic sites remained un-occupied due to low drug loading. (Figure 21).

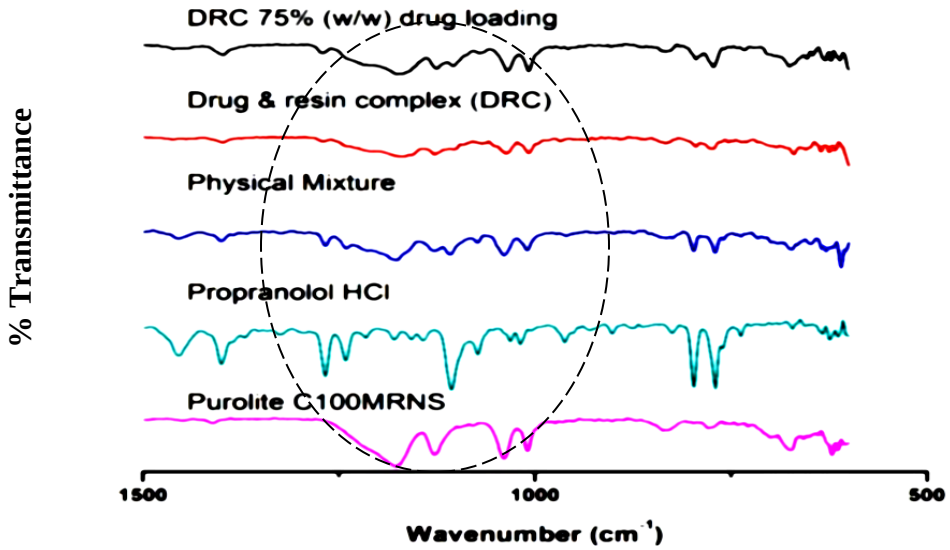

Figure 21. FTIR Spectrum of resin, drug, drug: resin physical mixture and drug-resin complex with 75% w/w drug loading.

The mean particle size of resinates increased to 17.39 ± 2.5 µm after drug loading. It might be due to the expansion of resin matrix after drug loading, as resin expands gradually from 20% to 75% drug loading and this expansion was irreversible. As even after the drug release, resin remained expanded (Boyd et al., 1947). The meaning thereby, mean particle size of resin remains constant 69.53 µm as compared to actual size 52.14 µm. The hydrated drug molecules form shells inside the structure of resin matrix with ionic sulphonic groups and led to the expansion of resin structure (Figure 22).

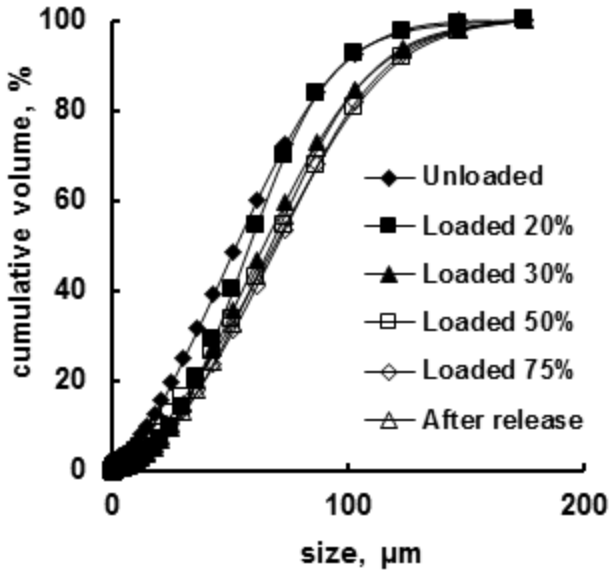

Figure 22. Cumulative volume distribution of resinates before and after drug loading with respect to mean particle size of unloaded and loaded resinates before coating (n = 3).

Effect of drug loading on the swelling, loss of moisture and appearance was investigated. The drug loading was also related to the swelling of the resin during batch process. Purolite® C100MRNS swelled by 22% and 30% in unloaded and loaded form respectively. The total moisture contents were removed in total 4 minutes. The initial quick loss of moisture was happened in the first minute. Then gradual increase of moisture loss was taken place and it was 10% for the unloaded and 6% for the loaded ion exchange resin. The lower moisture of the loaded resin was probably due to the occupancy of ionic sites with drug molecules and decreased the number of free ionic sites of drug loaded ion exchange resin (Figure 23A, B). The ion exchange resin appeared to be hollow from inside and with well-defined boundary in their swelled form under microscopic examination (figure 23 C, D). The hollow structure of ion exchange resins from inside was might be due to the increase of pore size upon expansion of resin matrix during swelling.

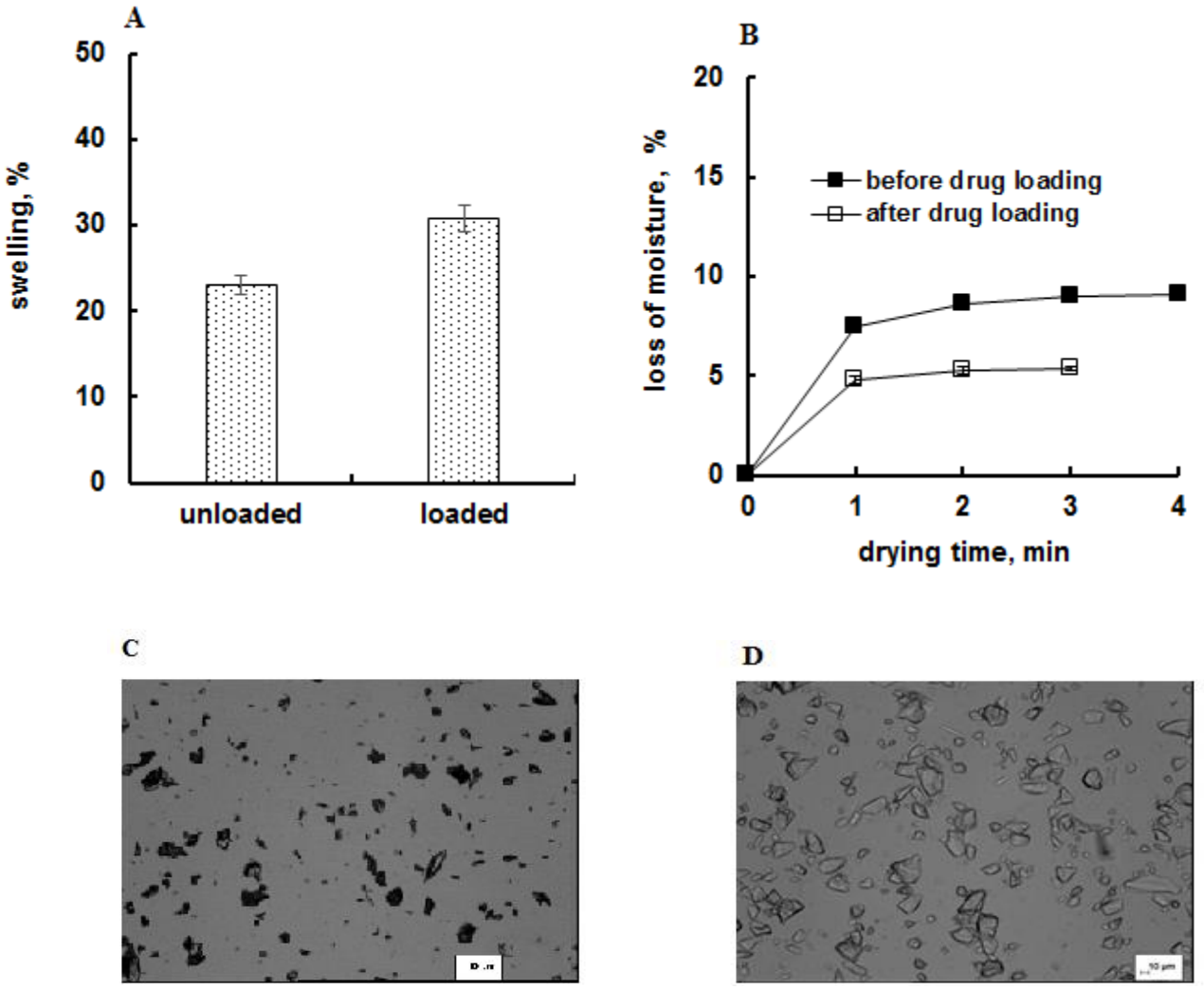

Figure 23. Effect of drug loading on A) swelling of the resin B) Kinetics of moisture loss and C) microscopic image of the resin before swelling and D) after swelling.

3.1.3 Drug release from uncoated and coated resinates

The drug release from uncoated resinates was performed in 0.1N HCl and sodium phosphate buffer pH 6.8. The drug release was incomplete and only 56% of the drug was released in 0.1N HCl and 65% in phosphate buffer pH 6.8 (Figure 24). The incomplete release of drug from uncoated resinates was probably due to the ionic equilibrium between drug and exchanging ions in the release medium. Moreover, less release in 0.1 N HCl was probably due to the utilization of HCl on two ways, it formed the propranolol HCl on one side and get dissociated the drug from resin ionic sites on other side by providing H^+ ions. Similar findings were observed by (Vuorio et al.,

2003). The incomplete release of drug from the drug-resin complex from uncoated resinates was probably due to the strong nature of the complex or non-availability of desired concentration of ions in the release medium to break the complex during drug release.

Approximately, 95% drug release was achieved, when 22 g NaCl was added into the 0.1N HCl medium (Figure 25A). It supported the second possibility of non-availability of desired concentration of ions in the release medium to break the complex. Nevertheless, 5% less release depicted the strong nature of complex or other hydrophobic interactions of drug inside or outside surface of ion exchange resin.

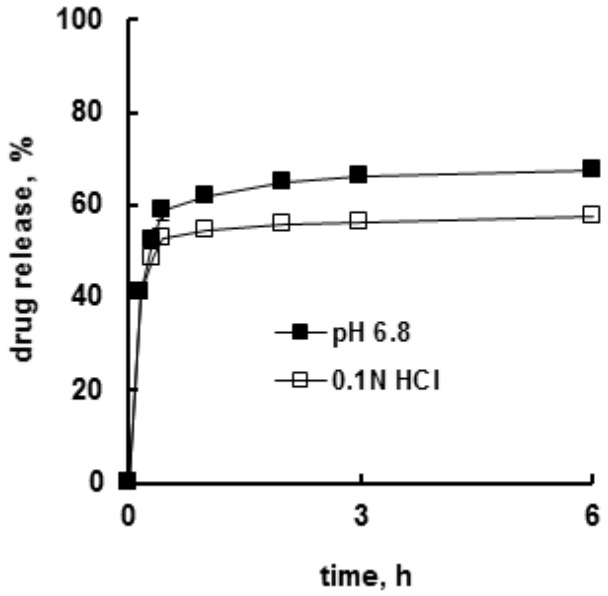

Figure 24. Drug release from uncoated resinates in 0.1 N HCl and 6.8 pH sodium phosphate buffer.

Irrespective to the release medium, with increasing NaCl concentration of the medium, drug release was increased. This could be due to the increased concentration of ionic strength of medium, to dissociate the drug from the ionic sites of the resin.

On the other hand, there was gradual increase of drug release till maximum 92% in pH 6.8 when simulated with 5.8g of NaCl to 17g NaCl. The total 372 mM of different ions (Na^+, OH^-, Cl^-, H^+, PO_4^{-3}) in 6.8 sodium phosphate medium released the same amount of drug which was released by 500 mM of HCl simulated with NaCl (H^+, Na^+, Cl^-). It could be due to the nature of higher affinity

of anionic ions (OH^-, PO_4^{-3}, Cl^-) for the propranolol to get dissociate it from the ionic sites of resin (Figure 25B).

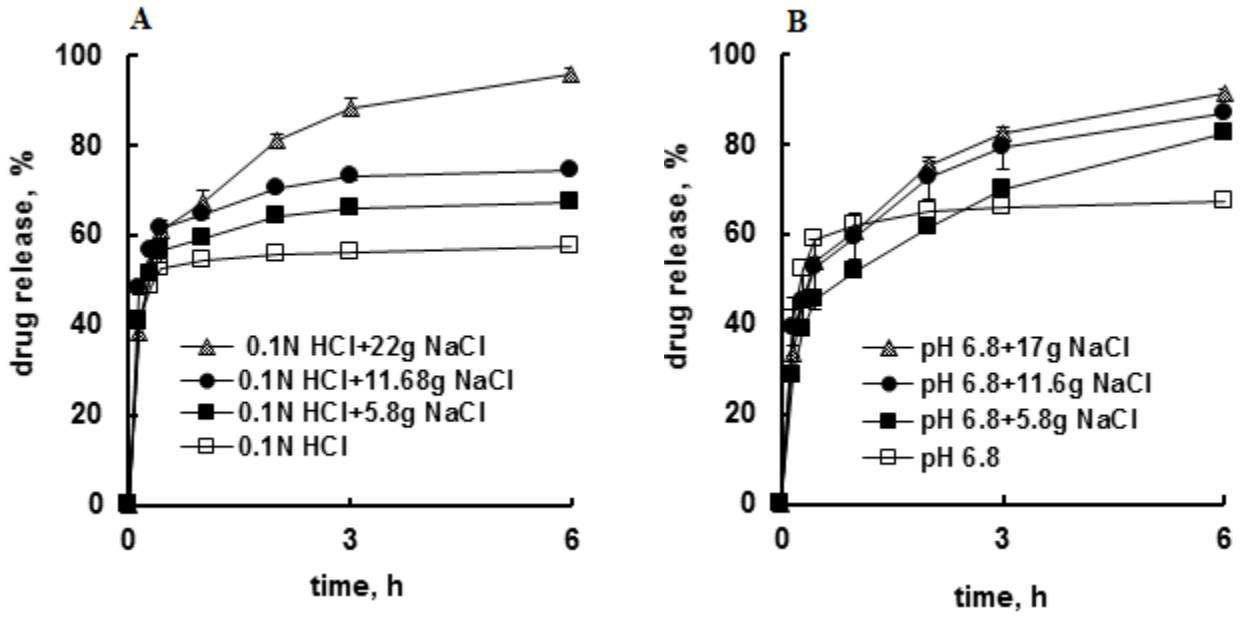

Figure 25. Effect of NaCl on A) the drug release from uncoated resinates in 0.1 N HCl and B) in pH 6.8 phosphate buffer.

In order to control the rapid drug release, resinates were coated with water insoluble, swellable polymer Eudragit® NE 30D. During coating process, there was an increase in particle size, which was due to the liquid bridges and nucleation of micro particle size of resinates 94.48 µm. It increased the size of coated resinates and led to the granulation process (size enlargement). During coating process both coating and granulation took place simultaneously. For every 10% coating level, there was an average increase of 69.64 ± 6.85 µm particle size. This result was similar with the findings by (Torres et al., 1998). Wherein, particle size of terbutaline–resin complex microcapsules increased with increasing concentration of the coating polymer. For total 15% coating level (% average weight gain) mean particle size increased from 94.48 ± 1.5476 µm to 213.22 ± 1.1548 µm which further grew up with 25% to 35% coating level. For maximum 35% coating level, the average particle size grew up to 357.51 ± 2.5789 µm which exceeded the USP

limit 50-250 µm for liquid controlled release formulations. In liquid formulation, bigger particle size gives the mouth feel to the patients and contributes in patient's incompliance. But drug release was controlled with only 15% coating level of the resinates. The maximum increase of particle size was up to 213.22 ± 1.5467 µm (Figure 26 A, B).

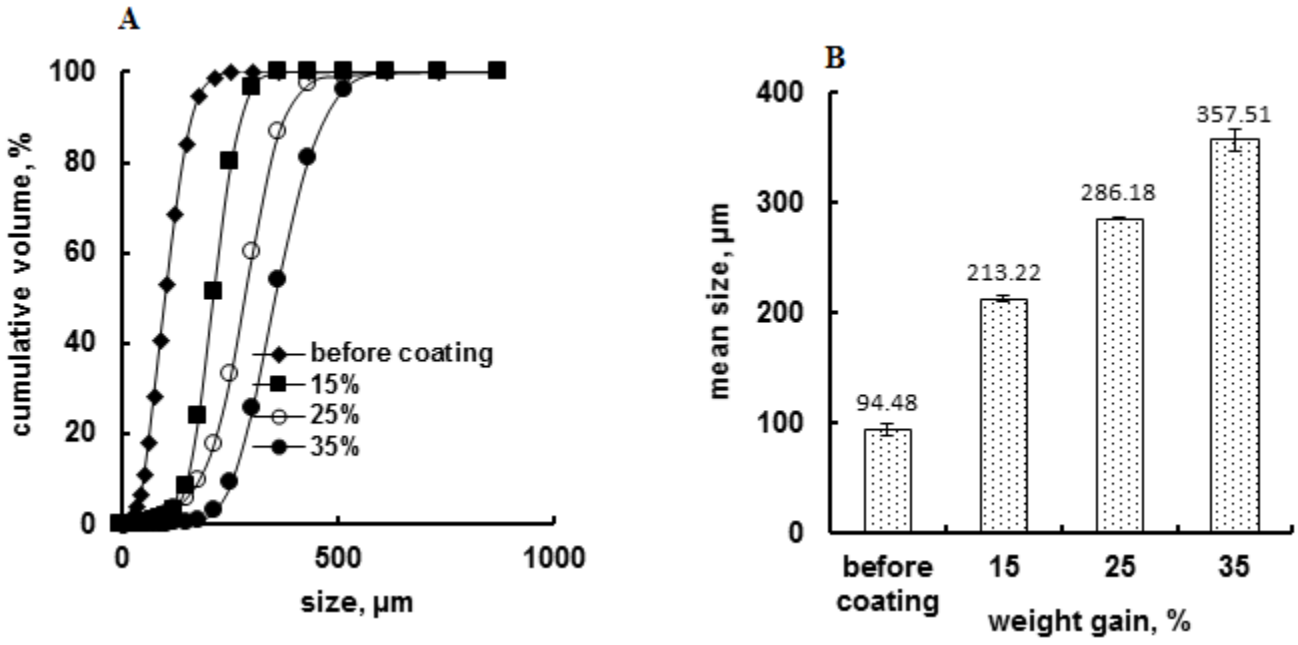

Figure 26. A) Effect of coating level on A) cumulative volume distribution and B) mean particle size of resinates (n = 3).

In addition, drug release from coated drug: resin complex was studied. There was no drug release in milli-Q® water even for 24 hours due to non-availability of counter ions in the media. Similar results were reported in literature (H. Ichikawa et al 2001). However, the drug release was significantly lower in 0.1N HCl than pH 6.8 sodium phosphate buffer (Figure 27A). Unlike the uncoated complex, the drug release was unchanged with an additional layer of KCl and NaCl before actual coating on resinates (Figure 27B). In pH 6.8 phosphate buffer, 72.5mM strength of (small ions K^+, Cl^-, OH^-, PO_4^{-3} and Na^+) used to dissociate drug from resin as counter ion. Similar findings were reported in case of alginate matrix systems with the additional coating of

polycationic polymers (Xu et al., 2003; Zarate et al., 2011). However, drug release was significantly higher in pH 4.5 when 200 mM NaCl was added than pH 6.5 added with 100 mM NaCl and pH 1.6 added with 30 mM NaCl. The faster drug release in pH 4.5 (sodium acetate + 200 mM NaCl) might be due to higher concentration of ionic strength of Na^+ in the buffer or release medium (Figure 28A). On the other hand, the release of highly soluble drug, tramadol HCl and diltiazem HCl, was faster and complete with same coating level than the soluble propranolol HCl (Fig. 28B).

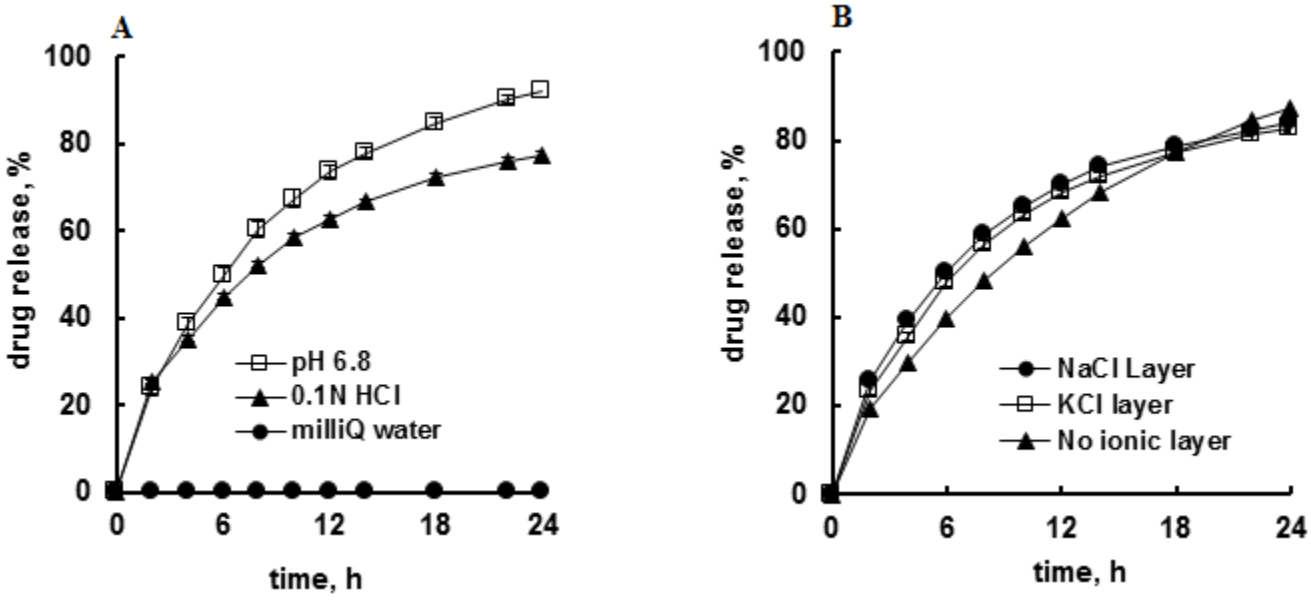

Figure 27. The effect of A) pH of the medium and Milli-Q® water B) an additional layer of salt and no ionic layer coated with Eudragit® NE 30D 15% c.l cured at 60°C for 12 h.

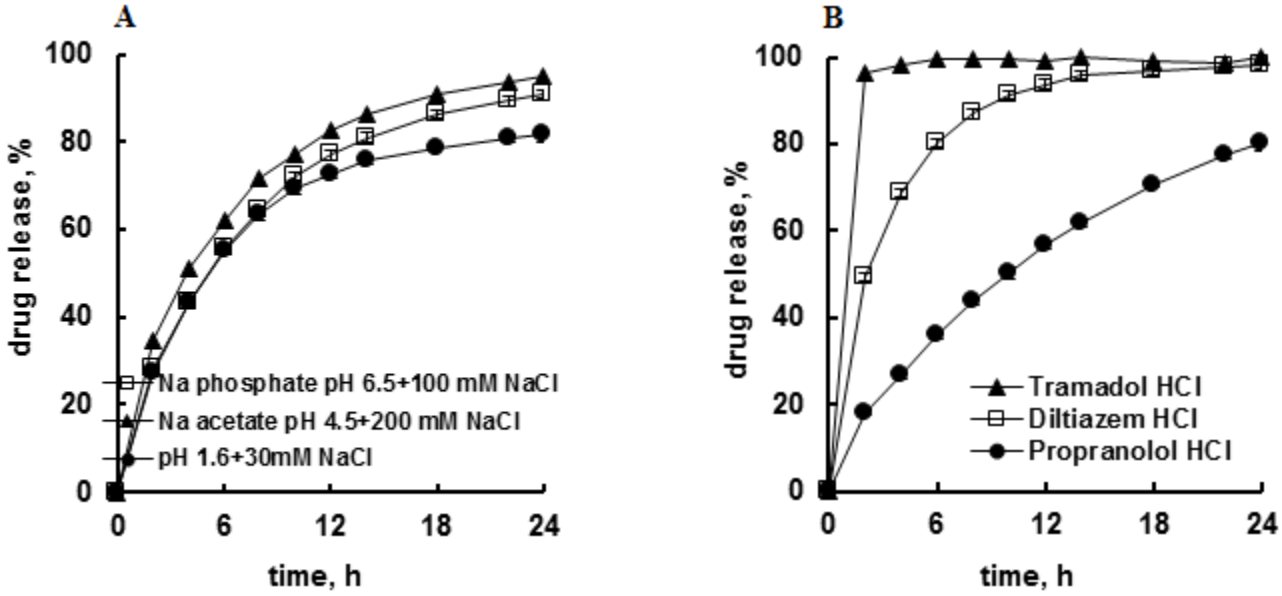

Figure 28. The effect of A) pH and NaCl and B) drug solubility on the release from coated resinates with Eudragit® NE 30D 15% c.l cured at 60°C for 12 h.

The drug release was significantly higher in 200 mM and 300 mM NaCl than 100 mM NaCl. It might be due to the increased ionic strength of release medium than 100 mM NaCl (Figure 29 A). The drug release was almost similar for investigated range of particle sizes 160-250 µm, 250-315µm but slower and incomplete for the particle size 315-425 µm. It could be due to the increased diffusion path length for the drug after being dissociated from the ionic sites of the Purolite® C100MRNS (Figure 29 B). However, drug release was slower with increased drug loading on the resin for investigated range of 20% w/w to 75% w/w drug loading. The drug release from ion exchange resin was always equilibrium dependent. There was always an equilibrium between counter ion and associated drug in drug-resin complex. So, higher drug loading might shift the equilibrium towards un-dissociated form, which ultimately made the drug release slow and incomplete (Figure 29 C).

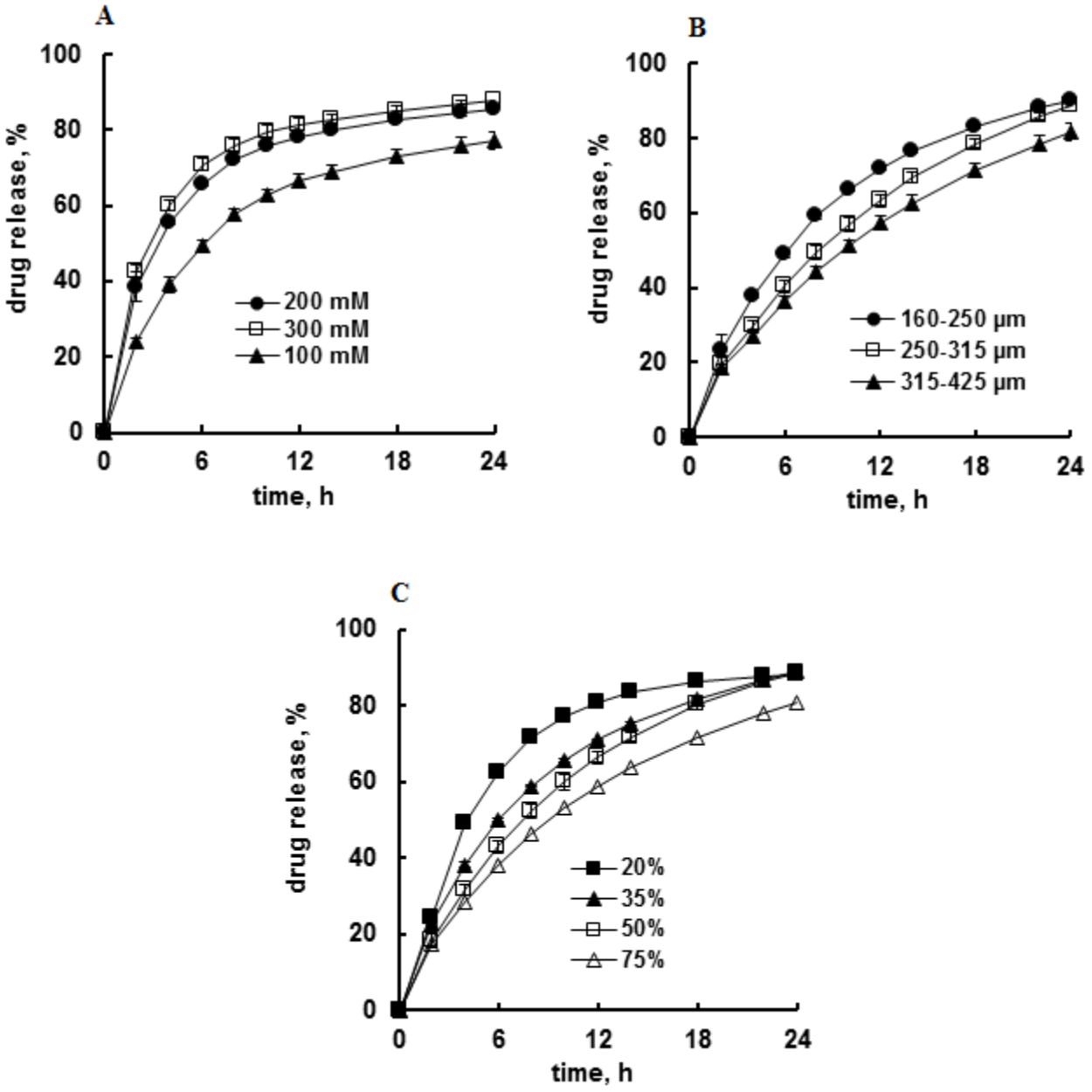

Figure 29. Effect of A) the ionic strength (160-250 µm and 20% w/w drug loading), B) particle sizes (20% w/w drug loading) and C) drug loadings (160-250 µm) on the release from complex coated with Eudragit® NE 30D 15% c.l in phosphate buffer pH 6.8.

Different conditions of curing, presence of talc and coating levels were evaluated and investigated. There was a fast release of drug from coated resinates in un-cured form. It might be due to incomplete film formation. But drug release was decreased with cured resinates and slowest

release was observed when curing was done at 40 ºC and 75% RH and 80 ºC. With increased humidity, there could be an extra plasticization effect, which decreased the drug release (Osterwald, 1985; Sun et al., 1999). With addition of 30% talc in the coating solution, there was a fast drug release it could be due to reduced amount of polymer with an addition of talc in the coating solution. During drug release talc particles leached out quickly and making the polymer film more permeable and led to faster release as compared to the system where no talc was involved (Li et al., 1990; Erdmann et al., 2000) (Figure 30 A, B). There was a fast and complete release when resinates were coated only with 5% coating level (% weight gain). The drug release was controlled with increasing coating level in the formulation. With 15% to 20% coating level, it was presumed that all sides of resinates were completely covered by coated polymer and underwent uniform swelling during drug release. With increase of the coating thickness, drug release was slow even incomplete with higher coating level. It was probably due to the increased diffusion path length of drug after being dissociated from ionic sites in the ion exchange resin. (Figure 31).

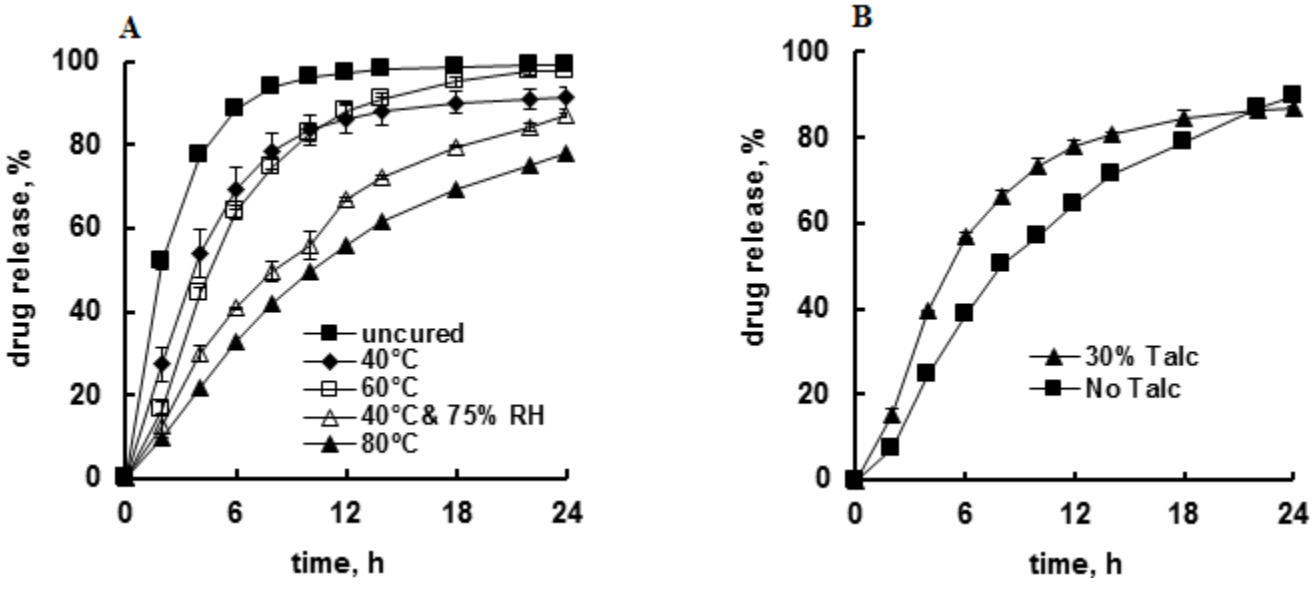

Figure 30. Effect of A) curing conditions and B) anti-tackiness on propranolol HCl release form resinate coated with Eudragit® NE 30D 15% c.l.

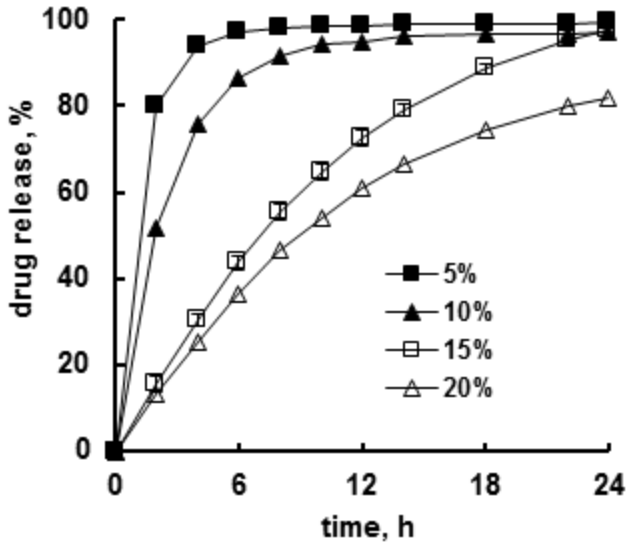

Figure 31. Effect of different coating levels on propranolol HCl release in pH 6.8 sodium phosphate buffer.

The resinates were wet granulated with ethyl cellulose (ethocel c.P 100) and HPMC E5. There was no effect on drug release when same concentration of both binders was used during granulation process. As release profile was similar for formulations prepared with 15% w/w of each HPMC E5 and ethyl cellulose (ethocel c.P 100) during granulation with both binders and in the formulation without granulation. The only difference observed was the hardness of granules when HPMC E5 and ethocel 100 c.P were used in higher concentration than 20% w/w. The granulation only made the flow of particles better in the mini-glatt during coating process. The ethocel 100 c.P was taken as binder and release retardant when used with combination of HPMC E5. But it did not retard the release significantly (Figure 32A). Furthermore, drug release was similar with 5%, 10% use of Tween® 80 in the coating formulation as compared to the formulation without Tween® 80. It might be due to its talc dissolving property in the coating formulation without being had any influence on the release of the drug from the system where drug was released with help of counter ions in the system of ion exchange resins (Amighi and Moes, 1997, Bajdik et al., 2003) (Figure 32B).

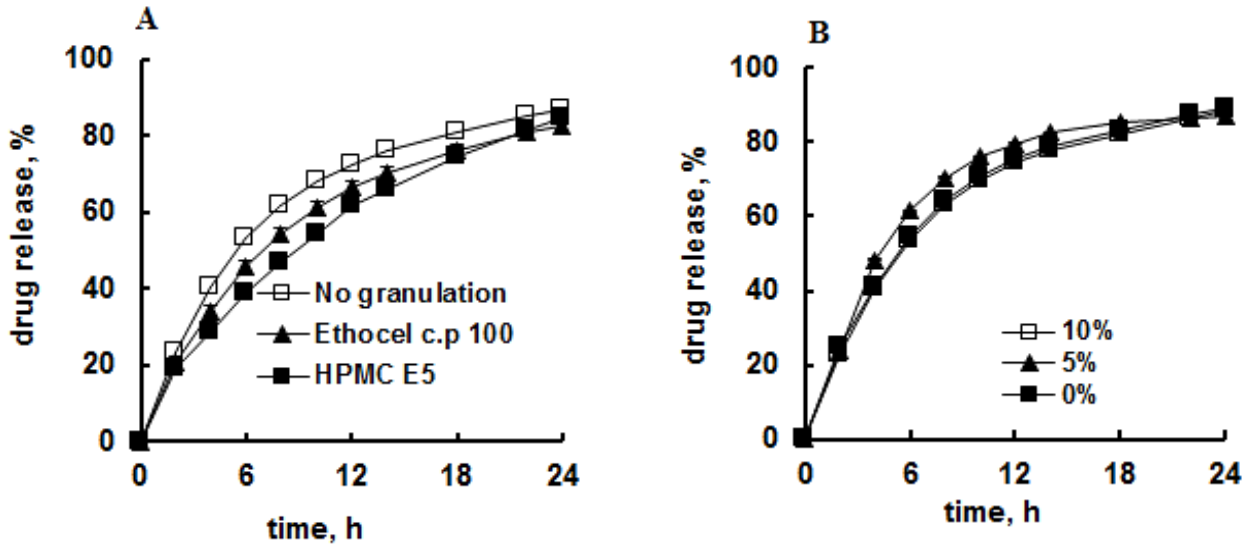

Figure 32. Effect of A) binders for granulation and B) Tween® 80 in the coating solution on propranolol HCl release from coated resinate with Eudragit® NE 30D 15% c.l. in phosphate buffer pH 6.8.

It had been observed that the drug release from drug–resin complex and its microcapsules was controlled by three possible mechanisms (Gyselinck et al., 1982). These were (1) the exchange reaction between drug and the counter-ion (present in the release medium) and drug molecules in the resinates (drug-resin complex). (2) The release of drug through the pores within the resin structure with divinyl benzene (DVB) crosslinking (particle diffusion control). (3) The release of drug across the thin layer of coated polymer around the resinates (membrane diffusion control). However, particle diffusion played a pivotal role in the release of drug from drug–resin complex (Irwin, 1987). The time for total 20%, 50% and 80% release were significantly lower for ion exchange resin, having less cross- linking i.e. 4% than those having double (8%) DVB cross linking (Table 11). The time for 80% release of Dowex® 50W was only 5 hours and it was lower than the time for Purolite® C100MRNS which was almost 18 hours. When resinates of both ion exchange resins were coated with 15% coating level of Eudragit® NE 30D cured at 60 ºC for 12 hours for same drug loading of almost 20% w/w for both resins. Similar findings were reported in literature by Atyabi and his co-workers (Atyabi et al.,1995).

Table 11. Effect of divinyl benzene cross linking (4% and 8%) on drug release from coated resinates

Release time (h)	Dowex® 50W	Purolite® C100MRNS
	4% DVB	8% DVB
t20	1 ± 0.12	4 ± 0.13
t50	3 ± 0.25	9 ± 0.35
t80	5 ± 0.34	18 ± 0.12

Contrary to the fast drug release with HPMC E5 when mixed in the coating formulation to disperse talc homogenously in the coating solution. There was similar drug release with 0%, 5% and 10% HPMC E5 (Figure 33A). It might be due to the two reasons. (1) 10% HPMC E5 was not sufficient enough to create pores in the coating layer of flexible polymer Eudragit® NE 30D when used in the coating formulation with said concentrations. (2) The non-dependent nature of drug release on pores in coating layer. As drug release was only affect by ionic strength of release medium and divinyl benzene cross (DVB) linking inside resin. On the other hand, no significant effect of granulation fluid was observed as the release profile for all three formulations was similar when different ratios of alcohol and water were used as granulation fluid (Figure 33B).

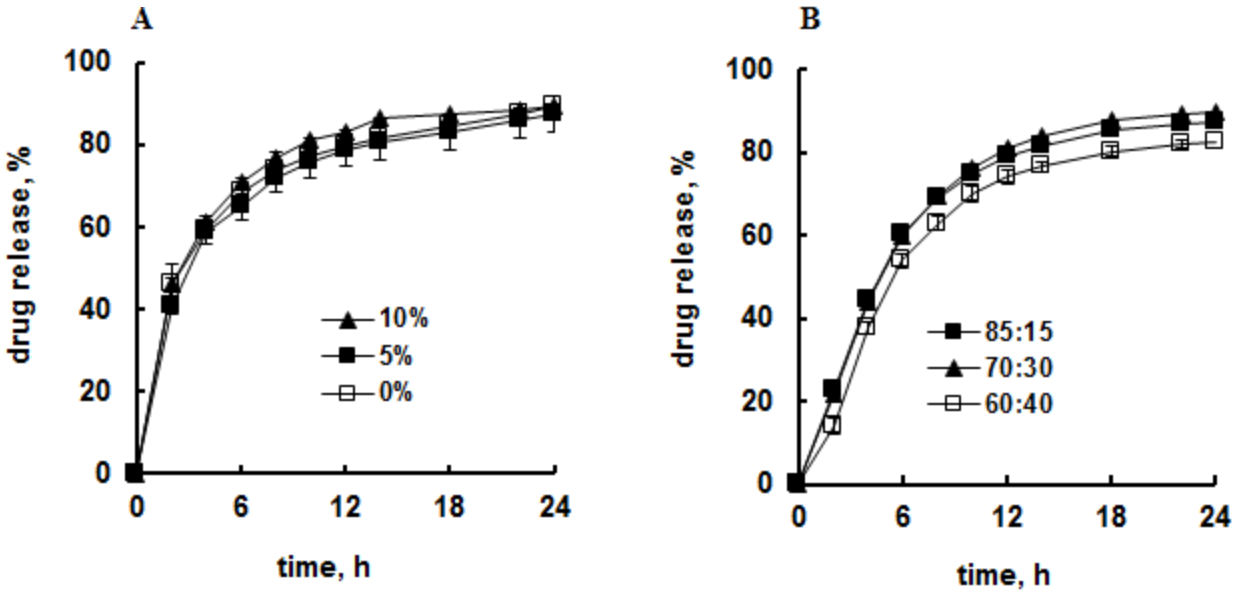

Figure 33. Effect of A) HPMC E5 in coating solution and B) granulation fluid (alcohol: water) on propranolol HCl release from coated resinate coated with Eudragit® NE 30D 15% c.l.

3.1.4 Stability Studies

The formulation was stable over one month when tested for its release profile at accelerated conditions 40ºC/75% RH and optimum conditions 25ºC/60% RH defined by the ICH guidelines. The drug release was slight faster on first day, but similar for one week to one month. When formulation was tested at 40ºC with enhanced humidity 75% RH and 25ºC with relative humidity 60% RH (Figure 34). It could be due to the additive curing effect of the coated polymer with increased humidity. The similar findings were reported by (Adeyeye et al. 2005), where release of diclofenac–resin microcapsules in methylcellulose suspensions decreased with increased temperature due to polymer relaxation, which sealed the drug within the matrix.

Therefore, the release profiles of coated resinates of propranolol at different storage temperatures, humidity and times were equivalent to that of coated resinates tested at 2-8 °C after reconstitution, leading to the conclusion that there was no effect of the storage time, temperature and humidity over the release profile of the propranolol–resin reconstituted powder over one month.

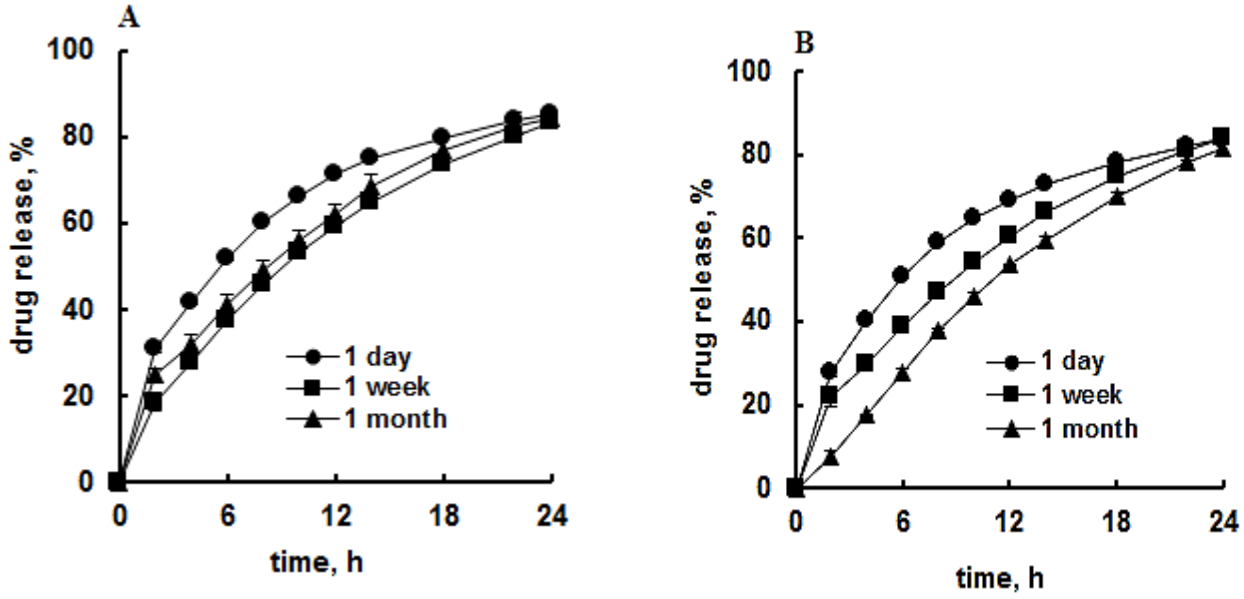

Figure 34. Effect of storage conditions A) 40 ºC/75% RH and B) 25ºC/60% RH on propranolol HCl release from (160-250 µm, 20% w/w drug loading) resinate coated with Eudragit® NE 30D 15% c.l.

X-ray diffraction studies were undertaken to investigate the crystalline nature of the drug. The drug showed characteristic crystalline peaks at 2θ = 7.5, 10.2, 13.5, 20, 22.5 and 25° and in physical mixture with resin. While drug-resin complex, exhibited amorphous characteristic with absence of crystalline peaks. The disappearance of the crystalline peaks of drug shows that upon complexation with resin, drug became part of resin. It was molecularly attached to the binding sites of the resin within the resin matrix. Similar findings were also observed by Vuorio and his co-workers (Vuorio et al., 2004). Moreover, the drug-resin complex was stable over one day at room temperature and one week when heated up to 60ºC (Figure 35).

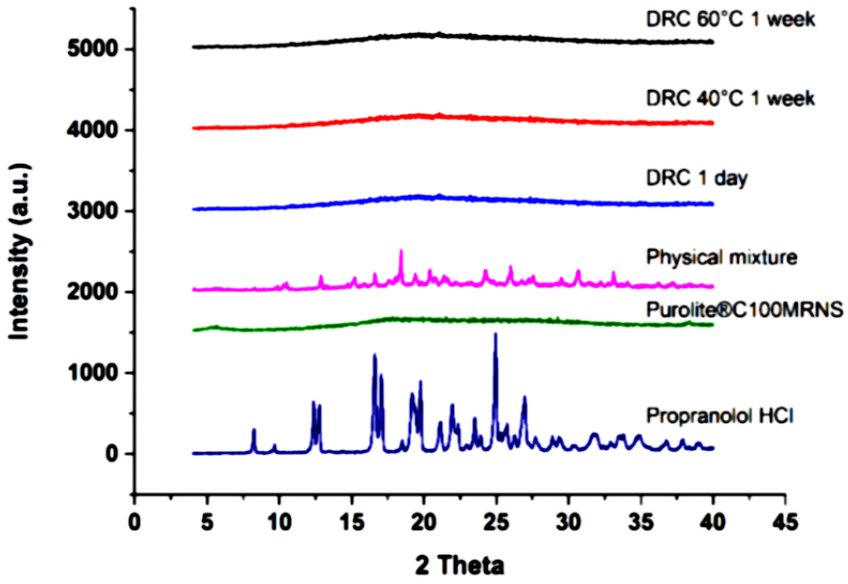

Figure 35. Powder X- ray diffractogram of propranolol HCl, Purolite® C100MRNS, physical mixture, drug-resin complex (DRC) at different time interval and temperature.

As drug always forms a complex with resin, to establish the interaction of quaternary ammonium group of polymers with resin ionic sites of the resin, the complex was coated with Eudragit® RS 30D and Eudragit® RL 30D blend with the ratio of 7:3 w:w. The drug release from the drug-resin complex coated with the blend was similar to that coated with Eudragit® RS 30D alone (Figure 36). Which meant, there was no additional effect of 5% extra quaternary ammonium group of Eudragit® RL on drug release from resinates. It was probably due to the flexibility of Eudragit® RS 30D which masks the net effect of Eudragit® RL 30D. Most recently, a similar results were reported in the terbutaline-loaded resinates coated with Eudragit RS: RL polymers by (Cun˜a et

al., 2000). As established, that drug was released by dissociation from ionic sites inside the resin matrix. But drug release from Eudragit® RS 30D, Eudragit® RL 30D and Kollicoat® SR 30D used to be sigmoidal from the matrix and reservoir systems (Ichikawa., et al, 2001).

The chloride counter ions (Cl^-) of the quaternary ammonium groups were exchanged with the anionic buffer species (PO_4^{-3}, OH^-) in the release medium. The water uptake of the coated beads correlated well with the drug release (Sun et al., 2001; Lehmann, 1986; Watts et al., 1991; Bodmeier et al., 1996). No lag phase was observed, when drug-resin complex was coated with Kollicoat® SR 30D even during one-month stability studies. The drug release was also stable over one month at 40ºC/75% RH both from Eudragit® RS 30D and Eudragit® RL 30D blend (ratio 7:3 w/w) (Figure 37 A, B). The similar findings were also observed by (Ichikawa., et al, 2001). Wherein, drug-loaded ion exchange resin with a Eudragit® RS 30D coating, the coating material necessary for prolonged release was only 3% w/w based on the weight of the drug-loaded ion exchange resin. Consequently, it was made stable for one week with high drug content of 54% w/w in the resin. The drug release from coated resinates with Eudragit RS 30D 15% c.l. cured at 60°C for 12 h was slightly increased under accelerated storage conditions (Figure 38).

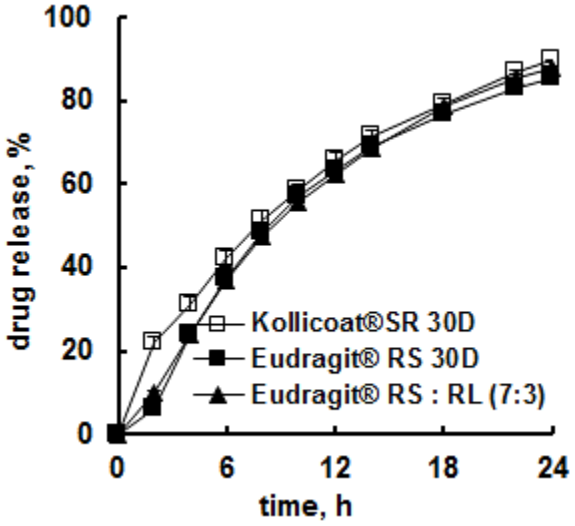

Figure 36. Effect of different polymers on propranolol HCl release from (160-250 µm, 20% w/w drug loading) resinate coated with Eudragit® NE 30D 15% c.l.

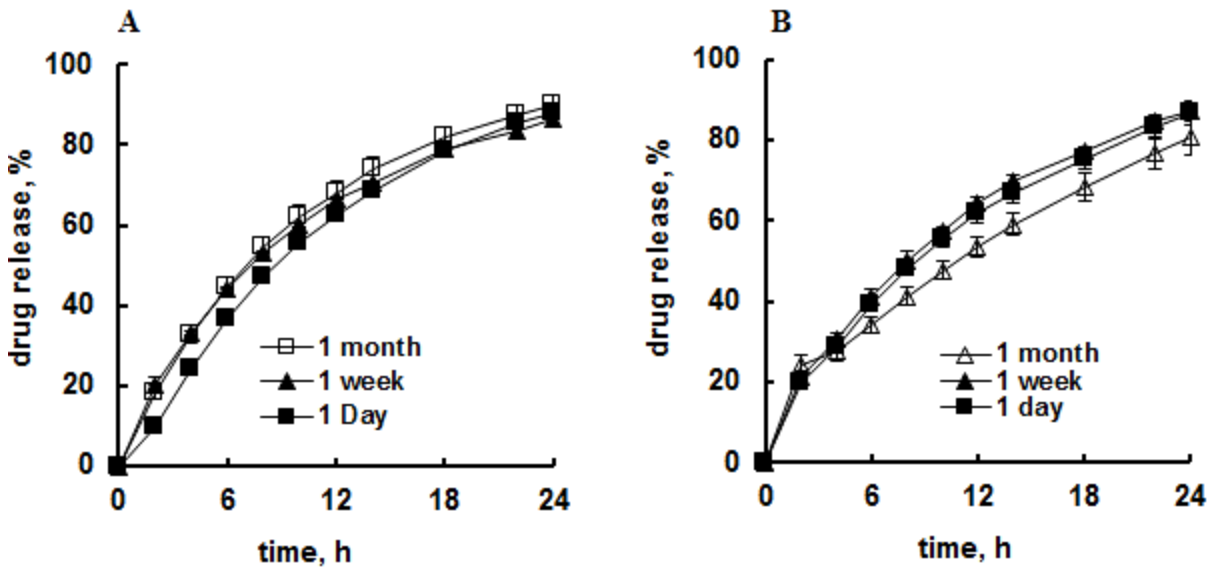

Figure 37. The effect of storage conditions (40ºC/75% RH) on the drug release from resinate coated with A) Eudragit® RS:RL c.l. 15% (7:3) and B) Kollicoat® SR 30D c.l. 15%.

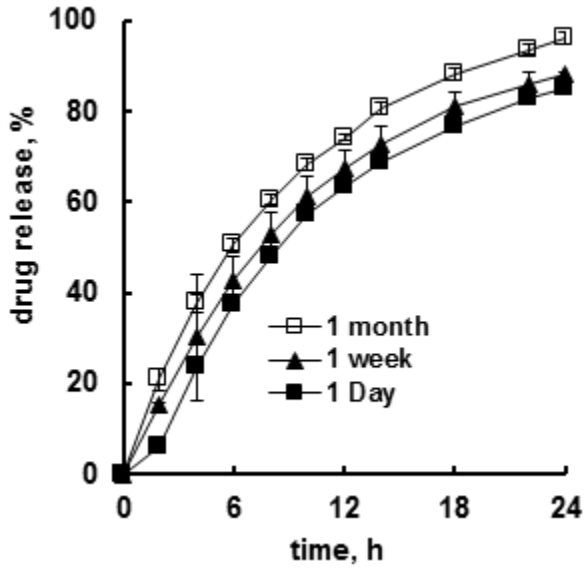

Figure 38. The effect of storage conditions (40ºC/75% RH) on drug release coated with Eudragit® RS 30D 15% c.l. and cured at 60°C for 12 h for.

3.1.5 Drug leaching and stability studies over one week after reconstitution

The formulation was mixed with extra soluble diluent granules of HPMC E5 of size 800 µm to aid reconstitution. The soluble granules of HPMC E5 were quite separately visible in macroscopic image of the formulation. The extra soluble granules upon contact with water immediately turned into suspending medium for reconstitution. The nature and concentration of soluble granules determined the final redispersibility, sedimentation and viscosity of the reconstitutable suspension (Pongjanyakul et al., 2005). The formulation after reconstitution clearly showed suspended resin particles without any agglomeration, which ultimately ensures the uniform dose after reconstitution (Figure 39 A, B, C, D).

The reconstitutable granules were prepared with different grades of HPMC. The particle size before reconstitution of the formulation was 212 µm. After reconstitution particle size was increased to 218 µm. The 2% increase in particle size is due to the swelling behavior of either coated Eudragit® NE 30D or the resin matrix itself. The coated resinates maintained their independent shape and geometry without being agglomerated with each other which confirms the stable nature of the formulation. Moreover, pH of the formulation was varied from 7.3 to 7.4. This pH showed the almost neutral nature of the coated particles suspended in the HPMC medium. Final dose of the formulation was 120 mg/ml (Table 12). Moreover, release profile of the formulation after reconstitution when stored at (2 – 8 °C) was stable over one week (Figure 40). In a nut shell, the medium taken for reconstitution does not affect the release profile of the formulation. It was similar with the findings of (Obitte et al., 2009) regarding suspensions of amoxicillin/clavulanic acid stored at (2 - 8°C) after reconstitution over one month.

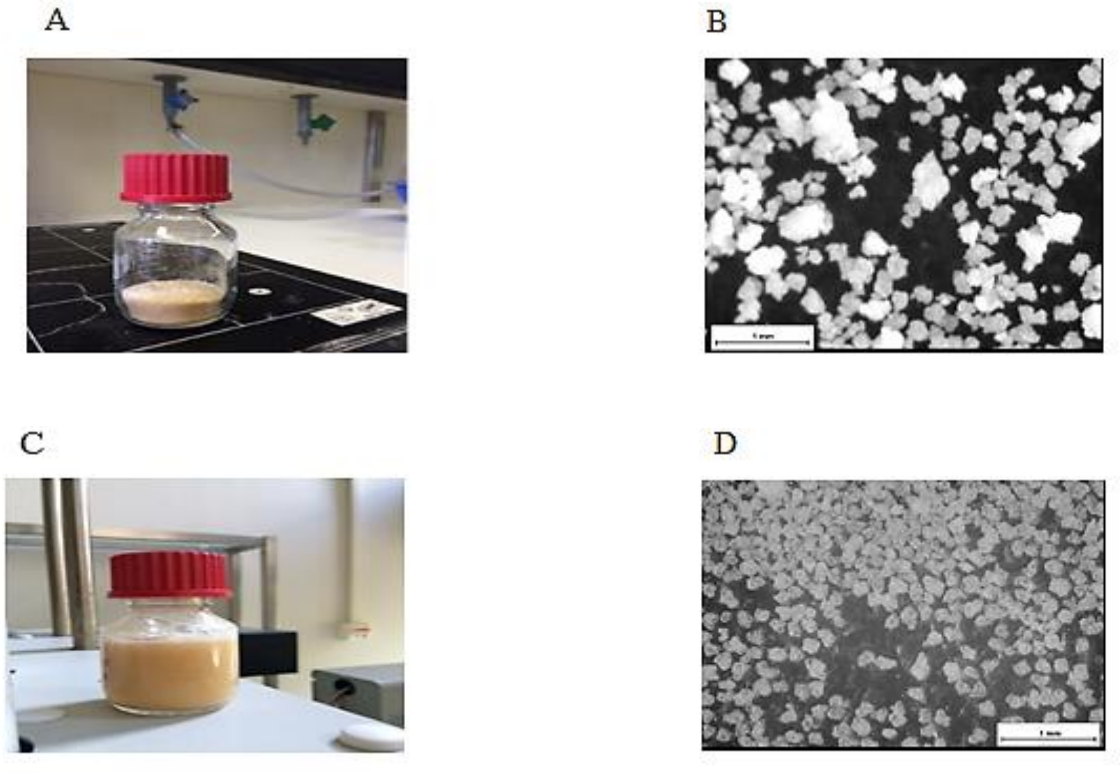

Figure 39. A) Formulation before reconstitution B) macroscopic image of formulation before reconstitution C) formulation after reconstitution D) macroscopic image of formulation after reconstitution.

Table 12 Summary of the formulation before and after reconstitution

Coated resin	**pH (0 day → 1 week)**	**Particle size (µm) 1 week**	**Dose (mg/ml)**
before reconstitution	---	212.11 ± 3.98	----
after reconstitution	7.3 ± 0.1 → 7.4 ± 0.1	218.15 ± 1.25	120 ± 8.75

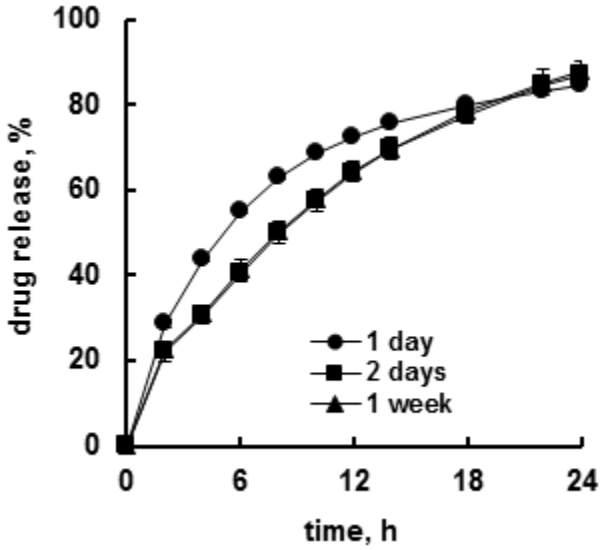

Figure 40. Effect of storage conditions at 2-8 °C after reconstitution on the drug release in pH 6.8 sodium phosphate buffer.

As reconstitutable powder is always taken with water, drug leaching in water had to be undertaken for one week. Less than 1% drug was leached in milli-Q® water. The 1% drug leaching was observed in 5 mM to 10 mM NaCl and KCl over one week. When leaching studies of the formulation were investigated till one week. However, drug leaching was slightly higher but not significant ($p \geq 0.05$) on 3rd day in 10 mM of NaCl and KCl as compared to 5 mM NaCl and KCl (Figure 41). It was probably due to attainment of equilibrium between un-dissociated and dissociated drug from the resin. It indirectly established the good drug retaining tendency of Purolite® C100MRNS. As drug retention in the resin after ionically bind with its ionic sites based on the pore size of the resin structure 12.54 Aº (Bilandi et al., 2014).

The pH of the leaching media varied in the range 6.8 ± 0.2. The conductivity of 5 mM KCl and NaCl was 667.5 µS/cm and 659.33 µS/cm respectively. On the other hand, conductivity of leaching medium of 10 mM KCl and NaCl was 1513.9 µS/cm and 1229.67µS/cm respectively. Both drug and resin remained ionized in the said pH range but exhibited drug leaching was less than 1% for both 5 and 10 mM KCl and NaCl over one week after reconstitution.

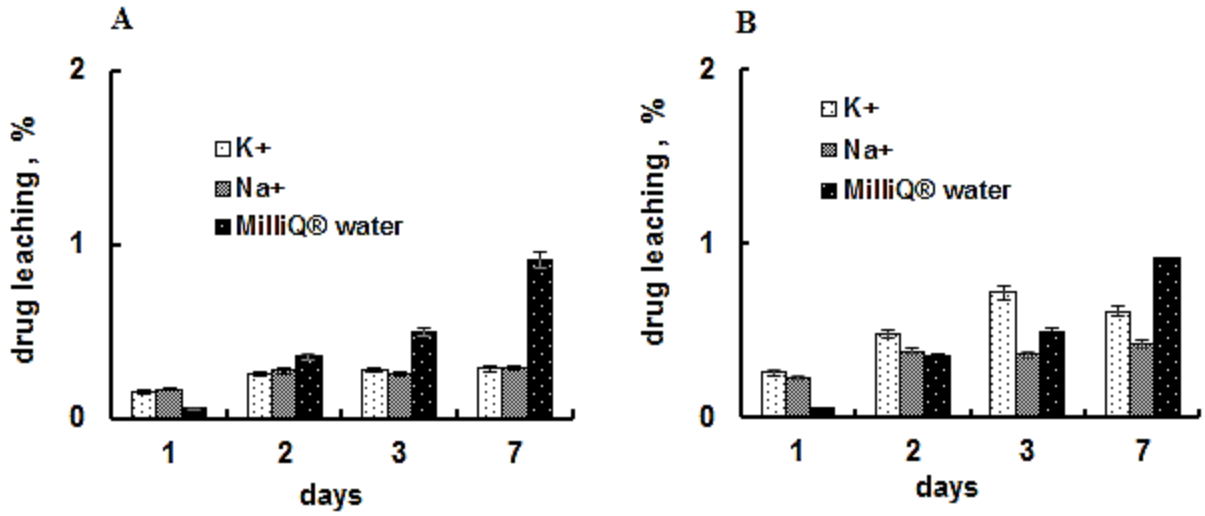

Figure 41. A) Propranolol HCl leaching over one week in A) 5 mM and B) 10 mM of KCl, and NaCl and in Milli-Q® water (n = 3).

3.1.6 Conclusion

A controlled release liquid formulation (reconstitutable powder) of propranolol HCl with high dose was achieved with Purolite®C100MRNS. The release kinetics from coated drug-resin complex was found to be particle diffusion controlled. Moreover, release had linear relationship with degree of divinyl benzene (DVB) cross-linking of the resin. The time for 80% drug release of Dowex® 50W (having 4% DVB cross-linking) was significantly less than Purolite®C100MRNS (8% DVB cross-linking). The drug release was also significantly influenced by thickness of the coating and ionic strength of the release medium. The coated resinates with Eudragit® NE 30D were stable over one month's storage at 40°C/75% RH and 25°C/60% RH. Finally, the sustained release reconstituted powder of propranolol showed chemical stability before and after reconstitution. As release profiles remained unchanged over one week, when stored at 2-8°C after reconstitution. The pH varied over one week was 7.3 ± 0.2. The ion exchange resin Purolite®C100MRNS exhibited significantly higher drug retention as only 1% drug was leached from drug-resin complex in Milli-Q® water. The drug leaching was less than 1% when formulation was treated with 5 mM to 10 mM KCl and NaCl over one week after reconstitution. In summary, Purolite®C100MRNS could be used as a carrier for preparation of a controlled-release liquid formulation, reconstitutable powder dosage form.

3.2 Development of enteric drug delivery system using Amberlite® IR69F (cation exchange resin)

Conventionally, drugs are released from dosage forms with an immediate or extended fashion. However, in present times, pulsatile drug release systems are gaining importance. A pulsatile drug delivery system, able to release the drug after a well-defined lag-time (Bussemer et al., 2001; Ritschel et al., 1994). The delivery of therapeutic agent at site specific to the intestinal region can be accomplished by providing an enteric coating on the solid or liquid dosage forms (reconstitutable powder). The enteric coated products are designed and formulated to release the drug in the upper intestine. These coated products are formulated to remain intact in the stomach. The rationale behind enteric coated formulations is well documented (Wilding, 2000).

The polymers used for enteric formulations are anionic polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit®, cellulose based polymers, e.g. cellulose acetate phthalate, polyvinyl derivatives, e.g. polyvinyl acetate phthalate). In these polymers, there is a functional group which is insoluble in acidic pH and soluble at neutral pH due to ionization and changing to soluble salt form in presence of sodium ions of the release medium of intestine (Dangel et al., 2000).

The liquid-controlled release enteric coated formulations have been a challenge to the formulation scientists. It was due to their stability concerns. To cop out, such challenges, drugs are first ionically complexed with ion exchange resins and then coated with appropriate pH dependent enteric polymer. The USP limit regarding release for such formulations, there is less than 10% drug release as long as the formulation stays in the stomach. The liquid formulations in form of reconstitutable powders has stability issues with respect to pH of the formulation and drug leaching after reconstitution in the carrier vehicle. As per USP limit, drug leaching in the suspending medium should not be more than 5%.

3.2.1 Drug loading

A drug loading of almost 7% w/w was achieved in 24 hours, when particle size of Amberlite® IR 69F was 300-1100 µm. However, drug loading was significantly increased up to 55% when particle size was reduced to 71-160 µm. It was probably due to increased surface area of the resin, which decreased the diffusion path length for the drug to reach ionic sites inside the resin.

Although, 30% w/w drug loading was achieved quickly in the first hour when particle size of resin was 71-160 µm. Moreover, for bigger particle size of 315-630 µm, loading was 28% after two hours which, gradually increased up to 40% in 24 hours of batch process. There was absolutely no drug loading on Amberlite® IR 69F till 2 hours when resin was taken in particle size 300-1100 µm. It might be due to the decreased surface area and increased diffusion path length into the resin for its ionic sites (Figure 42). Similar findings were also observed by Sriwongjanya and his coworkers (Sriwongjanya et al.,1995). The un-milled and milled form of Amberlite® IR 69F were shown in (Figure 43A, B).

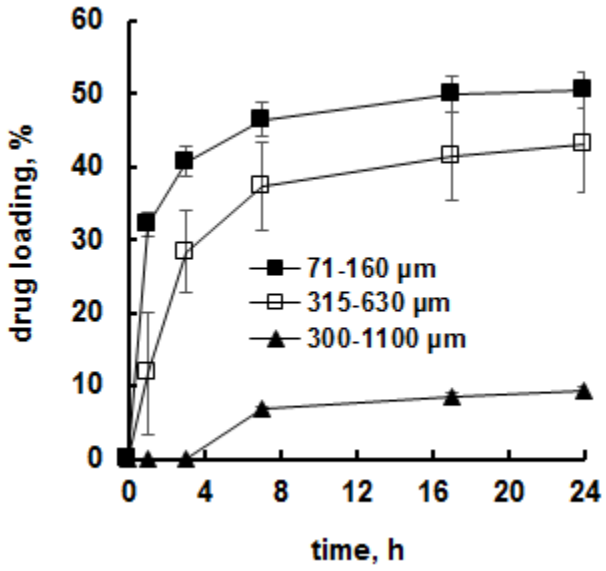

Figure 42. Effect of Amberlite® IR69F particle size on propranolol HCl loading in batch process (n = 3).

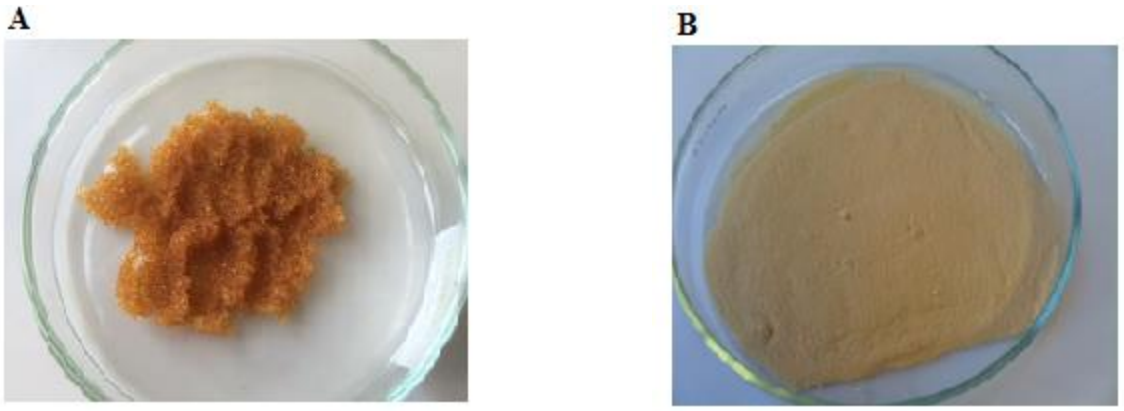

Figure 43. A) Image of Amberlite® IR69F (particle size 300-1100 µm) before milling B) after milling (particle size (45-160 µm).

During single batch process, for maximum drug loading of 52.41 ± 1.22 % w/w, total used ion exchange capacity of Amberlite® IR69F was 2.1 meq/g, when drug and resin were taken in ratio 2:1 w/w. The total 1% drug was adsorbed/attached hydrophobically on the surface of the resin. For this range of drug loading, association efficiency was 55.25 ± 2.64 %, which was further decreased up to 30.46 ± 8.96 % for 3:1 w/w drug and resin ratio. The sharp decrease in association efficiency was probably due to the total increased drug concentration in the system (Guo et al., 2009). The max used ion exchange capacity of Amberlite® IR69F was 2.9 meq/g, when drug loading was 74.93 ± 0.14 % in triple batch process. On the other hand, 1.1 meq/g ion exchange capacity of the resin was utilized when drug and resin were in a ratio of 1:2 w/w. The drug loading was reduced to 32.80 ± 0.07 % (Pongjanyakul et al., 2005). It was might be due to the increased number of ionic sites of resin in the system (Table 13).

The drug loading was independent of stirring speed (150-600) rpm (Figure 44). But it was significantly increased when already competing ions were taken out from the system by filtration. A total 24 % increase in drug loading was observed, from 52% to 76 % in triple batch process. Moreover, drug loading was also found to be independent of pH (2–8). It was probably due to the ionized state of both propranolol and resin at the experimental pH (2–8) during batch process (Figure 45).

Table 13. Summary of drug loading and drug association efficiency for Amberlite® IR69F

No.	Batch process	Drug (mg)	Resin (mg)	Drug :resin ratio	Association efficiency, % + (±SD)	Drug loading		Attached hydrophobically %
						% w/w (±SD)	meq/g	
1		100	100	1:1	94.53±2.41	48.59±0.63	1.8	1
2		200	100	2:1	55.25±2.64	52.41±1.22	2.1	1
3		300	100	3:1	30.46±8.96	46.46±7.68	2.1	1
4	Single	400	100	4:1	29.20±0.16	52.82±1.90	1.5	1
5		100	200	1:2	97.61±0.34	32.80±0.07	1.1	1
6		100	300	1:3	97.76±0.12	24.54±0.03	0.9	1
7		100	400	1:4	95.62±0.98	19.20±0.16	0.8	0.5
8	Double	*345[2]	100		49.67±0.95	67.47±0.41	2.6	0
9	Triple	*378[7]	100		45.70±2.52	74.93±0.14	2.9	1

*Superscript number means continued the respective batch

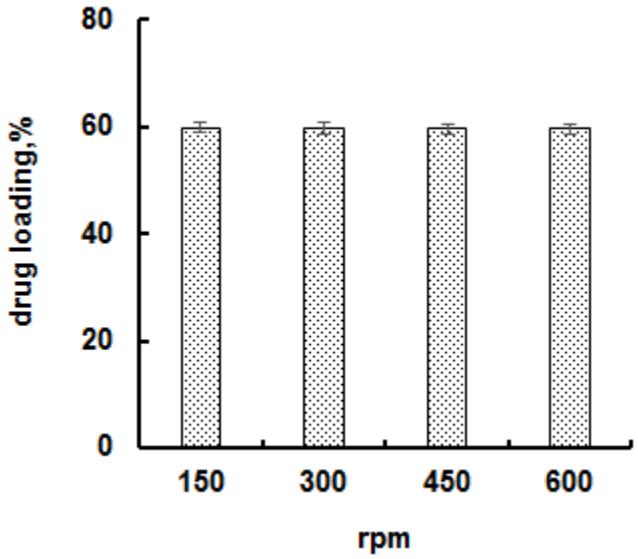

Figure 44. Effect of stirring speed on drug loading on Amberlite® IR69F in the loading medium of pH 6 and at temp 23 ºC (n = 3).

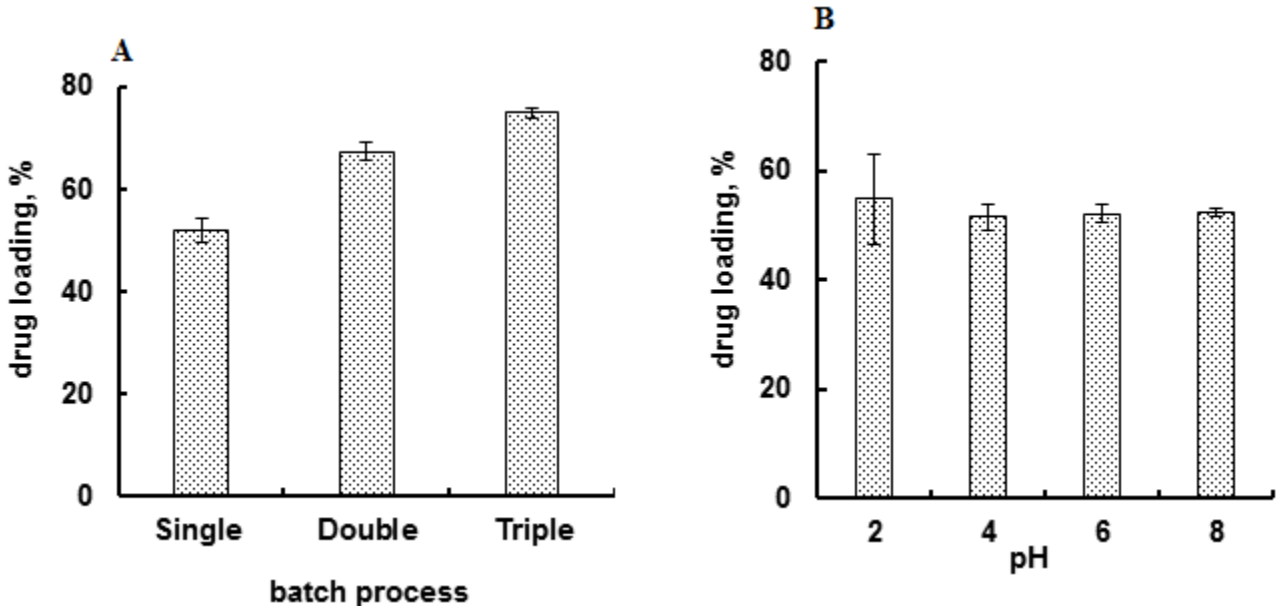

Figure 45. Effect of A) sequential batch process and B) pH of the loading medium on drug loading for Amberlite® IR69F (n = 3).

3.2.2 Characterization of resinates

The drug crystals were visible with polarized light microscopy for drug alone and drug resin physical mixture, but drug crystals were not visible in drug-resin complex. It confirmed the amorphous nature of drug-resin complex. On the other hand, same was confirmed by powder X-ray diffraction. It was undertaken to investigate the crystalline nature of the drug, drug showed characteristic crystalline peaks at 2θ = 7.5, 12.5, 17.78, 18.76, 20 and 25° and in physical mixture with resin. While drug-resin complex, exhibited amorphous characteristic with absence of crystalline peaks (Figure 46). The disappearance of the crystalline peaks of drug showed the complexation of drug with ion exchange resin. Similar findings were also observed by Vuorio and his co-workers (Vuorio et al., 2004).

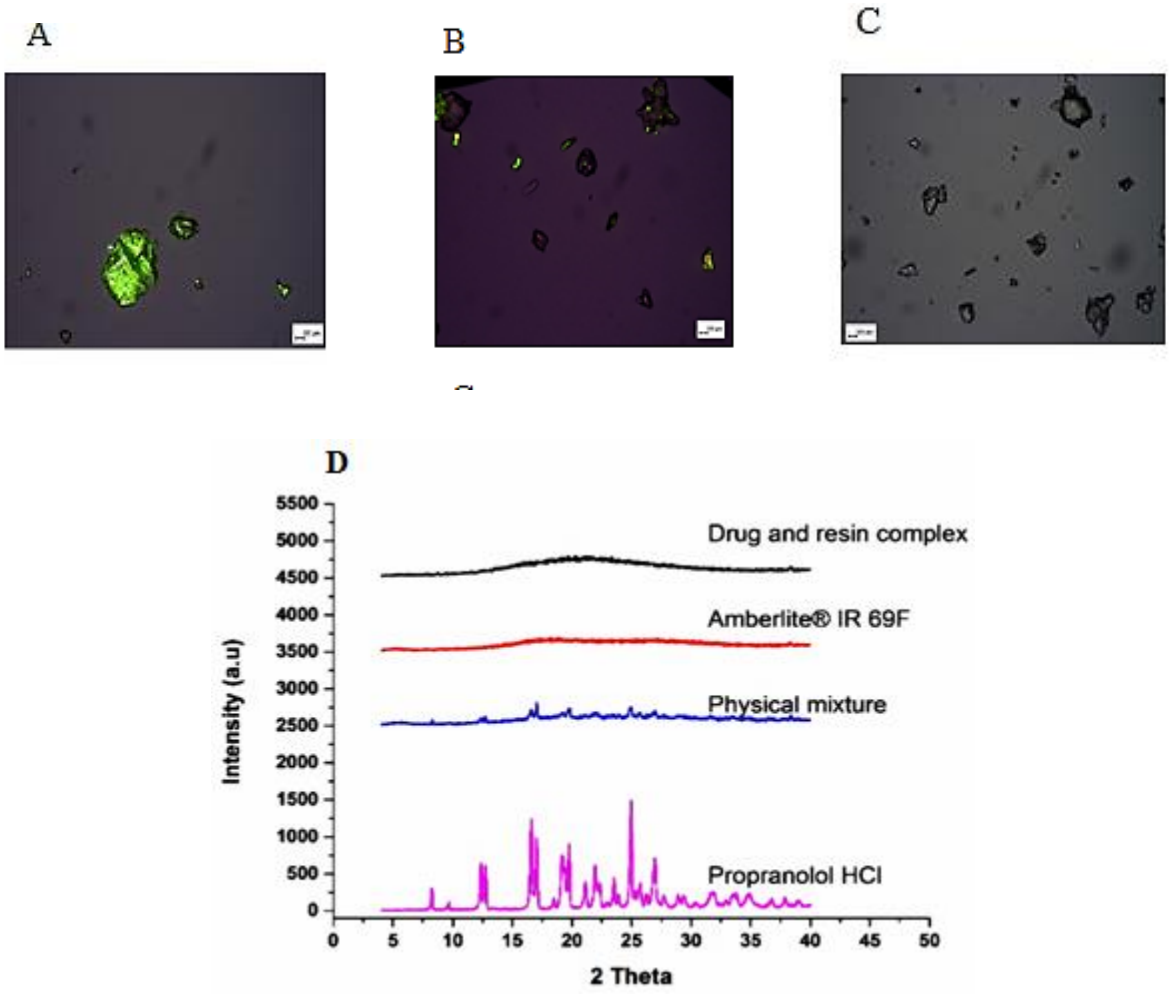

Figure 46. Polarized light microscopic image A) of drug, B) physical mixture and C) drug-resin complex (magnification 20x) and D) powder X-ray diffractogram of propranolol HCl, physical mixture, and drug-resin complex.

As drug loading had linear relationship with swelling of ion exchange resin during batch process. Amberlite® IR69F swelled 13 % in unloaded form and 28% in drug loaded form. Resins having hydrophilic ionic sites in their structures which attract moisture on their exposure to environment. The moisture contents of unloaded and drug loaded resins only 10% and 5% respectively. The moisture was removed in total 9 minutes for unloaded and 4 minutes for drug-loaded resin. The initial quick loss was in first minute. Then gradual increase up to 12% for unloaded and 5% for loaded Amberlite® IR69F respectively. The 5% lower moisture for drug loaded resin was probably

due to the occupancy of ionic sites with drug molecules. It ultimately reduced the free ionic sites for moisture. The ion exchange resin appeared to be hollow from inside with well-defined boundary in its swelled form under microscopic examination (Figure 47).

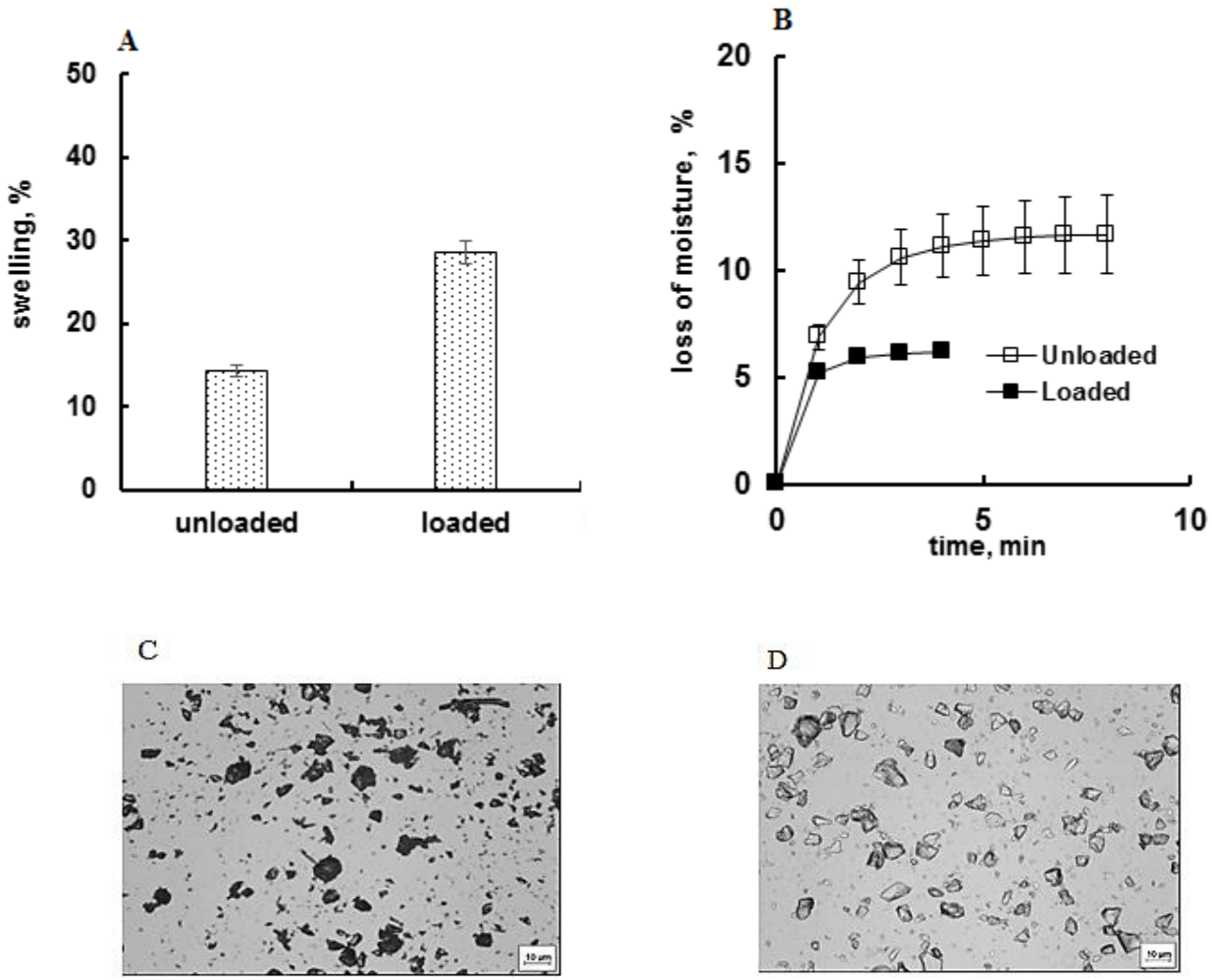

Figure 47. A) Swelling of Amberlite® IR69F in unloaded and drug loaded form. B) Kinetics of total loss on drying of Amberlite® IR69F at 103°C. C) Light microscopic image before swelling D) after swelling.

The overlay of FTIR spectra indicated the interactions between R-$SO_3^-Na^+$ and Prop-$NH_2^+Cl^-$ of drug and ion exchange resin. The shifting of stretching frequencies of transmittance bands from

1180.43 cm^{-1},1039.62 cm^{-1} and 833.24 cm^{-1} to 1172.65 cm^{-1},1031.91 cm^{-1},792.74 cm^{-1} respectively and broadening of peaks confirms the complex between $R\text{-}SO_3^-Na^+$ and $Prop\text{-}NH_2^+Cl^-$ (Figure 48). The above shifts in the wavenumbers and broadening of the peaks, suggested the ionic interactions and other interactions like hydrogen bonding between ion exchange resin and propranolol, resulted in the formation of drug-resin complex (Borges et al., 2005; Li et al., 2007; Ribeiro et al., 2005; Sarmento et al., 2006; Shang et al., 2007).

When drug was loaded on the ion exchange resin. The particle size of the resin increased. The increase in 12.15 ± 2.67 µm mean particle size of resinates was due to the expansion of resin matrix on drug loading (Figure 49 A, B).

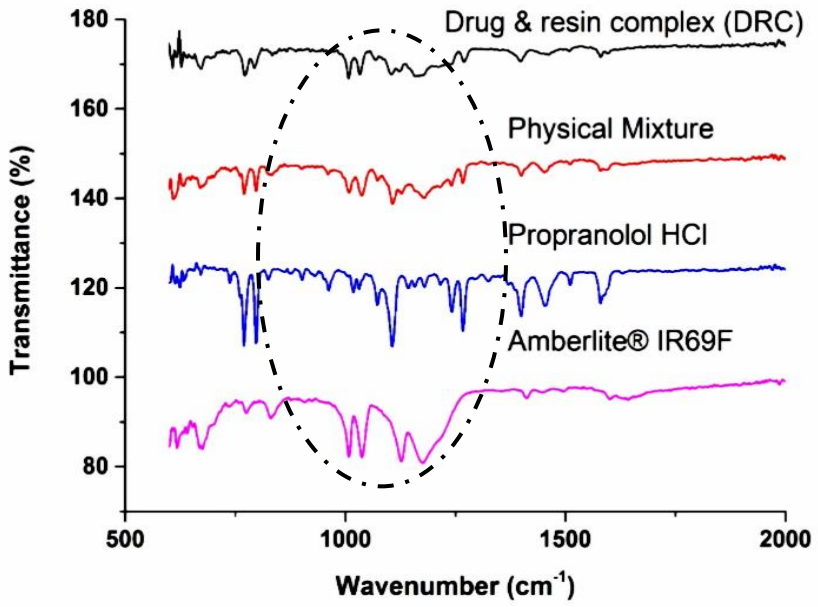

Figure 48. FTIR spectrum of Amberlite® IR69F, propranolol HCl physical mixture of drug and resin and drug-resin complex.

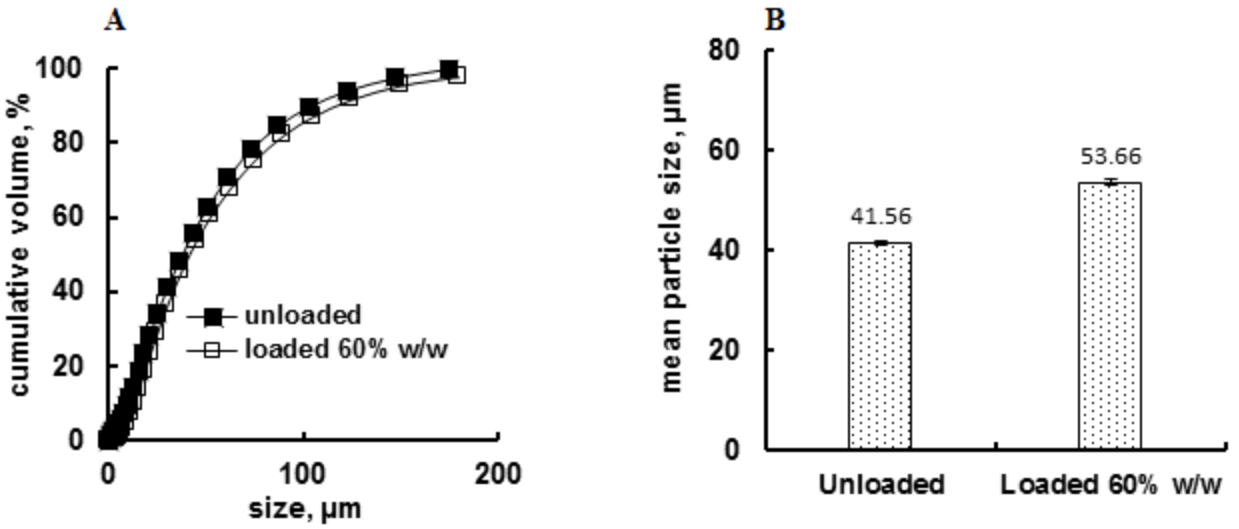

Figure 49. Effect of drug loading on A) cumulative volume distribution of resinates and B) mean particle size of resinates (n = 3).

The mean particle size of the powder (resinates) before coating was 119 µm and it was increased with increasing coating level (Figure 50). At 25% coating level, the size reached 414 µm which exceeded the USP limits of particle size (50-250 µm) for liquid controlled release reconstitutable formulations. Therefore, in order to avoid this problem of increasing particle size, resinates were wet granulated in an open tray/petri dish and dried at 60°C in an oven for overnight. Finally, dried granules were shifted to mini-Glatt for coating process. The mean particle size before coating was 191 µm which was negligibly increased up to 225 µm at 25% coating level (Figure 51). After granulation, individual particles/resinates retained/maintained their geometry and size, which further underwent negligibly increased in size on coating, instead of liquid bridging between non-granulated resinates and agglomerated them into bigger particles (Torres et al., 1998).

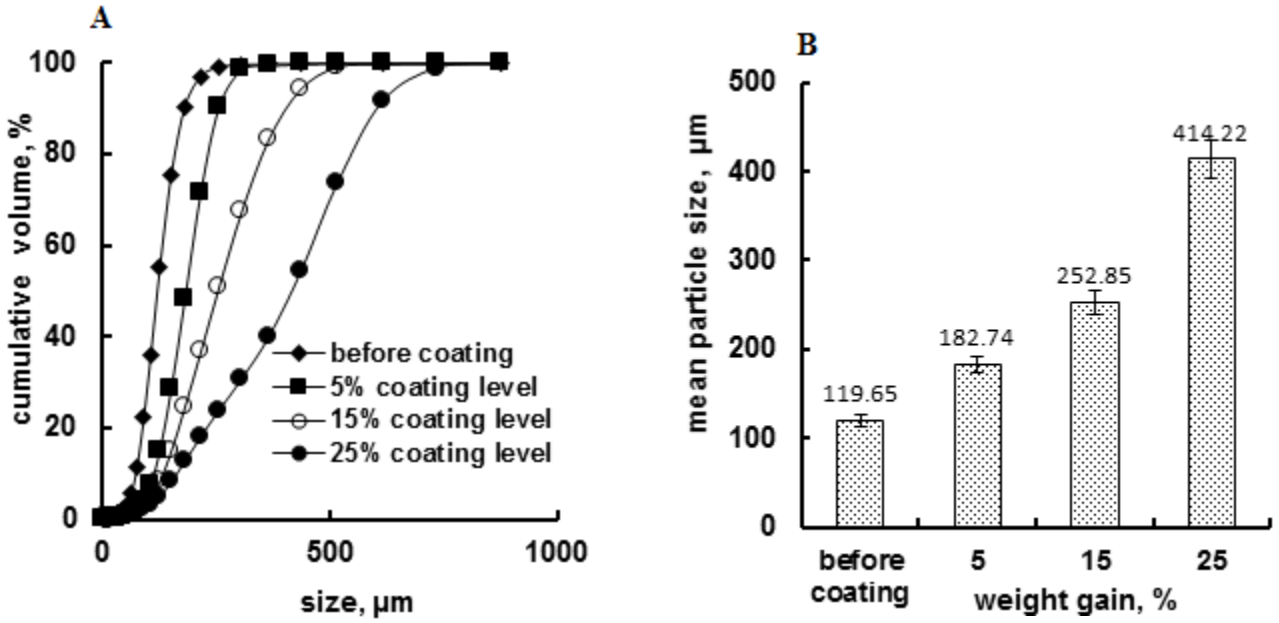

Figure 50. Effect of coating level on A) volume distribution of resinates and D) mean particle size of resinates (n = 3).

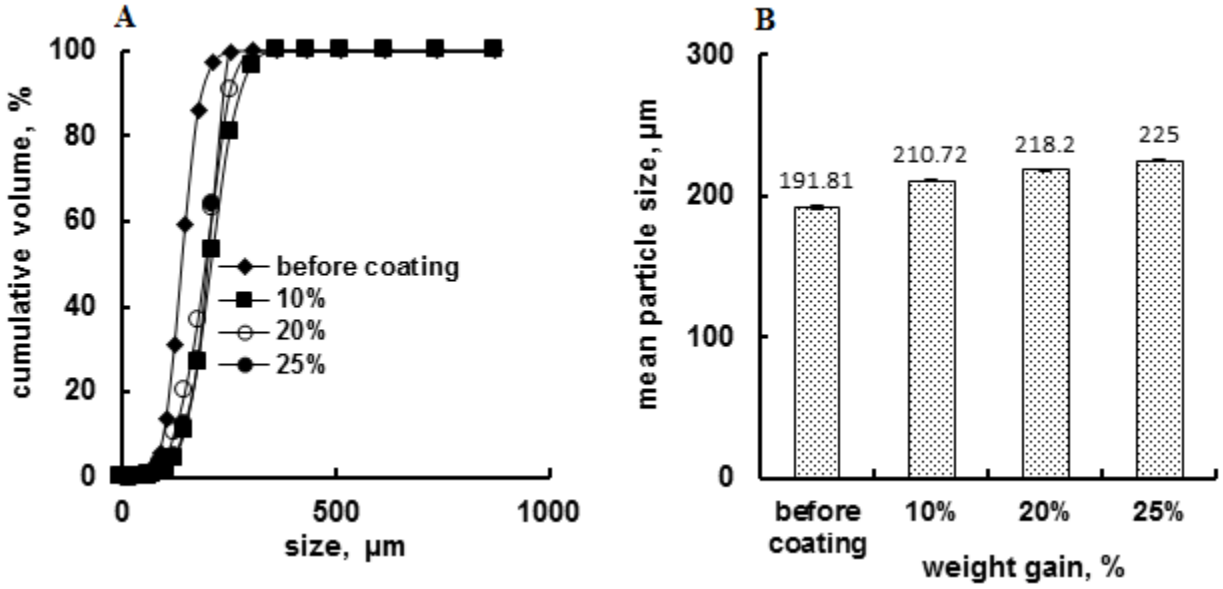

Figure 51. Effect of coating level after granulation on A) cumulative volume distribution of resinates and B) mean particle size before and after different coating levels (n = 3).

3.2.3 Drug release and influence of ionic strength

There was less than 10% drug was released in 0.1 N HCl during two hours and more than 75% release after first hour in pH 6.8 sodium phosphate buffer. It confirmed the enteric drug delivery system with cation exchange resin (Amberlite® IR 69F) when coated with 25% coating level of Eudragit® L 30D-55. The significance of ion exchange resin in the formulation was established, as without making complex with resins, there was a higher coating level (% weight gain) up to 45% was required to make the formulation enteric release. Whereas, coating level was reduced to only 25% when drug was complexed with resin. Moreover, almost 30% drug was released during first two hours in 0.1N HCl, when propranolol granules alone (formed with 15% w/w of HPMC E5) were coated with same thickness (25% c.l.) of Eudragit® L 30D-55 for the same size of 160 - 250 µm granules. Moreover, it was pertinent to described that, when granules were coated with 45% c.l. the final size of granules was increased and bigger than 250 µm (Figure 52A).

No change in release was observed when 200 mM and 400 mM NaCl was added to the release medium of pH 6.8 (sodium phosphate buffer). The total drug release achievable in the release medium pH 6.8 was up to almost 80% (Figure 52B). It was probably due to the strong nature of ionic complex between drug and resin. It could also be due to the enhanced consumption of Na^+ ions for the formation of salt of carboxylic group of Eudragit® L30D-55 and dissociation of propranolol from ionic sites in the resin. This salt formation of carboxylic group of coated polymer and dissociation of propranolol from the ionic sites of the resin, reduced the overall, concentration of counter ions specially (Na^+) in the release medium (Raju et al., 2011).

Furthermore, the drug release was remained unchanged after three months storage of the coated resinates at 40 ºC/75% RH and 25 ºC/60% RH (Figure 53A). In addition to above, drug-resin complex was stable at 40ºC and 60ºC over the period of one week, as there were no drug peaks were visible in graph obtained by powder X-ray diffraction.

Moreover, clear and conspicuous peaks were exhibited by drug alone and its physical mixture at at $2\theta = 7.5, 12.5, 17.78, 18.76, 20$ and $25°$. Which confirmed the amorphous nature of the resinates (Figure 53B).

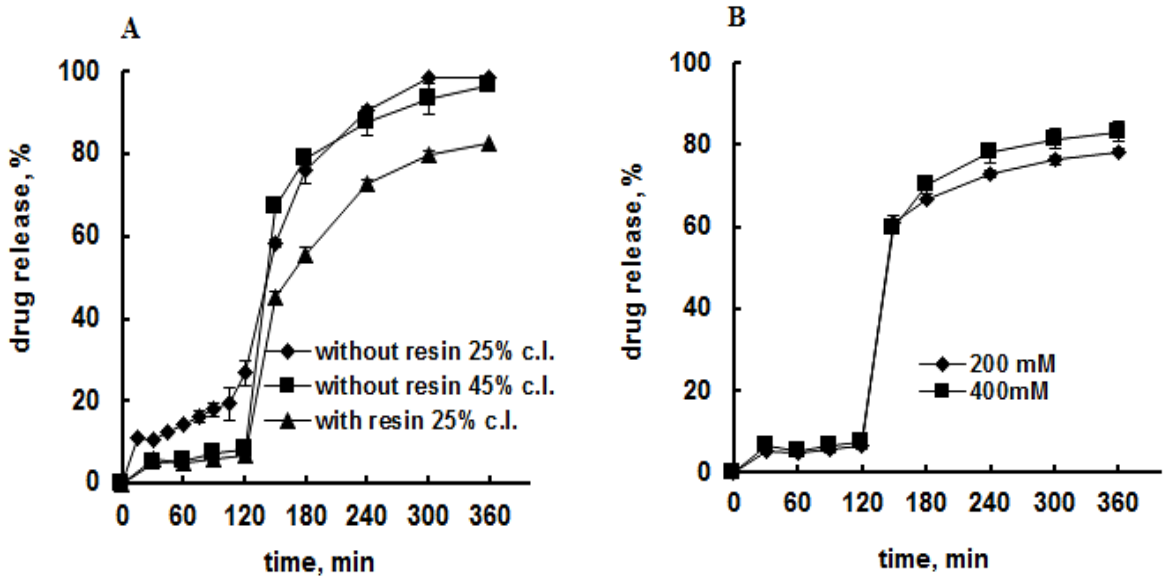

Figure 52. Effect of A) complexation and coating level B) ionic strength of the release medium in pH 6.8

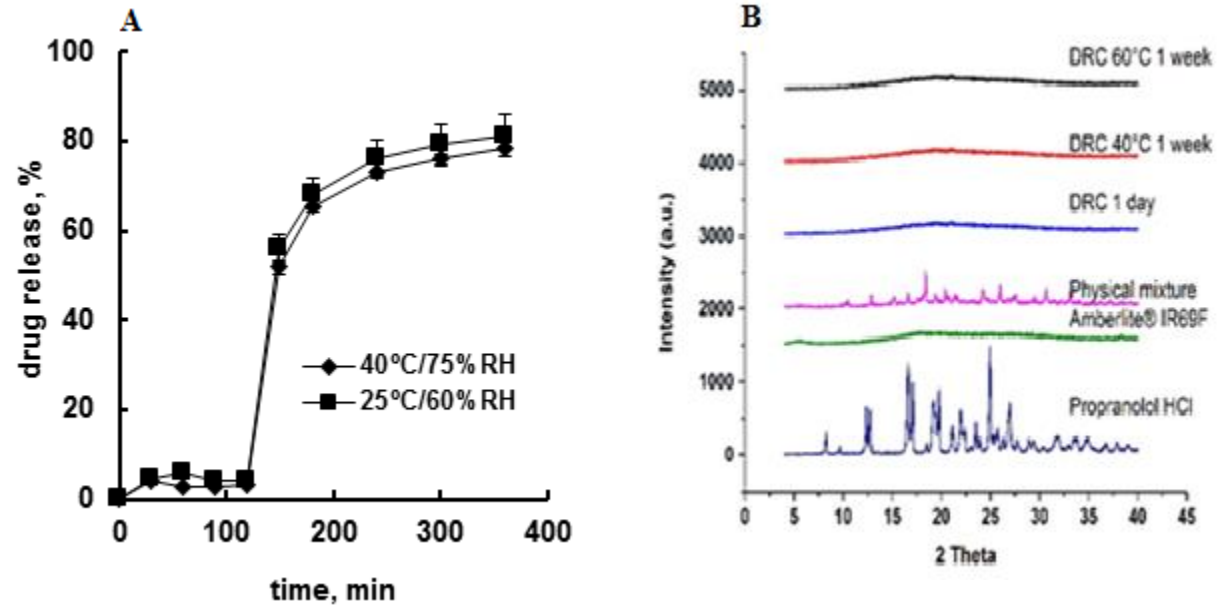

Figure 53. Effect of A) storage condition for three months on propranolol HCl release in pH 1 for 2 h then pH 6.8, and B) powder X-ray diffractogram.

3.2.4 Drug leaching and stability over one week after reconstitution

As enteric coated reconstitutable powders were to be mixed with water or any other liquid as a carrier (vehicle), prior to their administration. Therefore, there was need to establish leaching of drug in the carrier. There was less than 1% drug leaching in milli-Q® water over one week. Moreover, it was pertinent to mention that almost 1% drug was leached in 5mM and 10 mM NaCl/KCl over one-week storage. It might be due to the attainment of equilibrium between undissociated drug form and dissociated drug. Moreover, when ionic strength of the leaching medium was increased up to double the strength of ion exchange capacity of the resin, drug leaching was still less than 1% in both media NaCl and KCl. It indirectly, depicted the excellent drug retaining tendency of Amberlite® IR 69F on its ionic sites (Figure 54 A, B).

The pH of the suspending medium during drug leaching was varied in range. 6.3 ± 0.2. Moreover, no agglomeration of coated resinates was seen after reconstitution with suspending medium (formed by HPMC E5 granules) during one-week storage (Figure 55).

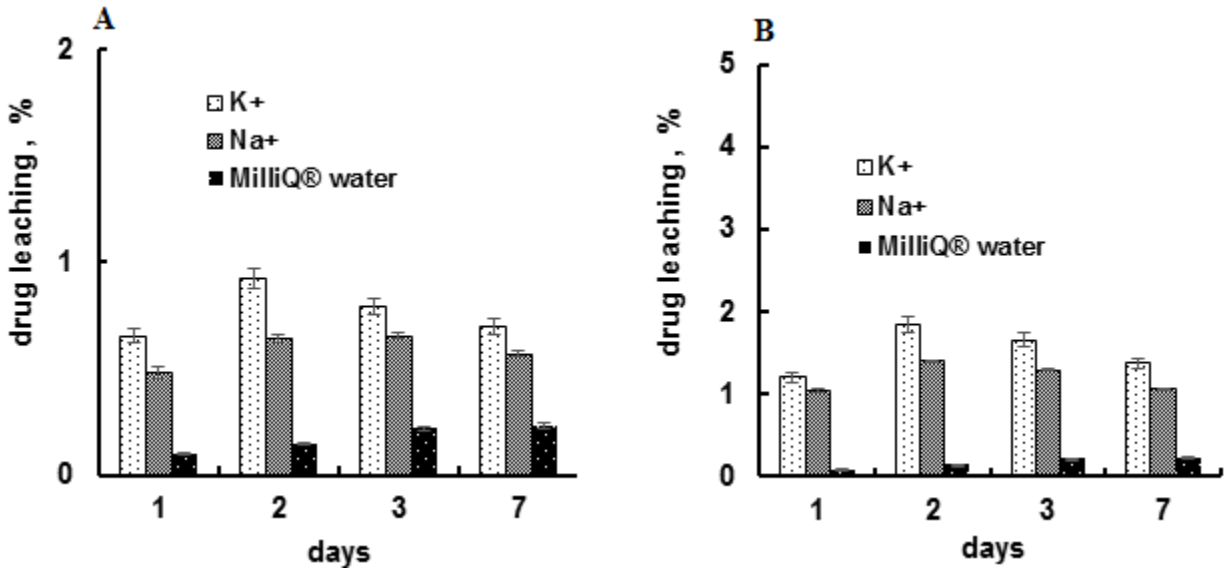

Figure 54. Propranolol HCl leaching with A) 5 mM KCl and NaCl and milli-Q® water and B) 10 mM of KCl and NaCl and milli-Q® water.

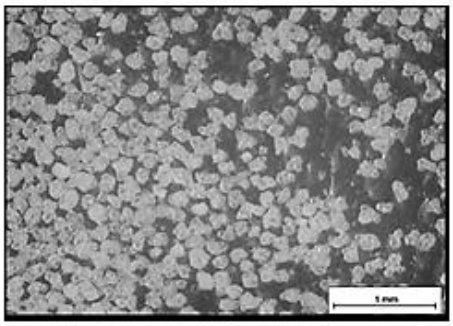

Figure 55. Macroscopic image of coated drug-resin complex (resinates) after reconstitution at temperature of 2-8°C.

3.2.5 Conclusion

A stable sustained release enteric formulation (reconstitutable powder) of propranolol HCl was achieved with cation exchange resin Amberlite® IR69F. The choice of the polymer and the thickness of the coated layer were critical to control the release of drug in pH 1 and pH 6.8 (sodium phosphate buffer). The formulation was also stable over one week after reconstitution at temperature of 2-8°C. The pH of the formulation during reconstitution was varied in range 6.3 ± 0.2. The ion exchange resin Amberlite® IR69F exhibited significantly higher drug retention as only 1% drug was leached from drug-resin complex in Milli-Q® water. The drug leaching was less than 1% when formulation was treated with 5 mM to 10 mM KCl and NaCl over one week after reconstitution. In summary, Amberlite® IR69F could be used as a carrier for preparation of an enteric liquid formulation of reconstitutable powder.

3.3 Evaluation of Purolite® C100CaMRNS (cation exchange resin) as a drug combination carrier

Oral combination drug delivery systems have been proven to be highly effective and beneficial in the treatment of several diseases such as cancer, acquired immune deficiency syndrome (AIDS), tuberculosis, diabetes (Type 2), heart diseases, central nervous system (CNS) disorders, and for treating several other microbial infections (Mayer and Janoff, 2007). Combination therapy may be achieved by prescribing/administering separate drugs, dosage forms that contain more than one active ingredient. Combination drugs most commonly refers to a fixed-dose combination (FDCs), which is a formulation including two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in certain respective fixed doses. The fix dose combinations are often claimed to make medicine-taking more convenient for patients taking multiple medication (Taupitz et al., 2013).

Fix dose combinations are mostly tablets and capsules. There is a need to develop fix dose combination for geriatric and pediatric patients in form of a liquid formulations in reconstitutable powder form. Liquid dosage forms from ion exchange resins have certain key challenges with respect to stability of the formulation. Ion exchange resins are polyelectrolytes, which are insoluble both in water and organic solvents. Two drugs might react each other if they are not complexed with ion exchange resins especially, it happened when free acid and free basic drugs are formulated together. It is not confined to the two acidic/basic drugs. Two basic/acidic drugs might also undergo incompatibility when taken into same formulation together, so chemical and physical stability of such drugs in a formulation could be enhanced by complexing with ion exchange resins (Jenquin et al.,1990).

3.3.1 Drug loading

Both drugs diltiazem HCl and tramadol HCl were loaded on the Purolite® C100CaMRNS by a batch process at room temperature. The drug loading was significantly higher when both drugs were individually/separately loaded on the Purolite® C100CaMRNS. The drug loading of tramadol and diltiazem was 50% w/w and 42% w/w respectively. On the other hand, tramadol HCl loading was reduced by 18% and diltiazem HCl was 17% when both drugs were loaded simultaneously (Figure 56A). In the solution, during drug loading process, both drugs compete for the ionic sites in the resin. Almost 18% less drug loading for diltiazem HCl might be due to its higher molecular

weight (407 g/mol) when compared to tramadol HCl (260 g/mol) (Zhang et al., 2000). During the first hour of drug loading, 20% of both drugs were loaded on the resin. Subsequently, tramadol HCl and diltiazem HCl loadings were total 40% and 22% w/w respectively till 24 hours of batch process (Figure 56B).

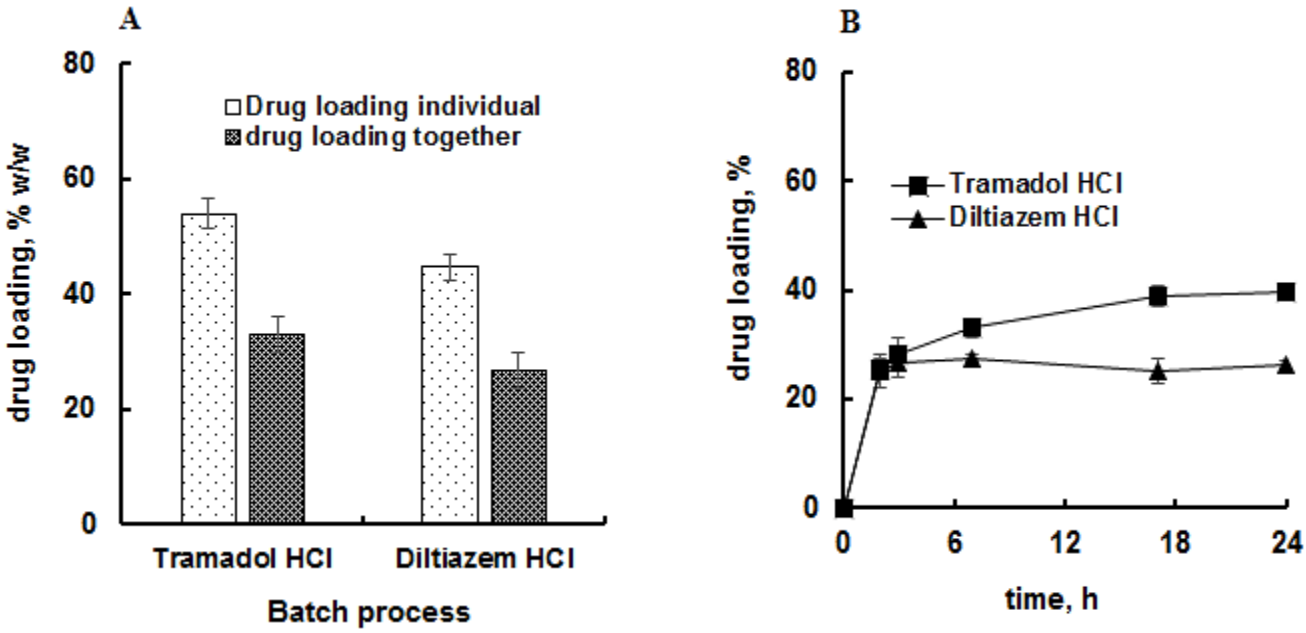

Figure 56. A) Tramadol HCl and diltiazem HCl loading on Purolite® C100CaMRNS individually and together when conditions were pH 6, temp 23ºC and rpm 300 B) Steps of both drugs loading for 24 hours (n = 3).

3.3.2 Characterization of resinates with X-ray powder diffraction and FTIR

The peaks of tramadol HCl and diltiazem HCl were clearly visible in powder X-ray diffractograms in their pure form and physical mixture with Purolite® C100CaMRNS. It was undertaken to investigate the crystalline nature of the drugs, both drugs (tramadol HCl and diltiazem HCl) showed characteristic crystalline peaks at 2θ = 10, 10.5, 15, 17.9, 20, 22.3, and 25° and 8, 10, 15, 18.9, 20, 22.45, 25, 27° respectively. In physical mixture with resin crystalline peaks were at 2θ = 10, 15, 18, 20, 25, 30°. Both drugs peaks were disappeared in the drug-resin complex, which ultimately confirmed the amorphous nature of the drug- resin complex (Vuorio et al., 2004).

On the other hand, shifting of frequency of transmittance bands of SO_3^{-1} group of Purolite® C100CaMRNS from 1039.62 cm^{-1} to 1035.91 cm^{-1} and 1030.62 cm^{-1} in drug-resin complex

confirms the formation of ionic complex between -HN group of both drugs and $-SO_3^{-1}$ group of Purolite® C100CaMRNS (Figure 57 A, B).

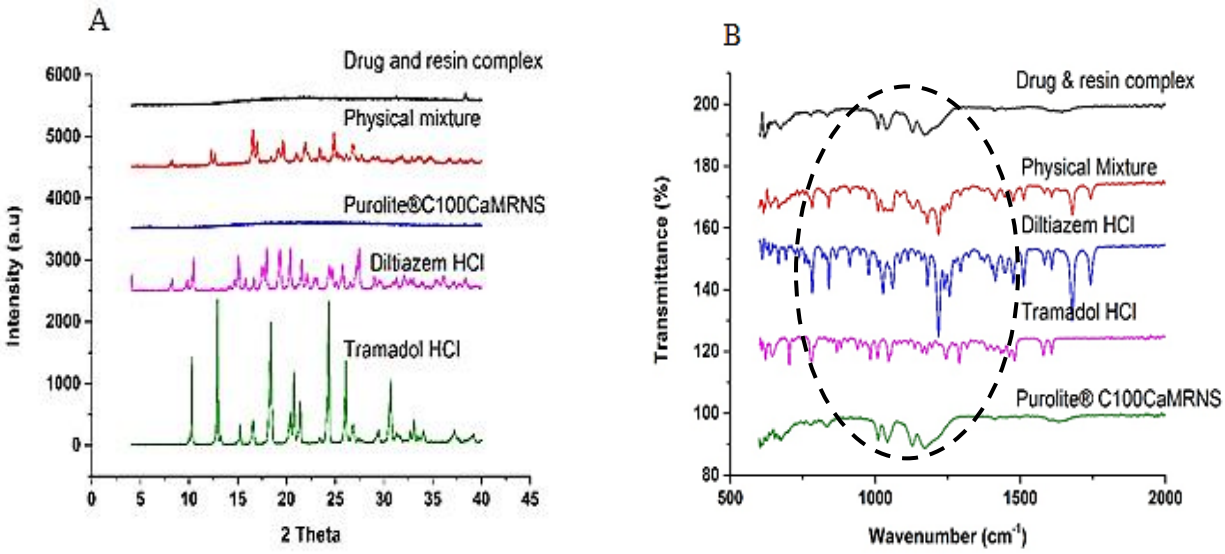

Figure 57. A) Powder X-ray diffractogram of tramadol HCl, diltiazem HCl, Purolite® C100CaMRNS, both drugs and resin, physical mixture, drug-resin complex B) FTIR spectrum of purolite® C100CaMRNS tramadol HCl, diltiazem HCl, physical mixture and drug-resin complex.

The drug loading depends on the swelling of resin during batch process. Purolite® C100CaMRNS swelled up to 38% and the moisture was removed in total 9 minutes for unloaded form and took 6 minutes for drug loaded resinates. The initial quick loss of moisture was in first minute, then gradual increase up to maximum 12% for the unloaded resin and 8% for the drug loaded resin. The lower moisture in drug loaded resins compared to unloaded resins was probably due to the occupancy of ionic sites with drug molecules (Figure 58 A, B). The Purolite® C100CaMRNS was in powder form and viewed as irregular shape and it became quite conspicuous after swelling under light microscope (Figure 59 A, B).

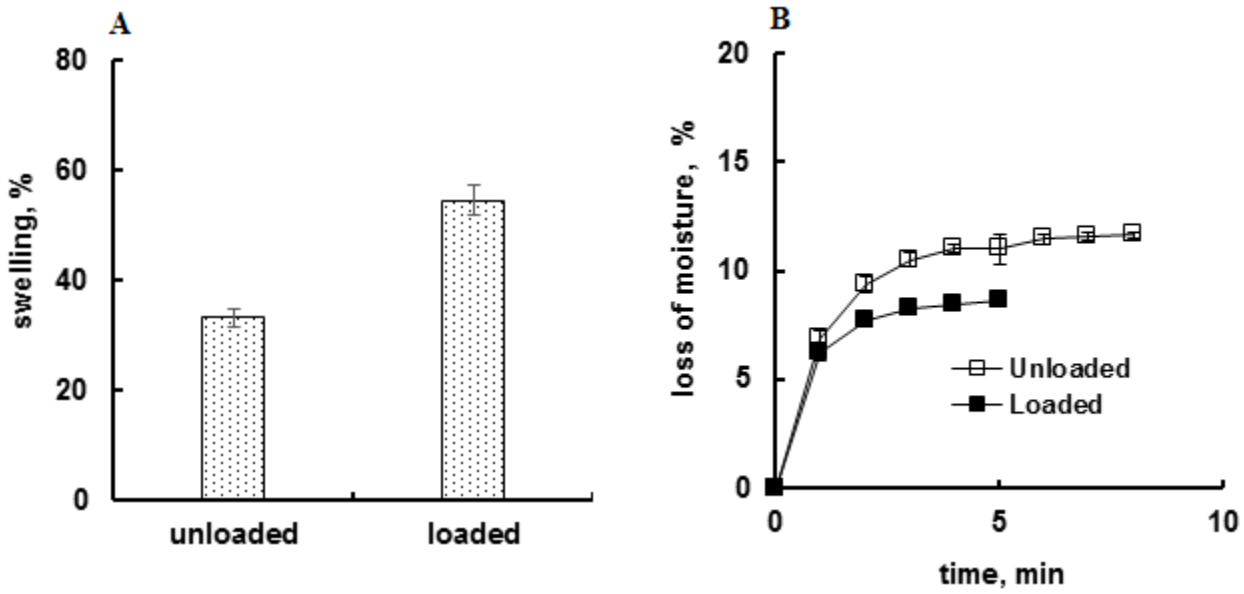

Figure 58. Effect of drug loading on A) swelling of resin and B) kinetics of loss on drying for resin before and after drug loading (n = 3).

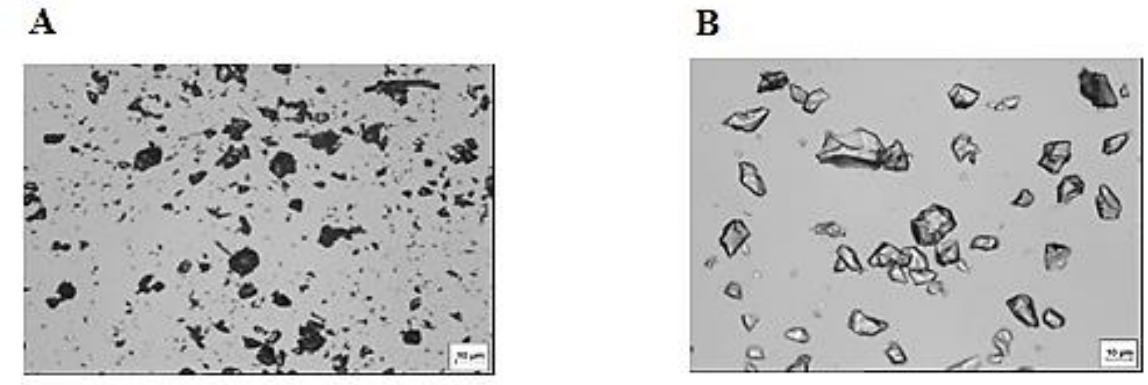

Figure 59. Light microscopic image of Purolite® C100CaMRNS A) before swelling B) after swelling (magnification 20x).

During batch process of drug loading, average conductivity of resin alone was 6.33 ± 0.67 µS/cm, whereas, conductivity of diltiazem HCl and tramadol HCl were 670 ± 19.41 µS/cm and 1024 ± 3.57 µS/cm respectively. When temperature of the loading medium was 17.7 ± 1.23 °C during conductivity measurement. The 52.83% lower conductivity of diltiazem HCl as compared to

tramadol HCl could be due to its higher molecular weight (450 g/mol) than tramadol HCl (260 g/mol) (Table 14).

At the ending of the batch process, the conductivity increased up to 78.90%. The increase in total conductivity of the loading medium after batch process might be due to formation of additional ions of (Ca^{+2} and Cl^{-}) $CaCl_2$ during exchange of Cl^{-} ions of both drugs and Ca^{+2} ions of Purolite® C100CaMRNS (Burton et al., 1995). On the other hand, there was not any significant change in pH of the loading medium, before and after drug loading of batch process (Figure 60).

Table 14. Conductivity studies during batch process

Sample	Resin 4mg/ml (µS/cm)	Diltiazem 4mg/ml (µS/cm)	Tramadol 4mg/ml (µS/cm)	after batch process (µS/cm)	Temp ºC
A	7.10	695	1024	1832	18
B	5.62	659	1028	1810	17.5
C	6.32	656	1020	1815	17.2
Avg	6.33	670	1024	1819	17.7
S.D	0.67	19.41	3.57	11.53	1.23

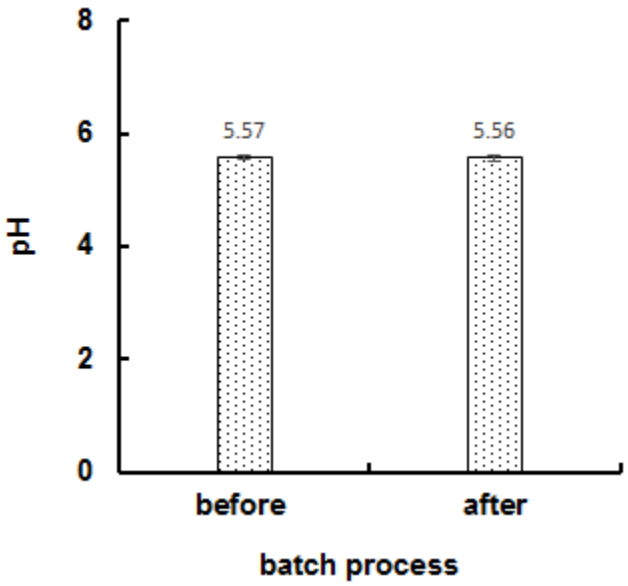

Figure 60. Effect of diltiazem HCl and tramadol HCl loading on pH resin during batch process (n =3).

Mean particle size of resin increased up to 21.39 ± 2.5 µm after drug loading. It might be due to the expansion of resin matrix during drug loading. Ion exchange resin expands gradually during single batch process to double batch process of drug loading. Moreover, this expansion of ion exchange resin is irreversible. As ion exchange resin remained expanded even after the drug release. The increased mean particle size of resin after drug release was 69.09 ± 2.54 µm as compared to original size 47.14 ± 2.4587 µm (Figure 61 A, B). It could be due to the reason that resin uncoiled from inside and drug molecules make a space in the resin pores. This whole process ultimately, led to a steric hindrance (repulsion) between two adjacent drug molecules and caused the resin to expand till its maximum strength (Torres et al., 1998).

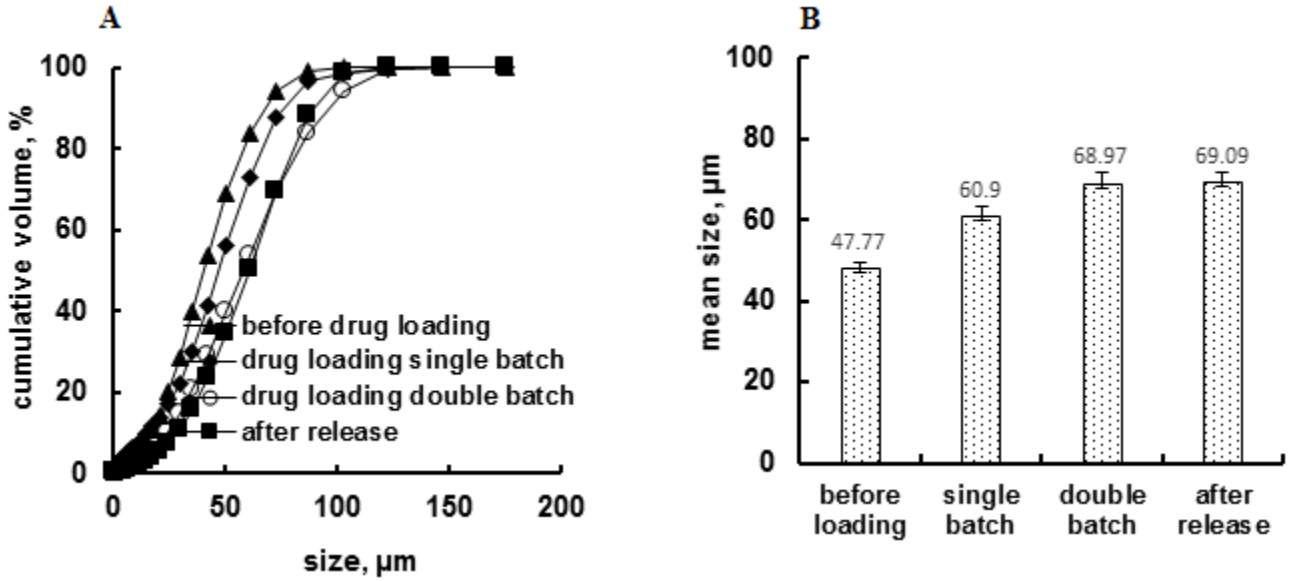

Figure 61. Effect of drug loading on A) the cumulative volume distribution of resinates and B) mean particle size (n = 3).

The resinates were dried overnight in the oven at 60ºC. Very fine particles ≤ 71µm were removed by sieving. The mean particle size 97.07 ± 1.5478 µm were transferred to mini-Glatt for coating. During coating process, there was an increase in particle size of coated resinates which depicted, that during coating process there were liquid bridges and nucleation of small microparticle (resinates) of size 97.07 ± 1.54 µm, which led to the granulation process (size enlargement). During coating process both coating and granulation took place simultaneously.

For every 10% coating level, there was an average increase of 97.09 ± 2.85 µm particle size. It was granulation of resinates in the mini-Glatt. It was due to the comparable binding properties of Eudragit® NE30D. Furthermore, for 15% coating level (weight gain w/w) mean particle size increased from 97.61 ± 1.9875 µm to 204.50 ± 2.14 µm only. The increase of mean particle size further grew up with 25% to 30% coating level (Lange 1992).

The size was grown up to 393.44 ± 3.1548 µm with maximum coating level of 30%. This increased size of coated resinates exceeded the USP limits of particle size (50-250 µm) for liquid controlled release formulations (Figure 62 A, B). An increased particle size may give the mouth feel to the patient and thus contributes to patient's incompliance. Therefore, controlled release formulation was obtained only with 25% coating level of the resinates.

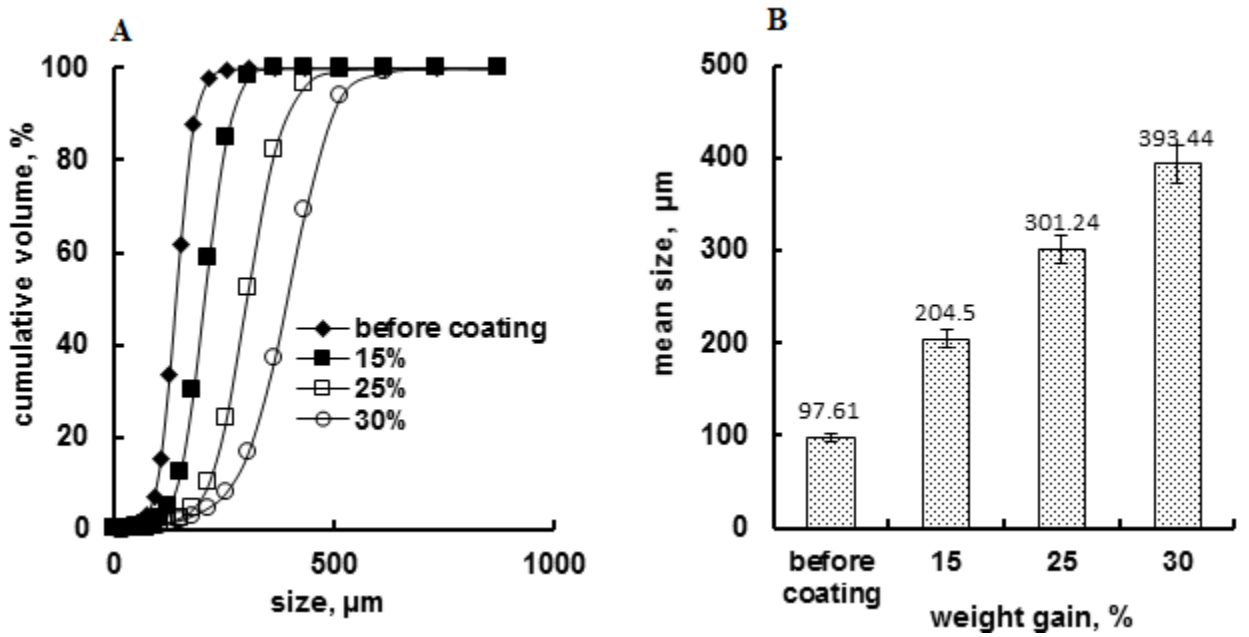

Figure 62. Effect of coating level on A) the cumulative volume distribution and B) mean particle size of coated resinates (n = 3).

3.3.3 Drug release from uncoated and coated resinates

The release of both tramadol HCl and diltiazem HCl from uncoated resinates was burst and incomplete both in 0.1 N HCl and pH 6.8 sodium phosphate buffer. This incomplete release in 0.1 N HCl could be due to the non-availability of desired strength of (H^+, Cl^-) ions in the release medium or might be due to the strong nature of ionic complex of both drugs with resin (Xu et al., 2003; Zarate et al., 2011).

However, drug release in release medium of pH 6.8 (sodium phosphate buffer) was almost 10% more than 0.1N HCl. It was probably due to (Na^+, Cl^-, OH^- and PO_4^{-3}) ions to dissociate the drug from ionic sites of ion exchange resin (Figure 63).

On the other hand, there was complete release of drugs in both media when media was mixed with 300 mM of KCl (Figure 64). Drug release even from uncoated resinates was dependent on ionic strength/concentration of the release medium (Zhang et al., 2000).

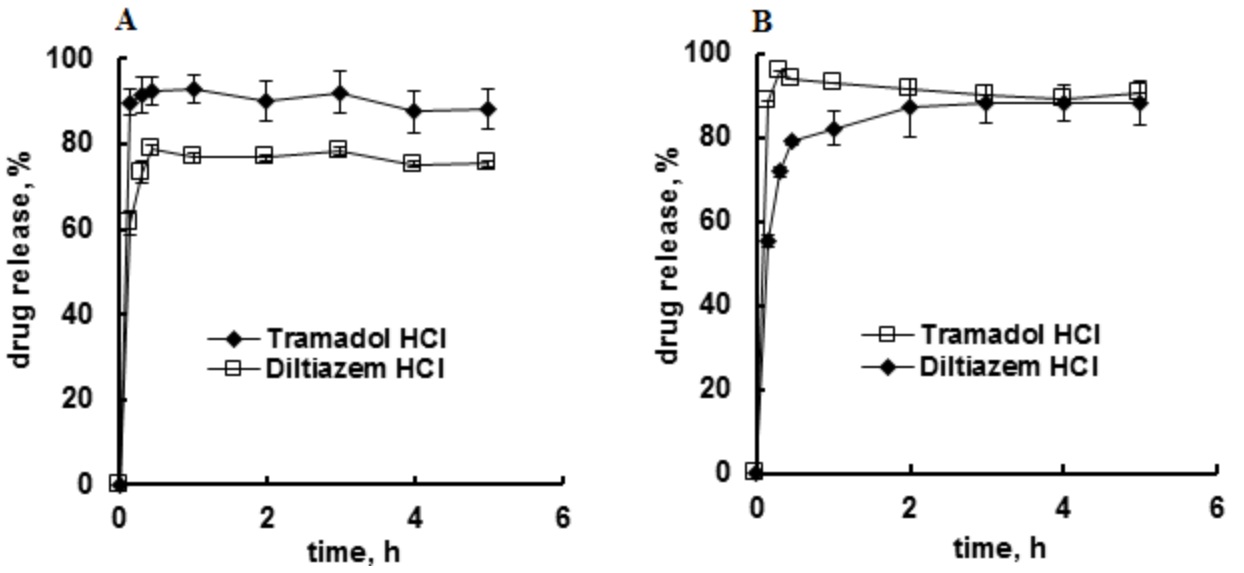

Figure 63. Tramadol HCl and diltiazem HCl release from uncoated resinates in A) 0.1 N HCl and B) pH 6.8 phosphate buffer.

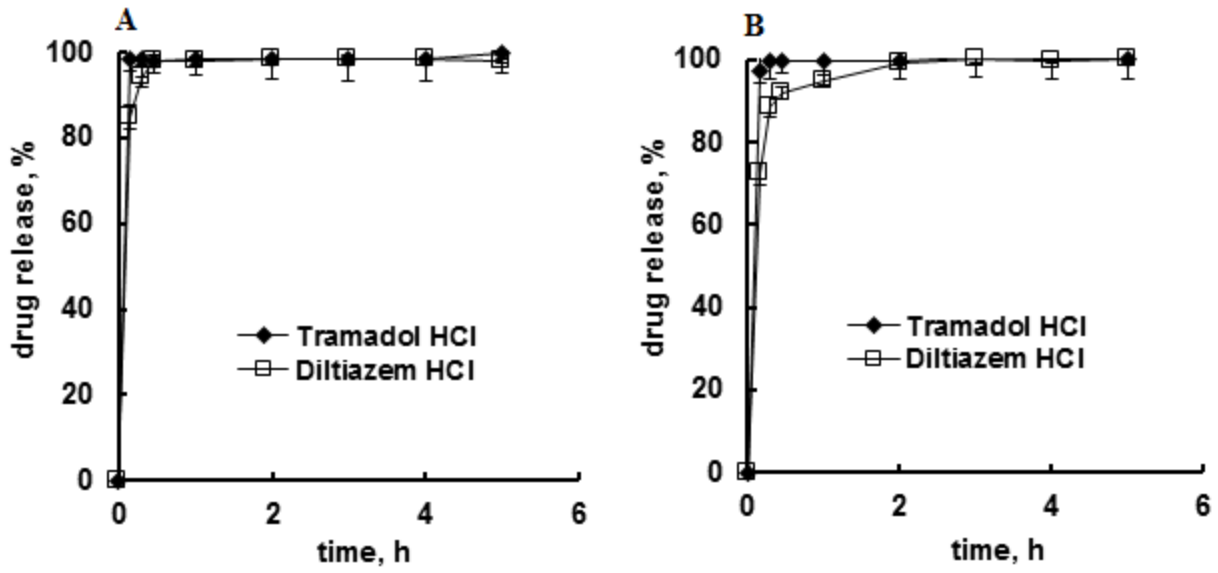

Figure 64. Tramadol HCl and diltiazem HCl release A) 0.1 N HCl mixed with 300 mM of KCl. B) pH 6.8 (sodium phosphate buffer) mixed with 300 mM of KCl.

The tramadol HCl release was bit faster than diltiazem HCl, when their resinates were separately coated. The bit faster release rate of tramadol HCl as compared to diltiazem HCl could be due to its low molecular weight (263 g/mol) than diltiazem HCl (450 g/mol).

Whereas, both tramadol HCl and diltiazem HCl were released with the same rate, when they were both complexed with the same resin and coated together with Eudragit® NE 30D. It was probably due to their highly soluble nature of both drugs (Figure 65).

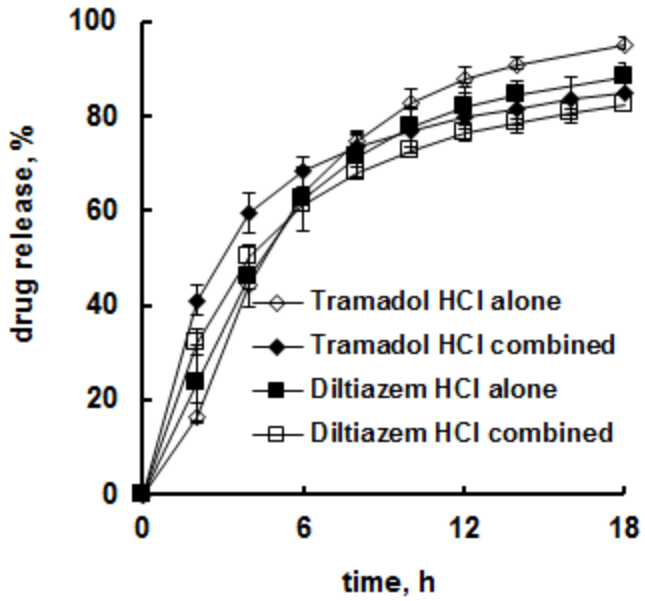

Figure 65. Drug release after coating with Eudragit® NE 30D, 25% coating level cured at 60 ºC for 12 hours.

Finally, reconstitutable powder was to be administered with water so it was necessary to establish drug leaching of the formulation in the water/carrier. There was less than 1% of both drugs (tramadol HCl and diltiazem HCl) leached in 5mM of KCl solution, when its conductivity was in range of 667.24 ± 8.256 µS/cm.

On the other hand, when strength of the leaching solution increased and made double (10 mM KCl) than ion exchange capacity of Purolite® C100CaMRNS. The leaching of both drugs was still less than 1%. when its conductivity was kept in the range 1513.9 ± 5.45 µS/cm. This negligible amount of drug leaching after reconstitution of coated resinates for one week confirmed the stable nature of the formulation (Figure 66).

Moreover, there was no leaching or negligible leaching of both drugs in milli-Q® water alone. It was probably due to the non-availability of ions in the milli-Q® water. This meant that both drugs ionically complexed with ionic sites of the resin and remained intact with resin even in the milli-Q® water having no ions (Ichikawa et al 2001).

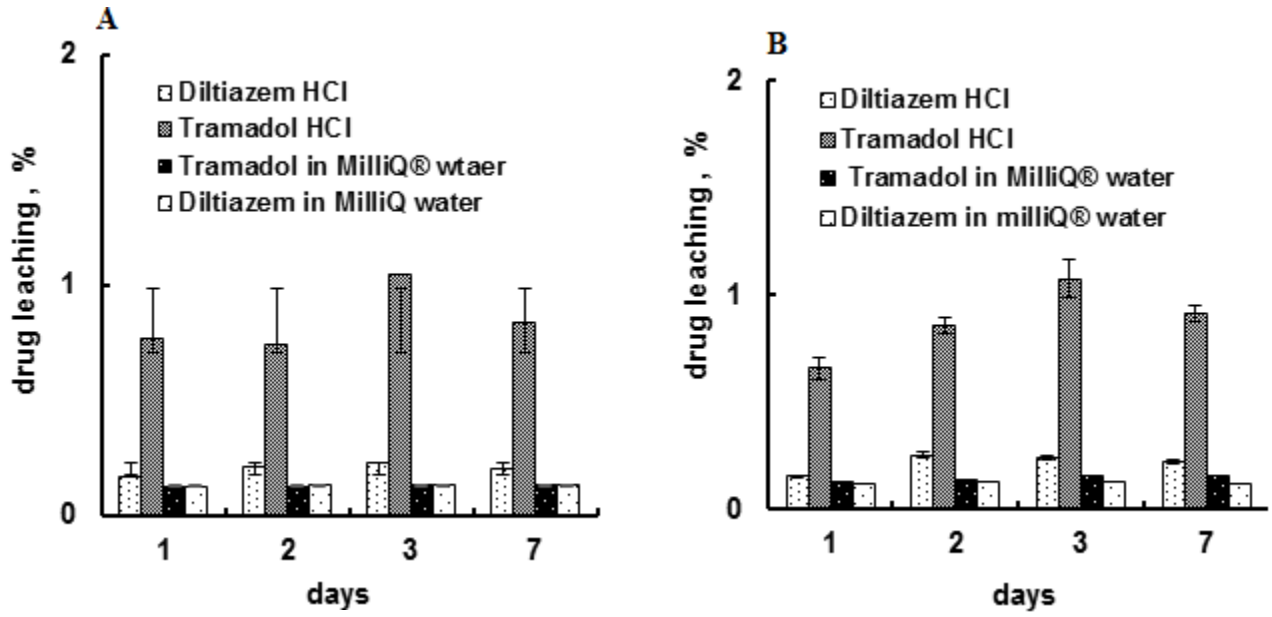

Figure 66. Drug leaching from coated particles in milli-Q® water with A) 5 mM KCl and B) 10 mM KCl.

3.3.4 Conclusion

Both highly soluble drugs, tramadol HCl and diltiazem HCl were successfully complexed/loaded with cation exchange resin (Purolite® C100CaMRNS). The nature of drug-resin complex for both drugs was amorphous, characterized by powder X-ray diffraction. The ion exchange resin Purolite® C100CaMRNS exhibited significantly higher drug retention as only 1% drug was leached from drug-resin complex of both drugs in Milli-Q® water. The drug leaching was less than 1% when formulation was treated with 5 mM to 10 mM KCl over one week after reconstitution. In summary, Purolite®C100CaMRNS could be used as a carrier for preparation of a controlled-release liquid formulation of two highly soluble drugs (tramadol HCl and diltiazem HCl) in form of reconstitutable powder.

3.4 To enhance the robustness of reservoir system (pellets) by preventing diffusion of drug into coated polymer by layering of drug-resin complex on NP core

In reservoir multiparticulate systems, a lipophilic drug, such as ibuprofen which has a low melting point, diffused into the coated polymer. When NP layered ibuprofen formulations were coated with aqueous polymer dispersion Aquacoat® ECD. The drug diffusion was happened during stability studies at accelerated conditions (Bodmeier et al., 1994). The same problem was addressed with Kollicoat® SR 30D by Dashevsky and his co-workers (Dashevsky et al., 2005). To prevent the drug diffusion into the coated polymer, an intermediate sealcoating was applied to the formulation. This sealcoating should be of a hydrophilic polymer, for instance, hydroxypropyl methylcellulose (HPMC) or polyethylene glycol (PEG). The aim of this study was to prevent the diffusion of the layered lipophilic drug into the coated polymer with the help of a drug-resin complex.

3.4.1 Drug loading on anion exchange resins

The ion exchange resins Purolite® A430MR and Duolite™ AP 143/1093 swelled up to 58% and 78% respectively. Moisture content for Duolite™ AP 143/1093 and Purolite® A430MR was 14% and 6% respectively. For Duolite™ AP 143/1093, the initial moisture loss occurred in the first minute and then gradually increased up to 14%. For Purolite® A430MR, the 6% moisture was removed/evaporated in the three minutes (Figure 67A, B). The adsorbed moisture may be due to the free ionic sites of the unloaded resins. The ionic sites which were associated with the drug, were not available for free moisture. Furthermore, during swelling studies water molecules went into the resin matrix and form solvation shells inside the resin matrix and started to uncoil and expand. This swelling of resin was inversely related to the percentage of divinyl benzene cross linking in the resin. Once Purolite® A430MR and Duolite™ AP 143/1093 swelled, they did not come back to their original state even after heating, which meant that both ion exchange resins were not flexible rather rigid and brittle. For both Purolite® A430MR and Duolite™ AP 143/1093 their swelled state exhibited a definite boundary under light microscope (Figure 67C, D, E, F). The moisture content for Purolite® A430MR were almost similar for both drug loaded and unloaded

forms. Whereas, it was 5 percent less than for drug loaded form of Duolite™ AP 143/1093 than unloaded form (Figure 68).

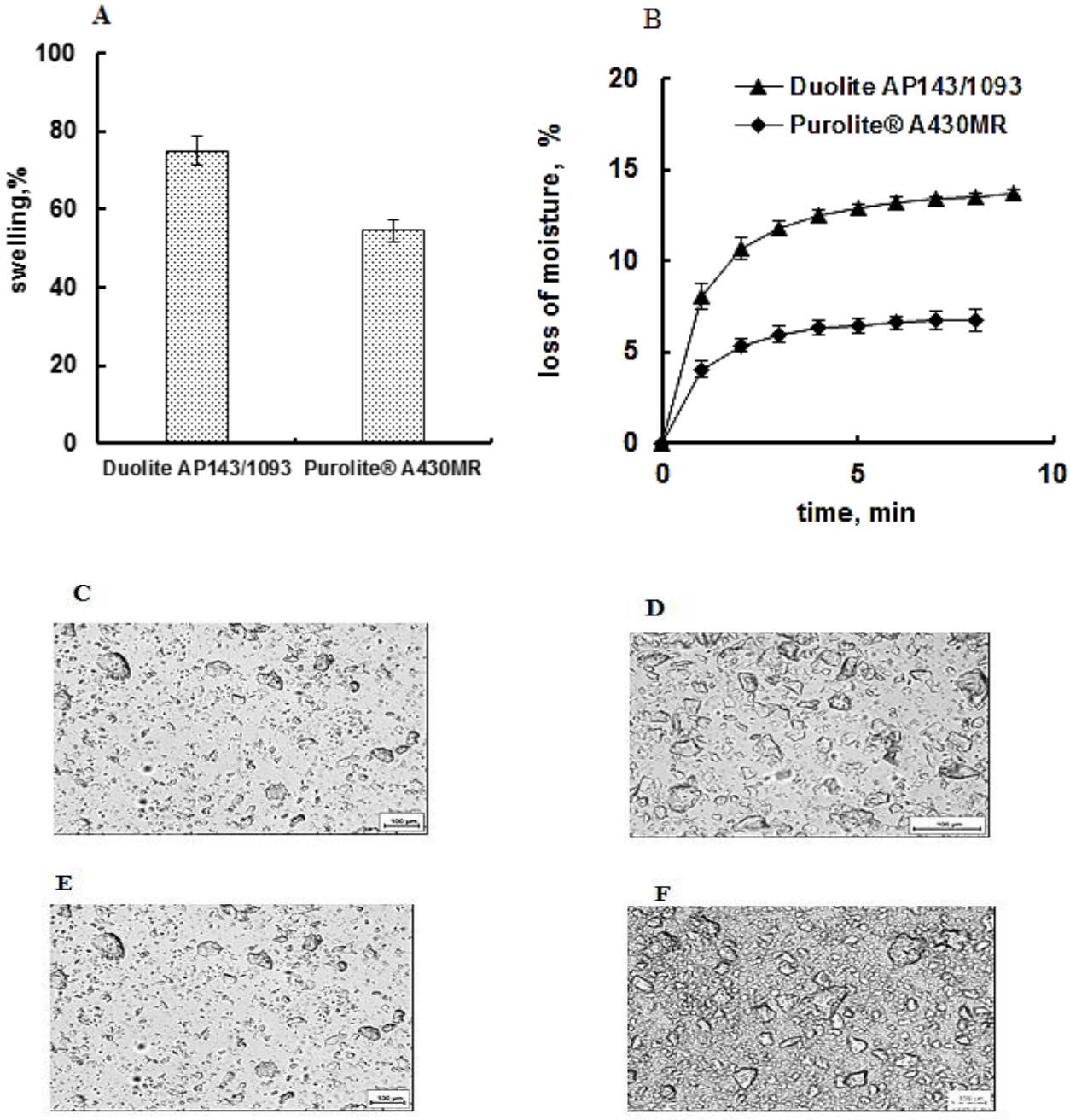

Figure 67. A) Swelling of Purolite® A430MR and Duolite™ AP 143/1093. B) kinetics of moisture content of Purolite® A430MR and Duolite™ AP 143/1093, and C) Light microscopic image of Purolite® A430MR before swelling, and D) after swelling, and E) Duolite™ AP 143/1093 before swelling, F) after swelling.

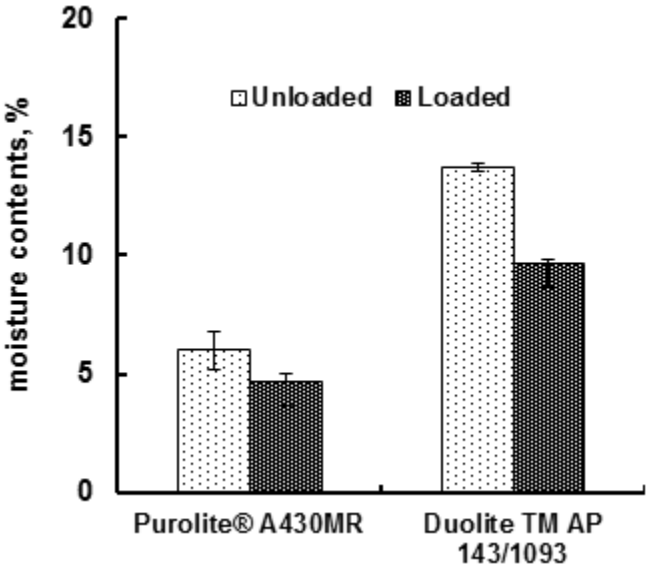

Figure 68. Moisture content of Purolite® A430MR and Duolite™ AP 143/1093 before and after drug loading.

The maximum drug loading for ibuprofen was 28% w/w. There was 58% drug loading for diclofenac sodium with drug:resin ratio 3:1 w/w. The 30% higher drug loading of diclofenac sodium was probably due to its higher solubility as compared to ibuprofen. The drug loading remains constant even with three-fold increase of the drug in the system, meaning that no further drug was loaded when the ionic sites of resin became saturated. On the other hand, the drug association efficiency was almost 100% for diclofenac sodium (Table 15 and 16). The conductivity studies of both diclofenac sodium and ibuprofen before and after drug loading were done in the batch process. The conductivity of the Duolite™ AP 143/1093 alone was 14 µS/cm and conductivity of diclofenac alone was 1394 µS/cm before batch process. After batch process the conductivity of the media was changed to 2045 µS/cm. 80% increase in conductivity after drug loading was probably due to the exchange of ions and release of NaCl. The Na^+ from drug and Cl^- from resin (Ashwini et al., 2012). On the other hand, ibuprofen alone had a conductivity of 7790 µS/cm. The 458% higher conductivity of ibuprofen than diclofenac sodium could be due to its lower molecular weight. The conductivity after batch process was increased to 8250 µS/cm. This 30% increase in conductivity after batch process could be due to the formation of HCl, H^+ from ionization of ibuprofen and Cl^- from the resin (Table 17).

Table 15. Drug loading w/w and drug association efficiency for diclofenac sodium with Duolite™ AP 143/1093 with batch process at 300 rpm at room temperature

Resin (mg)	Drug (mg)	Volume (ml)	Drug : resin ratio	(w/w) loading of diclofenac (%) + (±SD)	Association efficiency of diclofenac (%) + (±SD)
100	100	25	1:1	49.63±0.02	98.53±0.101
100	200	25	2:1	51.90±3.79	54.37±8.11
100	300	25	3:1	58.24±1.93	67.24±6.06

Table 16. Drug loading w/w and drug association efficiency for ibuprofen with Purolite® A430MR

Resin (mg)	Drug (mg)	Volume (ml)	Drug:resin ratio	(w/w) loading of ibuprofen (%) + (±SD)	Association efficiency of ibuprofen (%) + (±SD)
150	100	25	1:1.5	28.93±1.01	61.11±3.01
200	100	25	1:2	26.47±.83	72.02±3.07

Table 17. Conductivity studies of ibuprofen and diclofenac sodium during batch process at 23 ºC

sample	resin alone 100mg (µS/cm)	diclofenac alone 100mg (µS/cm)	ibuprofen alone 100mg (µS/cm)	diclofenac after batch process (µS/cm)	ibuprofen after batch process (µS/cm)
A	14.50	1407	7800	2060	8100
B	13.70	1378	7800	2048	8200
C	14.90	1397	7720	2038	8250
Avg	14.36	1394	7790	2045	8250
S.D	0.54	13.97	23.57	11.53	22.25

Moreover, drug loading on Duolite ™ AP143/1093, when it was having OH^- and Cl^- was similar around 58% w/w. Initially, it was a quick drug loading in the first hour then equilibrium was attained due to the saturation of ionic sites in the resin. It showed that drug loading remained constant when Duolite™ AP143/1093 had either OH^- or Cl^- ion as exchangeable counter ion. The

change of pH was from 9.48 to 8.78 for Duolite™ AP143/1093 during batch process before and after diclofenac sodium loading (Figure 69).

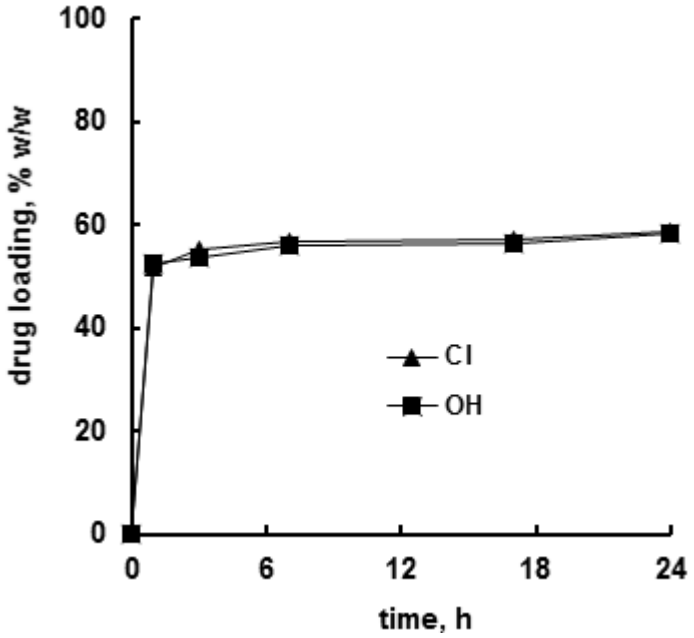

Figure 69. Kinetics of diclofenac sodium loading on Duolite ™ AP143/1093 for both OH^- and Cl^-.

The ion exchange resin, Purolite® A430MR was treated with 1N NaOH for twenty-four hours by stirring at 300 rpm. Finally, it was recovered by vacuum filtration and washed with milli-Q® water to remove excess NaOH from its surface. The initial pH of the eluent was 12.26 which became 9.15 and reached equilibrium on the fifth wash with milli-Q® water. On the other hand, Duolite ™ AP 143/1093 initial pH was 13.5 which became neutral, pH 7.15 on the fifth wash with milli-Q® water (Figure 70). There was not any significant change in pH was observed before and after drug loading when Duolite™ AP 143/1093 (OH^- ions) and Purolite® A430MR (Cl^- ions) were used in the batch process (Figure 71).

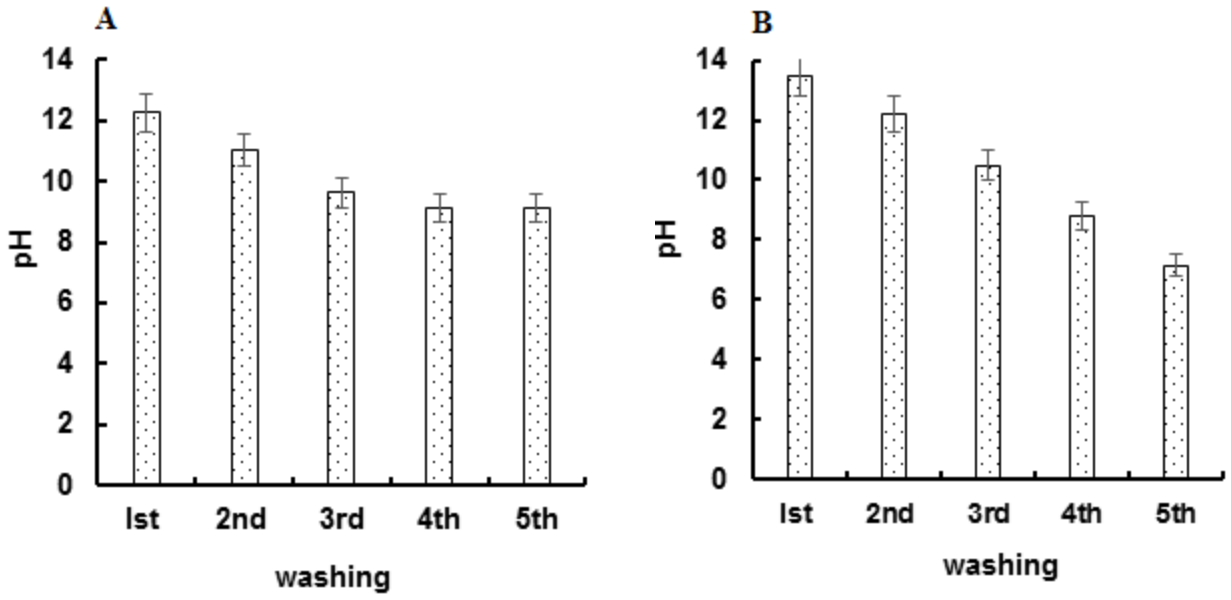

Figure 70. A) Treatment of Purolite® A430MR with 1N NaOH and washed with milli-Q® water B) Treatment of Duolite™ AP 143/1093 with 1N NaOH and washed with milli-Q® water (n = 3).

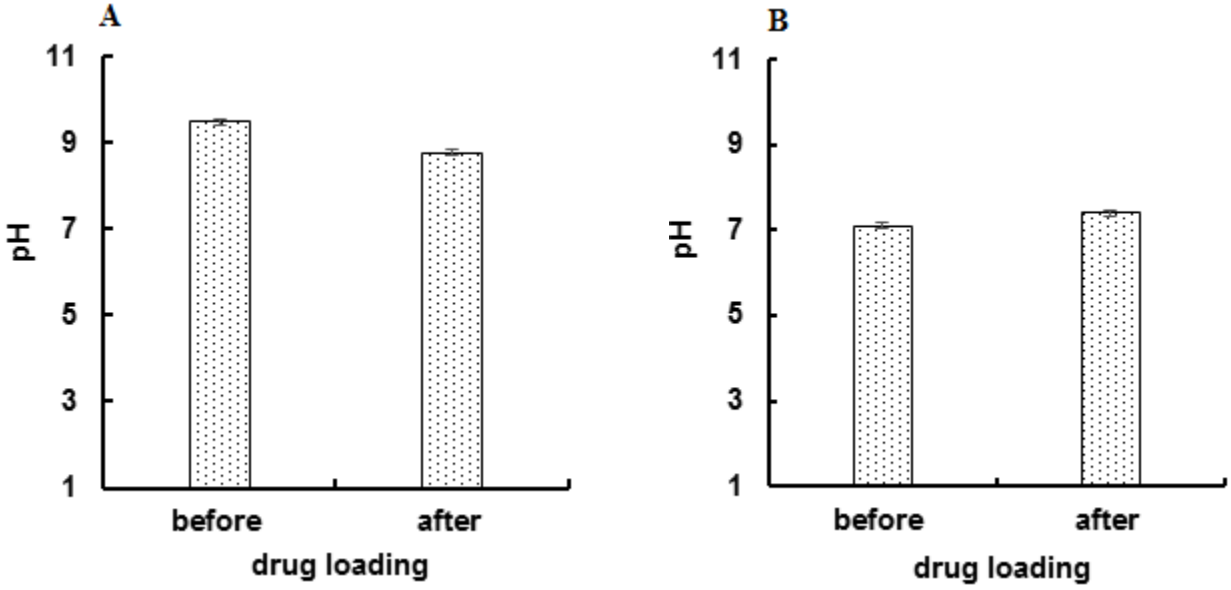

Figure 71. Effect of drug loading on change of pH during batch process for A) Duolite™ AP 143/1093 with OH^- ions and B) Purolite® A430MR with Cl^- ions.

3.4.2 Increase in solubility of ibuprofen from drug-resin complex

The saturated solubility of Ibuprofen was 0.02 ± 0.04 mg/ml in purified water. Moreover, saturated solubility of ibuprofen was 0.43 and 0.42 mg/ml, in NaCl (100 meq) and (300 meq) respectively by shaking flask method. On the other hand, solubility increased significantly from drug-resin complex up to 0.56 and 0.56 mg/ml in milli-Q® water when mixed with 100 meq and 300 meq NaCl respectively. Almost 3.5 folds increase in solubility of ibuprofen could be due to change in the salt form of ibuprofen in the presence of NaCl salts in their different concentrations (Table 18).

Table 18. Solubility of Ibuprofen from drug-resin complex

Solubility in Purified water (mg/ml) + (±SD)	**Solubility in NaCl (mg/ml) + (±SD)**		**Solubility from Drug resin complex in NaCl (mg/ml) + (±SD)**		**Increase in solubility (folds)**
	100 meq	**300 meq**	**100 meq**	**300 meq**	**NaCl**
0.02 ± 0.04	**0.43 ± 0.19**	**0.42 ± 0.03**	**0.56 ± 0.13**	**0.56 ± 0.01**	**3.5**

The particle size of Purolite® A430MR and Ibuprofen (drug-resin complex) was reduced by Dyno mill with 5 cycles of milling to 10.65 ± 0.55 µm from 75.68 ± 0.54 µm (Figure 72,73). Moreover, particle size distribution was varied from 4.14 ± 0.14 to 23.92 ± 1.5 with mean particle size 10.65 ± 0.55 µm after five successive cycles of milling (Table 19).

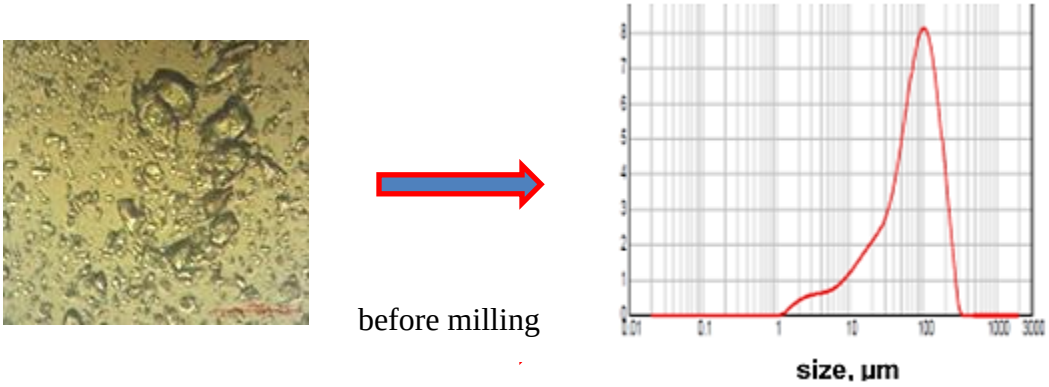

Figure 72. Light microscopic image of drug-resin complex before milling with mean particle size.

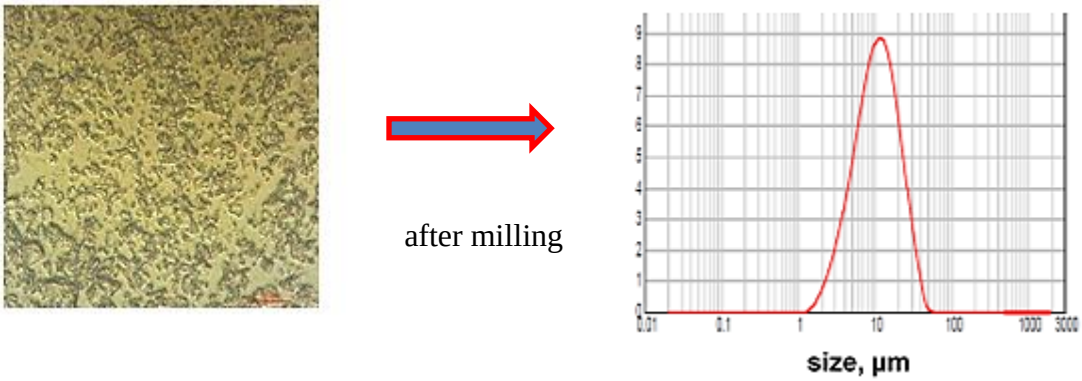

Figure 73. Light microscopic image of drug-resin complex after milling with mean particle size.

Table 19 Particle size distribution before and after milling with dyno-mill

Milling	D (0.1) (µm) (±SD)	D (0.5) (µm) (±SD)	D (0.9) (µm) (±SD)
before milling	12.75 ± 0.28	75.68 ± 0.54	172.91 ± 2.5
after milling	4.14 ± 0.14	10.65 ± 0.55	23.92 ± 1.5

3.4.3 Layering of drug-resin complex on NP core and drug release

There was significant difference in initial release during one hour of the first day formulation. And when it was stored at 40ºC/75%RH and 25°C/60%RH for one month. It was probably due to the leaching of layered ibuprofen into the coated polymer during storage which ultimately released the drug in the burst form for first hour (Figure 74).

The macroscopic images of pellets showed that pellets made by drug-resin complex layering were irregularly increased in size as compared to the pellets formed by simple layering of ibuprofen on NP core, it might be due to the non-uniform flow of pellets in the fluidized bed coater during processing (Figure 75).

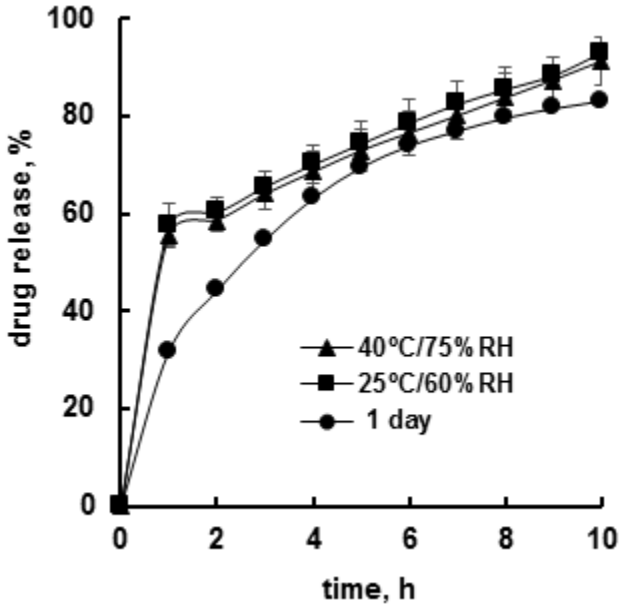

Figure 74. Ibuprofen release in pH 6.8 coated with 20% coating level of Kollicoat® SR 30D after storage at 40ºC/75%RH and 25ºC/60%RH.

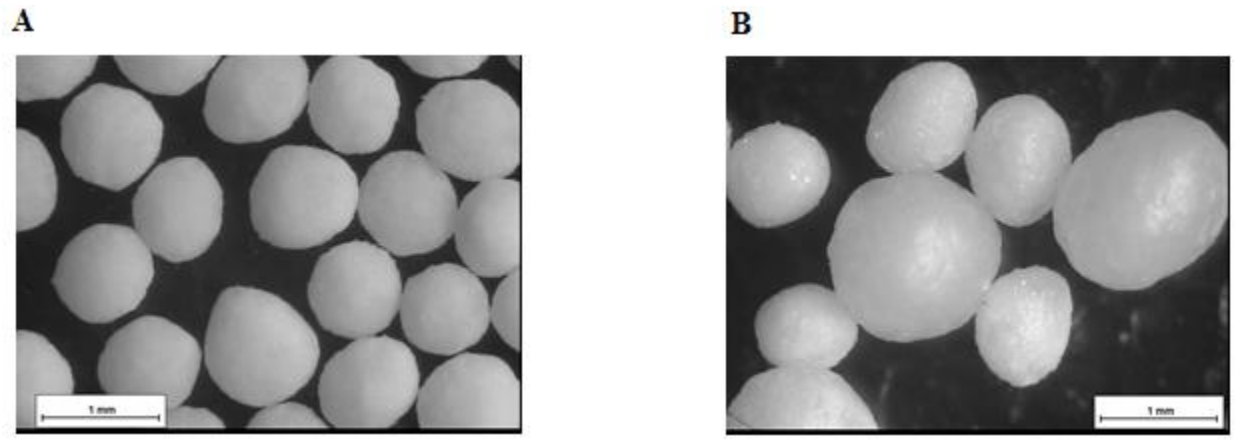

Figure 75. Macroscopic images of A) ibuprofen layered NP core pellets B) drug-resin complex layered NP core pellets.

In order to prevent the leaching of layered ibuprofen into coated polymer during storage, milled drug-resin complex was layered on NP core 710-850 µm. But drug release was incomplete from drug-resin complex layering. In order to get complete release, there was an additional layer of 10% KCl (weight gain) was applied before the final coating with Kollicoat® SR 30D. The drug release was bit fast and total release was increased up to 80% with this additional KCl layer but not of significant (f_2 = 82.52) (Figure 76).

It could be due to the increase in ionic concentration/strength in NP core below polymer coating. Without this additional layer of KCl, drug release was only 62%. It was due to insufficient strength of (Cl^-, OH^-, Na^+ and PO_4^{-3}) ions in the sodium phosphate release medium of pH 6.8. Whereas with an additional KCl layer there was overall increase in the cations and anions in form of K^+ and Cl^- below the coating layer in the system. These ions release the drug from the drug-resin complex layered NP core coated with Kollicoat® SR 30D (Woodworth et al., 1992).

Moreover, on macroscopic examination of pellets during and after release studies, it was evident that pellets made by drug-resin complex underwent uniform swelling and gave a smooth release profile even in the presence of weak points in the coating. On the other hand, swelling was localized in resin-free pellets, which caused rupturing of surface of pellets and made the release non-uniform (Figure 77, 78).

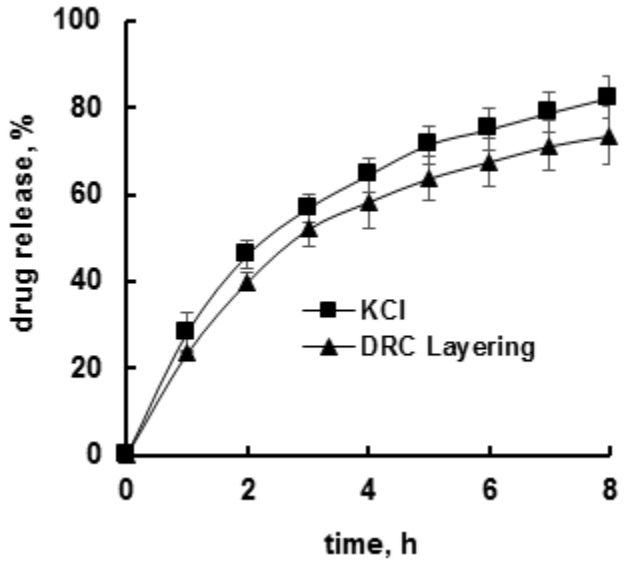

Figure 76. Ibuprofen release in pH 6.8 coated with 20% coating level of Kollicoat® SR 30D.

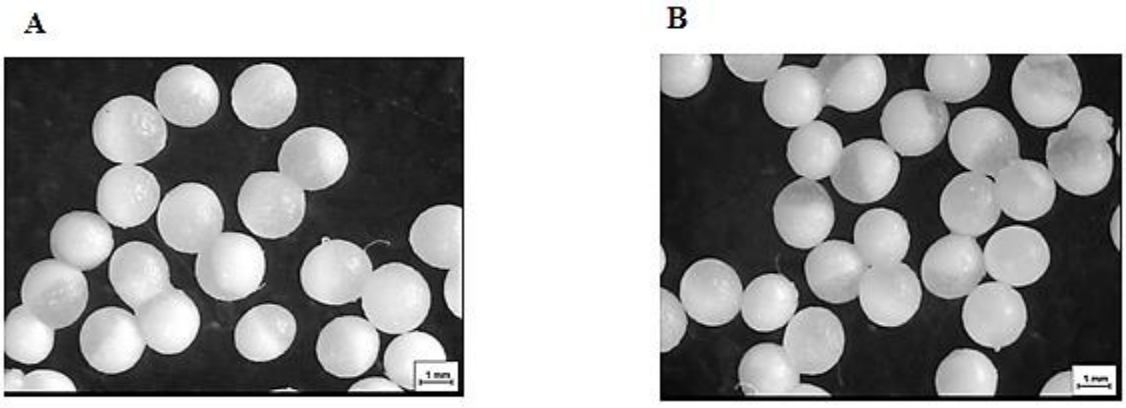

Figure 77. Macroscopic images of drug-resin complex layered pellets after drug release in A) pH 1 and B) pH 6.8 phosphate buffer.

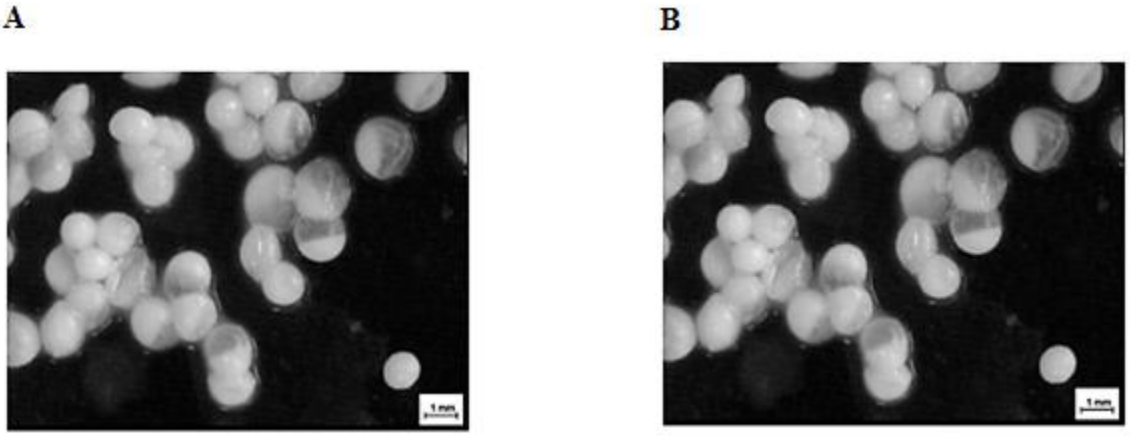

Figure 78. Macroscopic images of pellets without drug-resin complex layering after drug release in pH 1 A) and B) pH 6.8 phosphate buffer.

Furthermore, the drug release was similar, when drug-resin complex of ibuprofen and Purolite® A430MR was taken in the ratios 2:1 and 1:1. It could be stated that increased drug concentration in the complex had not any significant effect on the release. As drug release was only depend on the availability of counter ions in the dissolution medium instead of drug concentration in the complex (Figure 79). In drug-resin complex of ratio 2:1, less free ionic sites were available. It meant that when drug resin complex was in ratio 1:1, higher number of ionic sites remained free in the complex. These free ionic sites had no impact on retarding the drug release once the drug was dissociated from ionic sites of the resin (Chowhan et al., 1982).

Moreover, drug layering efficiency of DRC (drug-resin complex) on NP core always depends on the particle size of milled drug-resin complex by Dyno mill. The amount of binder was required more than 20% w/w with respect to DRC was necessary to be taken when particle size was bigger than 50 µm. Whereas, binder contents were reduced to 10-15% w/w when particle size of drug-resin complex was reduced to around 15 µm. (Siepmann et al., 2008).

For different percentage/strengths of layering thickness of drug-resin complex on NP core, release profile was similar, but coating level was reduced from 20% (where no resin in the formulation) to 15% (drug-resin complex layering on NP core) (Figure 80).

The layering of drug resin complex was varied from 2.5% to 10% w/w for a constant amount of coating level. The release profile was closer to zero order instead of first order. The reason of reduction of coating level from 20% to 15% was due to the reason that already complex state of

drug with resin retarded and controlled the release besides coating level. Moreover, drug release remained unchanged of the formulation after one-month storage at 40ºC/75% RH and 25ºC/60% RH (Figure 81).

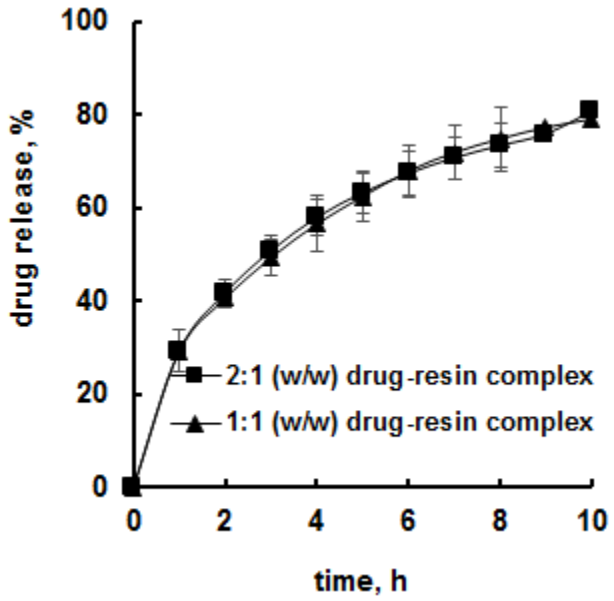

Figure 79. Release of ibuprofen in pH 6.8 for different ratios of resin and drug in drug-resin complex.

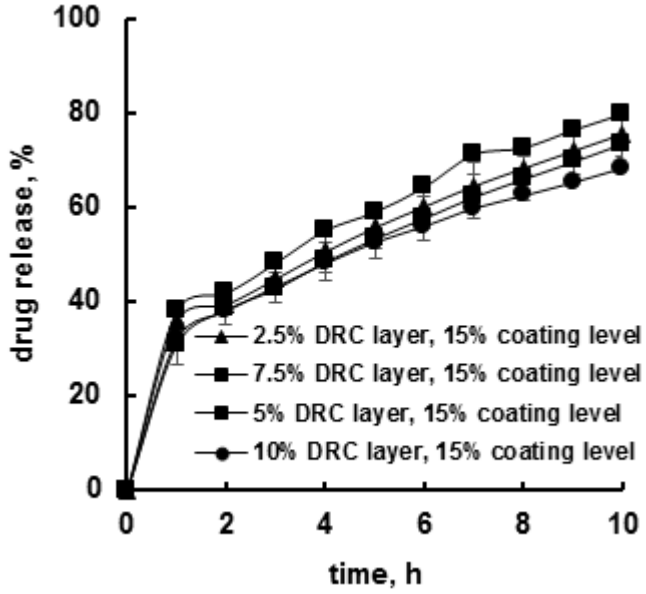

Figure 80. Release of ibuprofen from different layers of drug resin complex layering on NP core.

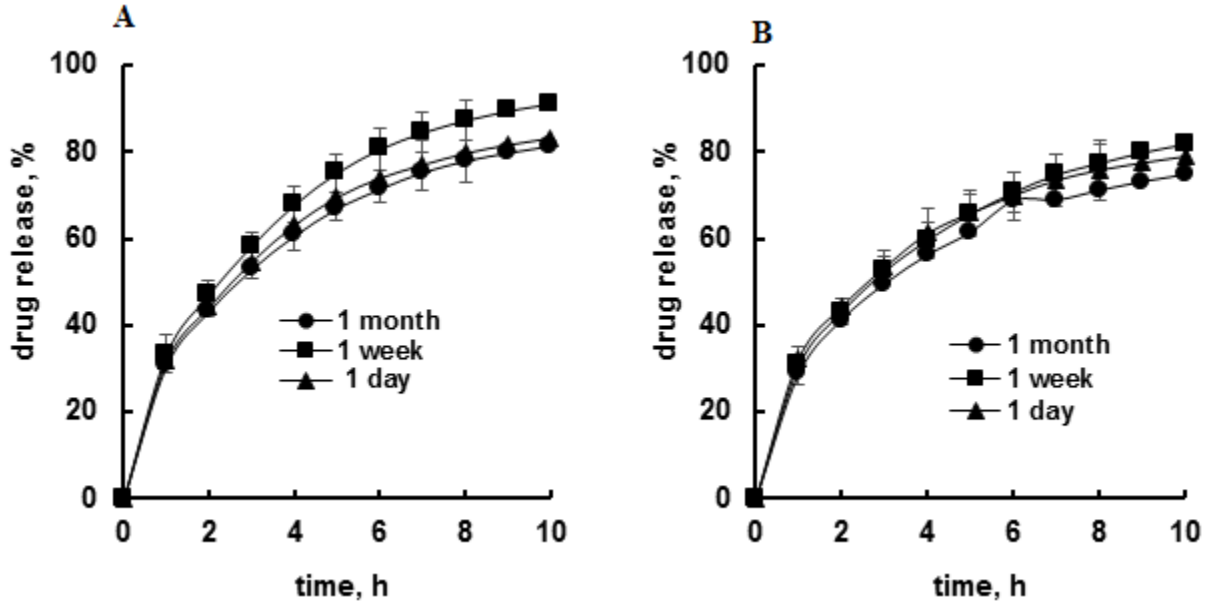

Figure 81. Effect of storage condition A) 25 ºC/60% RH and B) 40 ºC/75% RH on ibuprofen release in pH 6.8 phosphate buffer

3.4.4 Conclusion

There was no burst effect and increase of drug release observed in first two hours. When NP core (710-850 µm) was layered with drug-resin complex and stored for one-month storage at 40 ºC/75% RH and 25 ºC/60%RH. The robustness of reservoir system (pellets) was successfully enhanced by preventing of lipophilic drug (ibuprofen) into coated polymer Kollicoat® SR 30D by layering of drug-resin complex on NP core. The coating level was reduced from 20% to 15% when drug-resin complex layering was varied from 2.5% to 10% w/w on NP core. The saturated solubility of ibuprofen was increased up to 3.5 folds from Purolite® A430MR and Duolite™ AP143/1093 drug-resin complex. In summary, anion exchange resin (Purolite® A430MR) could be used as carrier to prevent the leaching of lipophilic drug into coated polymer.

4 Summary

Summary

A drug loading up to 55% w/w was achieved on Purolite® C100MRNS, which was independent of pH, temperature and stirring speed of the loading medium. The drug-resin complex was characterized by FTIR for functional group interactions of both resin and drug. The amorphous nature of drug-resin complex was characterized by powder laser diffraction. There was burst and incomplete release from uncoated resinates and it was probably due to an equilibrium between counter ions of release medium (H^+, Na^+) and exchanged drug molecules. An increase of 300 mM (Na^+ and Cl^-) ions of release medium had released the 95% of drug in 0.1N HCl. On the contrary, only 272.5 mM of (K^+, Cl^-, OH^-, Na^+ and PO_4^{-3}) ions of sodium phosphate buffer pH 6.8 were sufficient to release almost 90% drug. The complete drug release was not achieved. This was probably due to the strong nature of ionic complex between drug and resin or additional hydrophobic interactions of drug due to its amphiphilic nature. There was a significantly faster drug release with 4% DVB (divinyl benzene cross linking) than with 8%. As DVB cross linking influenced the interparticle diffusion, when drug was dissociated from the ionic sites of the resin. The release from Purolite® C100MRNS was depended on the pH and ionic strength of the media. The higher drug loading on ion exchange resin contributed to a decreased release rate. There was 17.46 ± 2.53 µm increase in mean particle size of Purolite® C100MRNS due to expansion of resin matrix on drug loading. Approximately 69.60 ± 6.95 µm increase of mean particle size of coated resinates for every 10% increase of coating level. The drug-resin complex was stable at 40ºC and 60ºC for one week. Moreover, drug release was also un-changed up to three months of storage at 40ºC/ 75% RH and 20ºC/ 60% RH. The drug release from resinates coated with Eudragit® RS 30D was increased after one month of storage at 40ºC/ 75% RH. This was probably due to an exchange of Cl^- with OH^- which increased the permeability of the coating. A formulation with a higher dose of 120.0 ± 9.13 mg/ml was successfully developed. The drug release remained unchanged over one week after reconstitution with a pH of 7.4. The formulation does not agglomerate when reconstituted with extra soluble granules of HPMC E5 of size 500-800 µm.

Another challenge with liquid controlled release formulations was the enteric coating due to the stability concerns and the drug release in the stomach. To address these challenges, drugs were first ionically complexed with Amberlite® IR 69F, then coated with the appropriate pH-dependent polymer (Eudragit® L30D-55). The USP criteria for such formulations, is less than 10% drug released in 0.1N HCl over two hours. The Amberlite® IR 69F swelled up to 45%. The drug loading

was only 7% w/w for 72 hours, when resin was regular shape (spherical particles) with a size of 300 to1100 µm. The drug loading was significantly increased up to 55% w/w when resin was milled by ball milling and particle size was reduced to 45-150 µm. The drug loading for a particle size of 45-150 µm was fast within the first hour and remained constant till 24 hours. It was probably due to saturation of all ionic sites in the resin. The shifting of transmittance peaks of $-SO_3^{-1}$ group of resin from 1180.43 cm^{-1}, 1039.62 cm^{-1} and 833.24 cm^{-1} to 1170.15 cm^{-1} 1030.62 cm^{-1} and 794.67 cm^{-1} respectively, confirmed the formation of a complex between $-N^+HCl^-$ group of propranolol HCl and $-SO_3^-$group of Amberlite® IR69F. The absence of drug peaks in P-XRD and crystalline nature of drug under polarized light microscope confirmed the amorphous state of the resinates. There was increase of particle size 12 ± 3 µm during drug loading. It was due to the expansion of resin matrix upon during loading process. There was increase in particle size of resinates up to 70.64 ± 5.85 µm for every 10% to 25% coating level (% weight gain). The drug release was less than 10% in 250 ml of 0.1 N HCl within two hours and more than 70% release during first hour in pH 6.8 sodium phosphate, confirmed the enteric drug delivery system. The drug-resin complex was stable at 40ºC and 60ºC for a period of one week. Furthermore, the drug release remained un-changed over 3 months storage at 40°C/75% RH and 25ºC/60% RH. Furthermore, there was no agglomeration of coated particles during one-week storage at temperature of 2-8°C after its reconstitution.

The model drugs (diltiazem HCl and tramadol HCl) were loaded on Purolite®C100CaMRNS (cation exchange resin) by a batch process. The drug-resin complexes were characterized for functional group interactions with FTIR and crystalline state of drug with P-XRD. The absence of drug peaks in P-XRD confirmed the amorphous nature of the resinates. The particle size distribution of powders was measured with powder laser diffraction. Uncoated resinates showed a burst and incomplete release in both 0.1N HCl and pH 6.8 sodium phosphate buffer. The release was successfully controlled by the Eudragit® NE30D, 25 % coating level (% weight gain) with a curing procedure at 60°C for 12 hours. The complete drug release for both drugs was achieved when the media was mixed with 300 mM KCl. The shifting of stretching vibrations of $-SO_3^-$ group of resin from 1039.62 cm^{-1} to 1035.91 cm^{-1} and 1030.62 cm^{-1} in drug- resin complex confirmed the formation of a complex between -NH group of both drugs and $-SO_3^-$group of resin. The leaching of drug was less than 1% when the formulation was treated with 5 mM KCl/NaCl over one week with pH 6.08 ± 0.02.

In reservoir multiparticulate systems, lipophilic drug such as ibuprofen, is leached out in the coating polymer during the storage of the formulation at 40 ºC/75% RH. The leaching was happened when the formulations were coated with an aqueous polymer dispersion like Aquacoat® ECD and Kollicoat® SR 30D. This ultimately affects the robustness of the reservoir systems. In order to prevent this drug leaching into the coated polymer, an intermediate seal coating of (HPMC) or (PEG) was applied. At the same time, the additional seal coating increases the production costs of the delivery system. So therefore, there was a need to address the leaching of the lipophilic drug into the coated polymer with help of drug-resin complex. The drug Ibuprofen was successfully loaded/complexed with anion exchange resin Purolite® A430MR and Duolite ™ AP143/1093. The particle size of drug-resin complex was reduced to 10.65 ± 0.55 µm using Dyno mill. The drug-resin complex was layered on NP core 710-850 µm in a fluidized bed coater. The layering formulation was prepared with 20% HPMC E5 as a binder w/w of drug-resin complex. There was no increased drug release observed during first hour of the release, when formulation was stored for one-month at 40 ºC/75% RH and 25 ºC/60% RH. This confirms the prevention of leaching of lipophilic drug into the Kollicoat® SR 30D coating during storage with help of drug-resin complex layering.

5 Zusammenfassung

Eine Arzneistoffbeladung bis zu 55% (m/m) wurde mit Purolite® C100MRNS erreicht, welche unabhängig von pH, Temperatur und Rührgeschwindigkeit des Beladungsmediums war. Der Arzneistoff-Harz Komplex wurde durch FTIR auf Wechselwirkungen funktioneller Gruppen von sowohl Harz als auch Arzneistoff hin charakterisiert. Die amorphe Natur des Arzneistoff-Harz Komplexes wurde durch Powder Laser Diffraktometrie charakterisiert. Es gab spontane und unvollständige Freisetzung von nicht-überzogenen Harzen und dies lag wahrscheinlich an einem Gleichgewicht zwischen Gegenionen des Freisetzungsmedium (H^+, Na^+) und ausgetauschten Arzneistoffmolekülen. Eine Zunahme von 300mM (Na^+ and Cl^-) Ionen des Freisetzungsmedium setzte 95% des Arzneistoffs in 0,1 N HCl frei. Im Gegensatz dazu waren nur 272,5 mM von (K^+, Cl^-, OH^-, Na^+ and PO_4^{-3}) Ionen des Natrium Phosphat Puffers pH 6,8 ausreichend um fast 90% des Arzneistoffes freizusetzen. Die komplette Freisetzung des Arzneistoffes wurde nicht erreicht. Dies liegt wahrscheinlich an einer starken Bindung des ionischen Komplexes zwischen Arneistoff und Harz oder zusätzlichen hydrophoben Interaktionen des Arzneistoffes aufgrund seiner amphiphilen Natur. Es gab signifikant schnellere Arzneistofffreisetzung mit 4% DVB (Divinyl Benzen quervernetzt) als mit 8%. DVB quervernetzt beeinflusst die interpartikuläre Diffusion, wenn der Arzneistoff von der ionischen Seite des Harzes dissoziert. Die Freisetzung aus Purolite® C100MRNS war abhängig vom pH und der Ionenstärke des Mediums. Die höhere Arzneistoffbeladung auf dem Ionenaustauscher Harz trug zu einer reduzierten Freisetzungsrate bei. Es gab eine Steigerung von 17,45 ± 2,53 µm in der mittleren Partikelgröße von Purolite® C100MRNS aufgrund der Ausdehnung der Harzmatrix nach Arzneistoffbeladung. Eine Zunahme von ungefähr 69,60 ± 6,95 µm der mittleren Partikelgröße von überzogenen Harzen für jede 10%ige Überzugsstufe. Der Arzneistoff-Harz Komplex war stabil bei 40°C und 60°C für eine Woche. Desweiteren war auch die Arzneistofffreisetzung unverändert nach drei monatiger Lagerung bei 40°C/75% LF (relative Luftfeuchte) und 20°C/ 60% LF. Die Arzneistofffreisetzung aus mit Eudragit® RS 30D überzogenen Harzen war erhöht nach einmonatiger Lagerung bei 40°C/75% LF. Dies lag wahrscheinlich an einem Austausch von Cl^- gegen OH^-, welcher die Durchlässigkeit des Überzuges erhöhte. Eine Formulierung mit einer höheren Dosis von 120,0 ± 9,13 mg/ml wurde erfolgreich entwickelt. Die Arzneistofffreisetzung blieb unverändert für eine Woche nach rekonstitutierung bei einem pH von 7,4. Die Formulierung agglomerierte nicht wenn sie mit besonders löslichen Granulaten von HPMC E5 der Größe 500-800 µm rekonsitutiert wurde. Eine weitere Herausforderung mit flüssigen kontrolliert freisetzenden Formulierungen war der

enterische Überzug aufgrund der Stabilitätsbedenken und der Arzneistofffreisetzung im Magen. Um diese Herausforderung zu adressieren wurden Arzneistoffe zuerst ionisch komplexiert mit Amberlite® IR 69F, dann überzogen mit dem angemessenen pH-abhängigen Polymer (Eudragit® L30D-55). Die USP-Kriterien für solche Formulierungen ist, dass weniger als 10% Arzneistoff freigesetzt wird in 0,1 N HCl über zwei Stunden. Das Amberlite® IR 69F quoll um bis zu 45%. Die Arzneistoffbeladung war nur 7% (m/m) für 72 Stunden, wenn sie als reguläre Form (sphärische Partikel) mit einer Größe von 300 bis 1100 µm genommen wurden. Die Arzneistoffbeladung wurde signifikant auf bis zu 55% (m/m) erhöht, wenn das Harz gemahlen wurde durch Kugelmahlung und die Partikelgröße auf 45 – 150 µm reduziert wurde. Die Arzneistoffbeladung für Partikel der Größe 45 – 150 µm war schnell während der ersten Stunden und blieb konstant für 24 Stunde. Dies lag wahrscheinlich an der Sättigung aller ionischen Stellen im Harz. Die Verschiebung des Transmissionspeaks der SO_3^{-1} Gruppen des Harzes von 1180.43 cm^{-1}, 1039.62 cm^{-1} und 833.24 cm^{-1} zu 1170.15 cm^{-1} 1030.62 cm^{-1} zu 794.67 cm^{-1} entsprechend, bestätigte die Formulierung eines Komplexes zwischen $-N^+HCl^-$ Gruppen des Propranolol-HCl und den $-SO_3^-$Gruppen des Amberlite® IR69F. Die Abwesenheit von Arzneistoffpeaks in P-XRD und die kristalline Natur des Arzneistoffs unter polarisiertem-Licht Mikroscope bestätigte die amorphe Gestalt des Harzes. Es gab einen Zuwachs der Partikelgröße um 12 ± 3 µm während der Arzneistoffbeladung. Dies lag an der Ausdehnung der Harzmatrix während des Beladungsprozesses. Es gab eine Zunahme der Partikelgröße des Harzes um 70.64 ± 5.85 µm pro 10% bis 25% Überzugsmenge (% Gewichtszunahme). Die Arzneistofffreisetzung war geringer als 20% in 250 ml von 0,1 N HCl innerhalb von zwei Stunden. Es war mehr als 70% während der ersten Stunde in pH 6,8 Sodium-phosphat Puffer. Dies bestätigte die enterische Arzneiform. Der Arzneistoff-Harz Komplex war stabil bei 40°C und 60°C für die Dauer einer Woche. Desweiteren blieb die Arzneistofffreisetzung unverändert über 3-monatige Lagerung bei 40°C/75% LF und 25ºC/60% LF. Desweiteren gab es keine agglomeration von überzogenen Partikeln während einwöchiger Lagerung bei 2-8°C nach der Rekonstituierung.

Beide Modell-Arzneistoffe (Diltiazem HCl und Tramadol HCl) wurden auf Purolite®C100CaMRNS (Kationen Austauscher Harz) in einem Chargenprozess geladen. Der Arzneistoff-Harz Komplexe wurden in Bezug auf Interaktionen ihrer funktionellen Gruppen mit FTIR und in Bezug auf die Kristallstruktur des Arzneistoffes mit P-XRD hin untersucht. Die Abwesenheit von Arzneistoffpeaks in P-XRD bestätigte die amorphe Struktur der Harze. Die

Partikelgrößenverteilung der Pulver wurde mit Pulver Laser Diffraktomerie gemessen. Unbeschichtete Harze zeigten eine plötzliche und unvollständige Freisetzung sowohl in 0,1 N HCl und pH 6,8 Sodium Phosphat Puffer. Die Freisetzung wurde erfolgreich kontrolliert durch Eudragit® NE30D, 25% Überzugsstufe (% Gewichtszunahme) mit einer Nachbehandlungsprozedur bei 60°C für 12 Stunden. Die komplette Arzneistofffreisetzung für beide Arzneistoffe wurde erreicht when das Medium mit 300 mM KCl gemischt wurde. Die Verschiebung der Streckungsvibrationen der $-SO_3^-$ Gruppe des Harzes von 1039,62 cm^{-1} zu 1035,91 cm^{-1} und 1030,62 cm^{-1} im Arzneistoff-Harz Komplex bestätigte die Bildung eines Komplexes zwischen –NH Gruppen beider Arzneistoffe und der $-SO_3^-$ Gruppe des Harze. Der Austritt von Arzneistoffen war weniger als 1%, wenn die Formulierung mit 5 mM KCl/NaCL über eine Woche mit pH 6,08 ± 0,02 behandelt wurde.

In Reservoir multipartikulären System, treten lipophile Arzneistoffe wie Ibuprofen, aus in das Überzugspolymer während der Lagerung der Formulierung bei 40°C/75% LF. Dies passierte als die Formulierung mit einer wässrigen Polymerdispersion überzogen wurden wie Aquacoat® ECD und Kollicoat® SR 30D. Dies betrifft letztlich die Robustheit des Reservoirsystems. Um dieses Austreten des Arzneistoffes in das Überzugspolymer zu verhindern, wurde ein intermediärer Versiegelungsüberzug von (HPMC) oder (PEG) appliziert. Gleichzeitig erhöht der zusätzliche Versiegelungsüberzug die Herstellungskosten der Formulierung. Daher gab es eine Notwendigkeit das Austreten lipophiler Arzneistoffe in das Überzugspolymer zu adressieren mithilfe des Arzneistoff-Harz Komplexes. Der Arzneistoff Ibuprofen wurde erfolgreichen geladen/komplexiert mit dem Anionen-austauscher Harz Purolite® A430MR und Duolite ™ AP143/1093. Die Partikelgröße des Arzneistoff-Harz Komplexes wurde auf 10,65 ± 0,55 µm reduziert mithilfe der Dynomill. Der Arzneistoff-Harz Komplex wurde aufgeschichtet auf NP-Kernen 710-850 µm in einem fluidized bed coater. Die geschichtete Formulierung wurde hergestellt mit 20% HPMC E5 (m/m) als Bindemittel des Arzneistoff-Harz Komplexes. Es war keine erhöhte Arzneistofffreisetzung sichtbar während der ersten Stunde der Freisetzung, wenn die Formulierung einen Monat lang bei 40°C/75% LF und bei 25°C/60% LF gelagert wurde. Dies bestätigt die Prävention des Austretens des lipophilen Arzneistoffes in den Kollicoat® SR 30D Überzug während der Lagerung mithilfe der Schichtung des Arzneistoff-Harz Komplexes

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7 Publications

Publications

Khan N.I., Dashevskiy A., Irfan M., Bodmeier. R., An insight into the oral liquid-controlled release formulations with ion exchange resins. (under preparation)

Khan N.I., Dashevskiy A., Irfan M., Bodmeier. R., Evaluation of Purolite® C100CaMRNS (cation exchange resin) as drug combination delivery carrier. (under preparation)

Poster Presentations

N.I. Khan, A. Dashevskiy, R. Bodmeier "Evaluation of Purolite® C100MRNS Ion Exchange Resin as Drug Delivery Carrier" Presented at American Association of Pharmaceutical Scientists (AAPS) 2015 conference held in Orlando, Florida, USA.

N.I. Khan, M. Irfan, R. Bodmeier "Evaluation of Purolite® C100CaMRNS (cation exchange resin) as drug combination delivery carrier" Presented at "Tag der Pharmazie" held on 1st July 2016 Freie Universität Berlin Deutsche Pharmazeutische Gesellschaft (DPhG).

N.I. Khan, M. Irfan, R. Bodmeier "Evaluation of Amberlite® IR69F (cation exchange resin) as an enteric drug delivery carrier" Presented at American Association of Pharmaceutical Scientists (AAPS) 2016 conference held in Denver, Colorado, USA).

L.Toufik, K. Mäder, R. Ali, **N. I. Khan,** A. Dashevskiy, R. Bodmeier "Cellulose acetate butyrate as an ethanol-resistant polymer for preparing coated multiparticulate" Presented at "Tag der Pharmazie" held on 1st July 2016 Freie Universität Berlin Deutsche Pharmazeutische Gesellschaft (DPhG).

R. Ali, **N.I. Khan,** R. Bodmeier "Improving compactibility of high pellet-loaded tablets using Eudragit®RL as top-coating polymer of pellets" Presented at American Association of Pharmaceutical Scientists (AAPS) 2016 conference held in Denver, Colorado, USA).

8 Curriculum Vitae

For reasons of data protection, the curriculum vitae is not included in the online version