Floating Systems for Oral Controlled Release Drug Delivery

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To my Family

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1. INTRODUCTION

1.1. Modified Release Oral Drug Delivery Systems

The oral route represents nowadays the predominant and most preferable route for drug delivery. Unlike the majority of parentral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body.

Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion.

Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects (Eisen et al., 1990; Getsios et al., 2004; Sansom, 1999). Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics (Longer and Robinson, 1990). Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration (Hoffman, 1998). Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as minitablets, pellets, beads or granules, either as coated (reservoir) or matrix devices (Kumar and Kumar, 2001).

Extended release DDS offer several advantages compared to conventional DDS (Siepmann and Siepmann, 2008) including:

i. Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub-therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects;

ii. Reducing the administered dose while achieving comparable effects;

iii. Reduced frequency of administration leading to improved patients' compliance and subsequently improved efficacy of the therapy and cost effectiveness;

iv. Targeting or timing of the drug action. Hence, it is highly desirable to develop sustained DDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

On the other hand, drugs administered as sustained or extended release oral dosage form should comply with the following parameters:

i. Maintain a constant plasma level over prolonged time periods;

ii. Have a broad therapeutic window to avoid health hazard to the patient in case of undesirable burst release of the nominal dose (Hoichman et al., 2004).

The maximum achievable sustained drug release is subject to inter individual variations, with an average gastrointestinal (GI) transit time of around 24 h in humans (Davis et al., 1984). The transit time is affected by age, gender, body mass index and the state of health of the individual as well as his emotional state and composition of meals. In addition, drugs affecting gastric motility, such as opioid analgesics or metoclopramide, have to be taken into account.

Numerous oral sustained drug delivery systems have been developed to prolong drug release. The key point in this respect is that the API has to be absorbed well throughout the whole gastrointestinal tract (GIT). Generally, the absorption of APIs from oral DDS is precluded by several physiological difficulties, such as inability to restrain and

localize the drug delivery system within desired regions of the GIT and the high variable nature of gastric emptying process (Rouge et al., 1996). The gastric emptying process can vary from a few minutes to 12 h, depending upon the physiological state of the subject and the design of pharmaceutical formulation. This variation, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine (Rouge et al., 1996). In addition, the relatively brief gastric emptying time in humans, through the stomach or upper part of the intestine (major absorption zone), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose.

1.2. Gastroretentive Drug Delivery Systems

The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance (Fell, 1996). Therefore, extended release DDS possessing gastric retention properties may be potentially useful (Streubel et al., 2006b).

1.2.1. Physiological Factors Affecting Gastric Retention

1.2.1.1. The Gastric Emptying Process

The stomach is anatomically divided into three parts: fundus, body and pylorus (pyloric antrum and pyloric sphincter). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region, pylorus, is the major site for mixing motions, acting as pump to accomplish gastric emptying.

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility have been identified.

In the fasted state, the process of gastric emptying is characterized by an interdigestive series of electrical events, which cycle both through the stomach and small intestine every 2-3 h (Fell, 1996). This activity is called the interdigestive myoelectric cycle or interdigestive migration myoelectric complex (IMMC), which is divided into four consecutive phases (Sarna, 1985; Sarna and Otterson, 1988; Schemann and Ehrlein, 1986; Wilding et al., 2001). Phase I is a quiescent period lasting from 40-60 min with rare contractions. Phase II is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progress. Phase III is a short period of intense, large regular contractions lasting from 4 to 6 min, also called "house keeper" wave, since undigested materials are swept out of the stomach and down the small intestine in this phase. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum. Phase IV, a brief transitional phase, occurs between phase III and phase I of two consecutive cycles.

In the fed state, the onset of IMMC is delayed and therefore the gastric emptying rate is slowed (Deshpande et al., 1996). In other words, feeding results in a lag time prior to the onset of gastric emptying.

Factors affecting the gastric emptying and hence the gastric retention time of an oral dosage form include:

i. Size, shape and density of the dosage form (Coupe et al., 1991; Khosla and Davis, 1990; Timmermans and Moes, 1994).

ii. Concomitant ingestion of food, its nature, caloric content and frequency of intake (Abrahamsson et al., 1993; Coupe et al., 1993; O'Reilly et al., 1987; Sangekar et al., 1987; Wilding et al., 1992). Interestingly, most studies related to effects of food on gastric residence time of floating systems share a common viewpoint that food intake is the main determinant of gastric emptying, while specific gravity has only a minor effect on the emptying process (Davis et al., 1986; Mazer et al., 1988; Sangekar et al., 1987), or not have an effect at all.

iii. Drugs such as anticholinergic agents (e.g. atropine, propantheline); opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride) (Hocking et al., 1988; Kaus et al., 1984).

iv. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease (Bennett et al., 1984; Coupe et al., 1992a, 1992b; Hermansson and Sivertsson, 1996).

Since many factors could lead to alterations in gastric emptying process, which may seriously affect the release of a drug from its delivery system, it is therefore, desirable to develop a DDS that exhibits an extended GI residence and a drug release profile independent of patient related variables (Whitehead et al., 1998).

1.2.1.2. The Gastric pH

The gastric pH is influenced by many factors like diet, disease, presence of gases or fatty acids, and other fermentation products (Rubinstein, 1990), age (Varis et al., 1979), pathological conditions (Holt et al., 1989; Lake-Bakaar et al., 1988), drugs, as well as intra- and inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in humans. It has been reported that the mean value of gastric pH in fasted healthy males is 1.7 ± 0.3 (Chung et al., 1986; Dressman et al., 1990; Russell et al., 1993), while that of females was reported to be slightly lower (Charman et al., 1997; Feldman and Barnett, 1991). On the other hand, in the fed state, the mean gastric pH in healthy males has been reported to be between 4.3 – 5.4 (Dressman et al., 1990), and the pH returned to basal level in about 2 to 4 hours.

About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5.0 (Varis et al., 1979). Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH (Holt et al., 1989; Lake-Bakaar et al., 1988). In addition, drugs like H_2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

Hence, the gastric pH is an important consideration when selecting a drug substance, excipients, and drug carrier for designing intragastric delivery systems.

1.2.2. Drug Candidates for Gastric Retention

Gastroretentive DDSs exhibiting controlled drug release are significantly important for drugs which are:

i. Acting locally in the stomach (e.g. antibiotics against Helicobacter Pylori, antacids and misoprostol) (Burton et al., 1995; Fabregas et al., 1994; Oth et al., 1992; Whitehead et al., 2000; Whitehead et al., 1996).

ii. Absorbed incompletely due to a relatively narrow window of absorption in the GIT, such as cyclosporin, ciprofloxacin, furosemide, L-DOPA, *p*-aminobenzoic acid and riboflavin (Drewe et al., 1992; Erni and Held, 1987; Harder et al., 1990; Hoffman et al., 2004; Ichikawa et al., 1991a; Klausner et al., 2003d; Levy and Jusko, 1966; Rouge et al., 1996).

iii. Unstable in the intestinal or colonic environment such as captopril (Matharu and Sanghavi, 1992) or

iv. Exhibit low solubility at high pH values such as verapamil HCl, diazepam and chlordiazepoxide (Chen and Hao, 1998; Elkheshen et al., 2004; Sheth and Tossounian, 1984; Soppimath et al., 2001).

In general the group of drugs, that benefits from an oral application using a gastroretentive DDS, includes analgesics, antibiotics, tranquilizers, diuretics, antidepressants, vitamins, hormones, antacids and antiparkinsonian drugs (Hoichman et al., 2004).

Gastroretentive DDS, on the other hand, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents and drug substances that are unstable in the strong acidic environment of the stomach. In addition, gastroretentive systems do not offer significant advantages over conventional dosage forms for drugs,

which are absorbed throughout the gastrointestinal tract (Talukder and Fassihi, 2004). It is recognized, however, that there are many physiological constraints which may limit development of such delivery systems.

1.2.3. Approaches to Gastric Retention

Various approaches have been pursued over the last three decades, to increase the retention of oral dosage forms in the stomach. The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include a) co-administration of the DDS with pharmacological agents that slow gastric motility (Gröning and Heun, 1984; Gröning and Heun, 1989), b) bioadhesive systems (Alvisi et al., 1996; Bravo-Osuna et al., 2007; Ponchel and Irache, 1998), c) size increasing systems, which are either due to expansion and shape modification (Cargill et al., 1988; Fix et al., 1993; Kedzierewicz et al., 1999; Klausner et al., 2003b; Klausner et al., 2003c; Klausner et al., 2003d) or swelling (Deshpande et al., 1997a; Gröning et al., 2007; Groning et al., 2006; Shalaby et al., 1992), and d) density controlled systems which are either, high density systems (Clarke et al., 1995; Clarke et al., 1993; Rouge et al., 1998; Tuleu et al., 1999) or floating systems (Hwang et al., 1998; Stops et al., 2008; Whitehead et al., 1998; Yang et al., 1999).

1.2.3.1. Coadministration of Pharmacological Agents that slow Gastric Motility

This includes the ingestion of indigestible polymers (Leung et al., 1993; Russel and Bass, 1985; Russell and Bass, 1985), or fatty acid salts (Gröning and Heun, 1984; Gröning and Heun, 1989; Keinke and Ehrlein, 1983; Malbert, 1999) which change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and accordingly permitting prolongation of drug release (Deshpande et al., 1996; Klausner et al., 2003c; Moes, 1993; Reddy and Murthy, 2002). A number of these techniques were reported to be successful in various in-vitro tests (Srivastava et al., 2005; Talukder and Fassihi, 2004; Umamaheshwari et al., 2003) or in preclinical investigations, particularly demonstrating prolonged retention in a dog model (Chen et al., 2000; Davis, 2005; Fix et al., 1993).

1.2.3.2. Bioadhesive Systems

This approach is used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner (Itoh et al., 1986). A bioadhesive can be defined as a substance with the ability to interact with biological materials and is capable of being retained on the biological substrate for a period of time. Bioadhesion always occurs in the presence of water (Andrews et al., 2009; Park and Robinson, 1985).

It involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GIT. These are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose (CMC), sodium alginate and carrageenan). A broad spectrum of polymers was studied for their bioadhesive properties. It was concluded that anionic polymers have better binding capacity than neutral or cationic polymers (Lehr, 1994; Pardeep K. Gupta et al., 1990). The proposed mechanism of bioadhesion is the formation of hydrogen – and electrostatic bonding at the mucus-polymer boundary (Pardeep K. Gupta et al., 1990), although it is not yet clear. Rapid hydration in contact with the muco-epithelial surface appears to favor adhesion.

Several types of dosage forms have been proposed to allow prolonged gastric residence based on bioadhesive polymers.

Jackson *et al.* (Jackson et al., 2000; Jackson and Perkins, 2001) observed extended gastric residence times of the positively charged ion-exchange resin cholestyramine, an anionic resin, due to adhering to and coating of the gastric mucosa. On the other hand, the oppositely charged cationic-exchange resin Amberlite IRP-69 did not possess the same characteristics. Such behaviors lead to concluding that the surface charge of the resin might play a significant role in mucoadhesion and subsequent retention.

Chitosan and thiolated chitosan (chitosan-TBA) - coated poly(isobutyl cyanoacrylates) *(PIBCA)* nanoparticles, prepared by radical emulsion polymerization were developed by Bravo-Osuna *et al.* (Bravo-Osuna et al., 2007). Mucoadhesion was evaluated *ex vivo* on rat intestinal mucosal surfaces. The presence of either chitosan or thiolated chitosan in the nanoparticle surface promoted the mucoadhesion behaviour of the colloidal system;

moreover the presence of thiol groups on the nanoparticle surface at high concentration further increased the mucoadhesion capacity of nanoparticles by forming covalent bonds with the cysteine residues of the mucus glycoproteins. On the other hand, changes in the polymeric shell composition (molecular weight of chitosan, presence of a cross-linked structure, density of active thiol groups on the surface) can clearly influence the bioadhesive behaviour of these colloidal systems.

Tetracycline–sucralfate complex was prepared under acidic conditions by Higo *et al.* (Higo et al., 2004) and its mucoadhesive properties both *in vitro* and *in vivo* were evaluated. The complex showed excellent mucoadhesive properties, where higher amounts of the complex were retained on the gastric mucosa compared with the physical mixtures of tetracycline and sucralfate.

Schmitz *et al.* (Schmitz et al., 2005) developed stomach-targeted oral minitablets for low molecular-weight heparin. Thiolated polycarbophil was used as the mucoadhesive carrier material and was compared with hydroxyethylcellulose (HEC) as a non-mucoadhesive control. The *in vitro* drug release profiles were similar for both polymers. In a gastric transit study in rats, the HEC formulations could not be observed in the gastric lumen at 4 h after administration, in contrast to thiolated polycarbophil-based delivery systems. Further *in vivo* evaluation in rats revealed that the relative bioavailability of oral formulations (compared with subcutaneous administration) was significantly higher in the case of thiolated polycarbophil compared with HEC.

Mucoadhesive microspheres containing drug and Carbopol® 934P have been developed, which were dispersed within a waxy matrix of polyglycerol esters of fatty acids. The microspheres were reported to prolong the GI residence of the drug after oral administration, by adhering to the stomach mucosa in rats and Mongolian gerbils, which was due to the hydration and swelling of the Carbopol in the microspheres on contact with water (Yohko Akiyama and Nagahara, 1999).

Although the concept of bioadhesion gains increasing interest in alternative routes of administration (e.g., nasal, buccal, ocular, vaginal and rectal), gastroretentive bioadhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucous present in the stomach. High turnover rate of the gastric mucous leads to difficulties in retaining a bioadhesive system

at site (Longer et al., 1985; Ponchel and Irache, 1998; Waterman, 2007) . Furthermore, it is difficult to specifically target the gastric mucus with bioadhesive polymers. For example, polycarbophil and Carbopol stick to the various surfaces they come into contact with (Khosla and Davis, 1987). This may lead to the risk of esophageal adherence which may cause drug-induced injuries (Kikendall et al., 1983).

1.2.3.3. Size-Increasing Systems

This approach involves retaining the dosage form in the stomach by increasing its size above that of the pyloric sphincter. Due to significant inter-individual variations, the cutoff size cannot be given exactly, but its diameter was reported to be 12.8 ± 7.0 mm (Quigley, 1996). Streubel *et al*. estimated, that dosage forms should exhibit a minimum size of 13 mm for being retained in the stomach, however, even bigger units have been reported to be emptied through the pylorus (Streubel et al., 2006a).

In order to facilitate swallowing, the dosage form should have an initially small size. Once in the stomach, the dosage forms should quickly increase in size, to prevent premature emptying through the pylorus. In order to avoid accumulation following multiple administrations, the system should be cleared from the stomach after a predetermined time interval. In addition, the dosage form should have no effect on gastric motility or emptying process and be inexpensive for industrial manufacture (Klausner et al., 2003c).

The increase in the systems' size can be based on several principles, including expansion due to swellable excipients or unfolding and/ or shape modification (to complex geometric shapes) in the stomach.

1.2.3.3.1. Expanding Swellable Systems

The expansion of this type of DDS is generally due to the presence of specific hydrogel formers, which after swallowing; drastically increase in size upon contact with aqueous media. This increase in size prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These

systems may be referred to as the "plug type systems" since they exhibit a tendency to remain lodged at the pyloric sphincter (Mamajek, 1980).

Deshpande *et al.* (Deshpande et al., 1997a; Deshpande et al., 1997b) developed a controlled-release gastric retention system composed of a swellable core, which consisted of the drug, chlorphenamine maleate or riboflavin 5′ phosphate, and the expanding agents polyvinyl pyrrolidone (PVP), Carbopol 934P and calcium carbonate. The tablet core was coated with a permeable coating, consisting of blends of Eudragit RL® 30 D and NE 30 D in different ratios. The tablets swelled to 2- 4 times their original volume, while releasing the drug in a controlled manner. The optimal ratio of Eudragit® RL 30 D: NE 30 D was found to be 70: 30, which was optimum for sufficient elasticity to withstand the pressure of expansion during the initial swelling phase, and allowing the breakdown of the tablet following release of the drug.

Shalaby et al. described enzyme-digestible hydrogels consisting of poly(vinyl pyrrolidone) crosslinked with albumin (Shalaby et al., 1992; Shalaby and Park, 1990). These gastroretentive hydrogels, swelled to a significant extent depending on the albumin content and degree of albumin alkylation and were degraded in the presence of pepsin. Even under fasted conditions, the gastric residence time in dogs exceeded 24 h. These hydrogels were used to deliver flavin mononucleotide, which is known to be absorbed only from the upper part of the small intestine, where the drug could be detected up to 50 h after administration in the blood, suggesting its efficient retention in the stomach.

The same group described superporous hydrogels, having gastroretentive properties due to rapid swelling and superabsorbent properties (Chen et al., 2000; Chen et al., 1999; Chen and Park, 2000a; Chen and Park, 2000b). Equilibrium swelling is reached in less than 1 min. Improved mechanical strength was achieved by adding a composite material, such as croscarmellose sodium. *In vivo* experiments in dogs, even under fasting conditions showed gastric retention for 2 – 3 h, after which they emptied into the intestine. On the other hand, in the fed state, the superporous hydrogel composites stayed in the stomach for > 24 h.

Omidian et al. developed superporous hydrogel hybrids, which are prepared by crosslinking a water-soluble or water-dispersible polymer to the formed superporous

hydrogel (Omidian et al., 2005; Omidian et al., 2006). Examples for hybrid agents are polysaccharides, such as sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers, e.g. poly(vinyl alcohol). Unlike superporous hydrogels and superporous hydrogel composites, superporous hydrogel hybrids are not easily breakable when stretched due to their highly elastic properties in the swollen state, which may be very useful for developing gastrointestinal DDS.

Gröning et al (Gröning et al., 2007; Groning et al., 2006) developed gastroretentive dosage forms prepared from compressed collagen sponges. The sponges were manufactured by freeze-drying a riboflavin-containing collagen solution. The precompressed collagen was transported into a tablet machine for tablet compression. A second type of tablet was manufactured by combining compressed collagen sponges with hydrophilic matrix layers of hydroxypropyl methylcellulose (HPMC) containing captopril or acyclovir into a bilayer tablet. Following contact with aqueous fluids, the collagen sponge expanded to a large size. Both systems released the drug in a controlled manner. *In vivo* studies on riboflavin tablets have shown that the drug was absorbed for a long time period. There was no indication, though, on how the drug was excreted from the stomach.

1.2.3.3.2. Unfolding and Modified-Shape Systems

These are non disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device (Caldwell, 1988a, 1988c; Cargill et al., 1988; Fix et al., 1993; Kedzierewicz et al., 1999).

Devices with different geometrical shapes such as continuous solid stick, tetrahedron, ring, cloverleaf, planer disk, string and pellet/sphere were investigated (Caldwell, 1988c, 1988a, 1988b). These systems consist of at least one erodible polymer (e.g., Eudragit® E, hydroxypropyl cellulose (HPC)), one nonerodible polymer (e.g., polyamides, polyolefins, polyurethanes), and a drug dispersed within the polymer matrix. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer, while tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene: vinyl acetate copolymer. The devices are compressible to a

size suitable for swallowing within a capsule, and are self-expandable to a size, which prevents their passage through the pylorus. Furthermore, they are sufficiently resistant to forces of the stomach to prevent rapid passage through the pylorus for a pre-determined period of time, and erode in the presence of gastric juices.

In vivo studies in beagle dogs have been performed to study the systems physical characteristics, such as size, shape and flexibility on the gastric emptying (Cargill et al., 1988), after they were folded and placed in a gelatin capsule. The tetrahedron-shaped devices remained in the stomach for longer periods of time than the other shapes, while strings and pellets were eliminated fairly rapidly.

Other shapes, which can be packed into gelatin capsules and increase in size following unfolding include Y-shaped systems (Sonobe, 1995) and sheet-like shaped devices (Brewer, 1980).

Another unfolding system, developed by Klausner *et al.* (Klausner et al., 2002), was composed of multilayer, polymeric films based on a drug-containing shellac matrix as the inner layer, with outer shielding layers on both sides composed of hydrolysed gelatin/ Eudragit S/ glycerine/ glutaraldehyde. The system was optionally framed with rigid polymeric strips composed of L-poly(lactic acid)/ ethylcellulose (EC). Such dosage forms were administered to beagle dogs, after placing them into gelatin capsules. The dimensions and the mechanical properties of the films influenced the *in vivo* gastric retention behaviour. Prolonged residence times and improved absorption properties could be achieved with the model drug riboflavin using a $\geq 2.5 \times 2.5$ cm large device.

In addition, levodopa-containing multilayer films were investigated in beagle dogs (Klausner et al., 2003a). The mean absorption time of the drug was significantly extended when it was compared to non-gastroretentive controlled release particles and oral solutions. The performance of levodopa-containing, multilayer films was also studied in humans (Klausner et al., 2003b), and gastric retention for ≥ 5 h could be achieved, due to the rigidity and size of the dosage forms.

However, due to the strong contractions of the IMMC the ingested dosage form may possibly pass the stomach. Expandable gastroretentive devices may also imply the risk of unfolding in the esophagus during swallowing and therefore potentially causing

serious complications. In contrary, systems expanding too slowly may pass the pylorus before being completely expanded and thus fail gastric retention (Waterman, 2007).

1.2.3.4. Density-Controlled Systems

1.2.3.4.1. High Density Systems

These devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice (~1.004 g/cm³), the device settles down to the bottom of the stomach, and remains located below the pylorus. This could be accomplished by including a heavy inert material such as zinc oxide, titanium dioxide, iron powder or barium sulphate (Clarke et al., 1995; Rouge et al., 1998) into the drug containing core pellets or coating drug containing pellets with it. These materials increase density by up to 1.5–2.4 g/cm^3

However, it has been reported that such devices did not significantly extend the gastric residence time (Gupta and Robinson, 1995).

1.2.3.4.2. Floating Systems

The concept of floating DDS was first described in the literature in 1968 (Davis, 1968), when Davis developed a method for overcoming the difficulty experienced by persons of gagging or choking while swallowing medicinal pills. He suggested that such difficulty could be overcome by providing pills with a density of less than 1 g/cm³, so that the pill will float on water surface. Since then several approaches have been used to develop an ideal floating system.

Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (<~1.004 g/cm³), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach.

This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations in some cases (Whitehead et al., 1998).

Floating properties based on the mechanism of buoyancy are divided into: non effervescent systems with inherent low density or low density due to swelling; and effervescent systems with low density due to gas generation and entrapment.

Most floating systems reported in the literature are single unit systems, such as HBS and floating tablets. The systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered due to their all or nothing empting process (Kawashima et al., 1991). On the other hand, multiple unit dosage forms, such as hollow microsphere (microballoons), granules, powder, and pellets, are more suitable since they are claimed to reduce the inter- and intra-subject variability in absorption and reduce the probability of dose dumping (Rouge et al., 1997).

1.2.3.4.2.1. Non-Effervescent Floating Drug Delivery Systems

Systems with initially low density are highly desired, since they prevent the risk of premature emptying from the stomach. Inherent low density can be provided by entrapment of air (Iannuccelli et al., 1998a; Kawashima et al., 1991; Kawashima et al., 1992; Nakamichi et al., 2001; Sato et al., 2003, , 2004b), or by the incorporation of low-density materials, such as fatty substances or oils (Spickett, 1993; Ushimaru, 1987), or foam powder (Streubel et al., 2002, , 2003a, 2003b).

One of the approaches involves mixing of the drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and bulk density of less than the unity, within the outer gelatinous barrier (Hilton and Deasy, 1992). The air trapped by the swollen polymer imparts buoyancy to these dosage forms for 6h. In addition, the drug is slowly released by controlled diffusion through the gelatinous barrier

Watanabe *et al.* (Watanabe, 1976) developed a single-unit, floating drug delivery system having an inherent low density, consisting of a hollow core composed of either an empty hard gelatin capsule, polystyrene foam or pop rice grain, and subsequently

coated with a subcoat of cellulose acetate phthalate, and an outer drug-containing coating of EC/ HPMC.

Sheth and Toussounian developed a HBS capsule containing a mixture of a drug and hydrocolloids (Sheth, 1978). Upon contact with gastric fluids, the capsule shell dissolves and the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. Pharmaceutical products, using the same principle, containing APIs have been developed, containing L-DOPA, combined with a decarboxylase inhibitor (Sheth, 1984).

The same authors developed sustained release floating tablets of an active ingredient and one or more hydrocolloids such as methylcellulose, HPC, HPMC, HEC and sodium CMC, which upon contact with gastric fluid provided a water impermeable colloidal gel barrier on the surface of tablets (Sheth, 1979a, 1979b).

Mitra (Mitra, 1984) described a multilayered, flexible, sheet like medicament device that was buoyant in the gastric juice of the stomach and had sustained release characteristics. The device consisted of self supporting carrier film(s) made up of a water insoluble polymer matrix with the drug dispersed there in, and a barrier film overlaying the carrier film. The barrier film consisted of a water insoluble and a water and drug permeable polymer or copolymer. Both films were sealed together along their periphery, in such a way as to entrap a plurality of small air pockets, which imparted the laminated films their buoyancy. The time for buoyancy and the rate of drug release can be modulated by the appropriate selection of the polymer matrix.

Ushimaru *et al.* (Ushimaru, 1987) developed sustained release capsules containing a mixture of a drug, a cellulose derivative or starch derivative which forms a gel in water, and a higher fatty acid glyceride or higher alcohol or a mixture thereof which is solid at room temperature (RT), with an inherent density of < 1 g/cm^3.

Another patent described a bilayer buoyant dosage form consisting of a capsule, which included a non compressed bilayer formulation. One layer was a drug release layer containing misoprostol and the other was a buoyant or floating layer. Each layer included a hydrocolloid gelling agent such as HPMC, gums, polysaccharides and gelatin (Franz, 1993). The dosage form had a large diameter and an initial low density of < 1 g/cm^3, which remained buoyant in gastric fluid for a period up to about 13 hours

Desai and Bolton (Bolton, 1989a; Desai and Bolton, 1993) developed controlled release floating moulded gel tablets of theophylline using agar and light mineral oil. The light mineral oil was essential for the floating property of the tablet. Additionally, it served to prevent the air entrapped within the gel matrix from escaping in the acidic environment of the stomach, due to its hydrophobicity. However, the mechanism is not yet clear. In another study, these authors developed a similar formulation without using an oil (Bolton, 1989b).

A multiple-unit gastroretentive DDS which contained air compartments was described by Iannuccelli *et al.* (Iannuccelli et al., 1998a; Iannuccelli et al., 1998b). The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or calcium alginate/ polyvinyl acetate (PVA). Floating *in vitro* and *in vivo* of drug-free systems was observed. When furosemide was incorporated into the units (Iannuccelli et al., 2000); only 20% of the dug was released after 8 h. Therefore, a solid dispersion of furosemide/PVP was prepared to improve the drug release.

Krögel and Bodmeier (Krögel and Bodmeier, 1999) developed a floating device consisting of two drug-loaded HPMC matrix tablets, placed within an open impermeable, hollow polypropylene cylinder. Each matrix tablet closes one of the ends of the cylinder so that an air-filled space is created between them, which in turn provided a low, overall density of the system. The device should remain floating until at least one of the tablets has dissolved.

Dennis *et al.* (Dennis, 1992) described a buoyant controlled release powder formulation, which may be either filled into capsules or compressed into tablets. The formulation consisted of a drug of basic character, a pH dependent polymer, sodium or potassium alginate, a pH independent hydrocolloid gelling agent such as HPMC, methylcellulose, HPC or a mixture of two or more, and a binder. The formulation was considered unique in the sense that it released the drug at a controlled rate regardless of the pH of the environment, being free of calcium ion and carbon dioxide (CO_2) producing material, and had drug release properties similar to a tablet of identical composition.

Other authors have also prepared tablets with alginate and HPMC that were able to float on gastric contents and provided sustained release characteristics (Davis et al., 1986; Sheth and Tossounian, 1984).

Streubel *et al.* (Streubel et al., 2003a) proposed a single-unit, controlled release floating tablet, consisting of polypropylene foam powder, matrix-forming polymer(s), drug and an optional filler. Polypropylene foam powder with its high porosity showed excellent *in vitro* floating behaviour of the system for at least 8 h in 0.1 N HCl. Different polymers were studied for this system and the release rate could be effectively adjusted by altering the type of polymer, matrix-forming polymer: foam powder ratio and drug loading.

Floating microparticles based on low-density foam powder has been proposed by the same authors and its performance investigated *in vitro* (Streubel et al., 2002). The floating microparticles were prepared with an oil-in-water solvent extraction/evaporation method and were composed of polypropylene foam powder; verapamil HCl as the model drug; and a controlled release polymer, Eudragit® RS, EC or polymethyl methacrylate (PMMA). The microparticles were irregular in shape and highly porous. Good *in vitro* floating behavior was observed. The increase in drug release was proportional to the drug loading and inversely proportional to the amount of polymer and the release profile varied with varying the polymer type.

Recently, controlled release gastroretentive floating gel beads of loratadine were formulated to increase the residence time in stomach and modulate the release behavior of the drug (Mishra and Pathak, 2008). Oil (mineral or castor oil) entrapped floating microbeads prepared by the emulsion gelation method were optimized by factorial design, and a polymer ratio of 2.5:1.5 (pectin/sodium alginate) and 15% of mineral or castor oil dropped in calcium chloride solution was found to be an optimum ratio for the desired buoyancy and physical stability. *In vitro* drug release demonstrated sustained release of loratadine for 8 h and the gel beads floated in all test media without any lag time and remained buoyant for 12 h.

Thanoo *et al.* (Thanoo et al., 1993) developed a drug loaded polycarbonate microspheres using a solvent evaporation technique. Drug-loaded microspheres were found to float on simulated gastric and intestinal fluid. Increasing the drug to polymer

ratio in the microspheres increased the release rate of the drugs. It was concluded that sustained drug delivery could be obtained using this matrix system.

Hollow microspheres (microballoons) were developed by Kawashima *et al.* (Kawashima et al., 1991; Kawashima et al., 1992; Sato et al., 2003), consisting of Eudragit S as an enteric polymer, and the drug loaded in the outer polymeric shell by an emulsion solvent diffusion method. The drug release profiles from the microballoons exhibited enteric behavior, and the drug release rates were controlled by changing the ratio of polymer to drug in the balloon. Consequently, many drugs were not released from this type of microparticles at the pH of gastric fluids (Lee et al., 1999). The system was therefore modified, by the addition of nonvolatile oil to the dispersed phase (Lee et al., 2001) or using Eudragit S/RL mixtures (El-Kamel et al., 2001).

Hollow microspheres using mixtures of Eudragit S and other hydrophilic or hydrophobic polymers (such as Eudragit L, hydroxypropyl methylcellulose phthalate, HPMC or EC) within the outer shell were also prepared by Sato *et al.* (Sato et al., 2004b), as an attempt to improve the drug release from the system at the gastric pH. Increasing the HPMC contents, increased the amount of riboflavin released; however, the floating properties of the microspheres decreased. *In vivo* studies of the riboflavin-containing microballoons were also performed by γ-scintigraphy and the urinary excretion of riboflavin was followed (Sato et al., 2004a; Sato et al., 2004c). The bioavailability of riboflavin was significantly higher compared with a non-floating control formulation.

Yuasa *et al.* (Yuasa et al., 1996) developed intragastric floating and sustained release granules of diclofenac sodium using a polymer solution of HPC-L grade and EC, and calcium silicate as a floating carrier, which has a characteristically porous structure. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer.

Whitehead *et al.* (Whitehead et al., 1996) developed multiple unit floating freeze dried calcium alginate beads. These beads maintained a positive floating force for over 12 h, and the density measurement, using a helium pycnometer, was less than 1 g/cm. The *in vivo* behavior of this system compared to non-floating multiple-unit dosage forms manufactured from identical material have also been performed using γ-scintigraphy in

the fed state (Whitehead et al., 1998). Prolonged gastric residence times of over 5.5 h were achieved for the floating formulations, while the non-floating beads displayed short gastric residence times, with a mean onset emptying time of 1 h.

A glycerol monooleate (GMO) matrix was recently proposed as a gastroretentive carrier system by Kumar *et al.* (Kumar M et al., 2004). The GMO matrices were prepared by melting GMO at 55°C in a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds. The GMO matrices significantly swelled in water and the swollen mass floated at the surface after a certain lag time.

A novel hot melt extrusion (HME) tablet was proposed by Fukuda *et al.* (Fukuda et al., 2006), containing Eudragit® RS PO and/or Eudragit® E PO as release controlling agents, acetohydroxamic acid and chlorpheniramine maleate were used as model drugs and the influence of sodium bicarbonate on the physicochemical properties of the tablet was investigated. The HME tablets had a porous structure, due to carbon dioxide (CO_2) gas generation during the thermal decomposition of sodium bicarbonate in the softened acrylic polymers at elevated temperature during the extrusion process, which was capable of floating on the surface of the media for 24h. The drug release rate from floating HME tablets was controlled by the Eudragit polymers incorporated into the matrix tablet.

1.2.3.4.2.2. Effervescent Floating Drug Delivery Systems

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate ($NaHCO_3$) or sodium carbonate, and additionally citric or tartaric acid (Rubinstein and Friend, 1994). Alternatively matrices containing chambers of liquids that gasify at body temperature could be used (Michaels, 1975; Micheals, 1974; Ritschel, 1991). Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme.

The CO_2 generating components may be mixed with the tablet matrix components, producing a single layered tablet (Hashim and Li Wan Po, 1987) or compressing the gas

generating components in a hydrocolloid containing layer and the drug in another layer formulated for a sustained release effect, thereby producing a bilayered tablet (Ingani et al., 1987). This concept has also been exploited for floating capsule systems (Stockwell et al., 1986) as well as for multiple unit drug delivery systems.

Floating tablets using the anionic exchange resin, cholestyramine, was described by Todd *et al.* (Todd, 1979). The directly compressed tablet was composed of granules containing anhydrous cholestyramine, low viscosity grade alginic acid and/ or citric acid, and sufficient sodium carbonate or bicarbonate mixtures thereof to neutralize the acidic groups of the alginic and citric acids. After swallowing, the components will react with the gastric acid to form a carbonated raft which then floats on the stomach contents.

Atyabi *et al.* (Atyabi et al., 1996a, 1996b) developed a similar system using the ion exchange resin Dowex. The resin beads were loaded with bicarbonate and theophylline which were bound to the resin. The loaded resin beads were coated with a semipermeable membrane to overcome rapid loss of CO_2. After exposure to gastric media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO_2, which was trapped within the membrane, causing the particles to float. Gastric residence time was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of sustaining the drug release.

Chitosan based sustained release floating tablets using a mixture of $NaHCO_3$ and citric acid have been investigated by Inouye *et al.* (Inouye et al., 1988). Two types of chitosan with different degrees of deacetylation, chitosan H and L, and prednisolone as a model drug were used and two types of preparations were examined. The first were directly compressed tablets using a mixture of sodium hydrogen carbonate and citric acid, while the second was composed of a directly compressed layer coated with chitosan layer enclosing CO_2. Both formulations imparted quick buoyancy to the preparations, but the drug release from the preparation using chitosan L was slower than that of chitosan H. In a further study, the release properties were controlled by regulating the chitosan content of the granules, or the chitosan L membrane thickness of the laminated preparations (Inouye et al., 1989).

Double layered matrix tablets have been proposed containing an effervescent layer loaded with carbonate and optionally citric acid, using HPMC K4M and K15M (Ingani et al., 1987) or mixture of HPMC K 4M and polyethylene oxide (PEO) (Fassihi, 1998; Yang et al., 1999; Yang and Fassihi, 1996) as gelling hydrocolloid and release controlling polymer. After contact with acidic aqueous media, CO_2 is generated and entrapped within the gelling hydrocolloid, causing the system to float; meanwhile the drug was released in a sustained manner.

In addition, capsules containing HPMC of different viscosity grades, Carbopol 934 and an effervescent mixture have been prepared and the effects of different formulation variables on drug release and floating behavior were studied (Li et al., 2002; Li et al., 2003). It was concluded that the HPMC viscosity, the presence of Carbopol as well as the polymer–polymer interactions had significant impact on the release and floating properties of the delivery systems.

Floating minitablets, using tartaric acid, $NaHCO_3$ and calcium carbonate as effervescent components and glyceryl palmitostearate as meltable binder, have been developed by Goole *et al.* (Goole et al., 2008a; Goole et al., 2008b). The system consisted of a 3 mm drug-containing gas-generating core, prepared by melt granulation and subsequent compression, and coated with a flexible polymeric membrane of Eudragit® RL 30 D. The minitablets were able to float within 10 min and remained buoyant for more than 13 h, independent of the pH. In addition, the drug release was sustained for more than 12h.

Umezawa (Umezawa, 1978) developed floating minicapsules with a diameter in the range of 0.1-2 mm and were consisting of a $NaHCO_3$ core, which is coated with an inner HPMC layer and an outer pepstatin layer. On contact with gastric acid, carbon dioxide is generated within the core causing the particles to float. Furthermore, the release and action of pepstatin within the stomach was prolonged, and the pepsin activity in patients with gastric and duodenal ulcers was suppressed.

A similar capsule was described by Ichikawa *et al.* (Ichikawa, 1989), which contained granules having different residence times in the stomach. The granules were composed of drug containing core, coated with an inner effervescent layer, and an outer polymeric swellable film layer. The film expanded due to CO_2 generation upon reaction of the bicarbonate and the acidic content of the medium.

A multiple unit effervescent floating pill has been developed by the same authors (Ichikawa et al., 1991a; Ichikawa et al., 1991b). The system consisted of sustained release pills as seeds surrounded by double layers. The inner layer was a double effervescent layer containing both $NaHCO_3$ and tartaric acid to avoid direct contact between sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly PVA and purified shellac. Following contact with aqueous media, it formed swollen balloon like pills, with a density much lower than 1 g/ ml, due to the carbon dioxide generated by the neutralization reaction in the inner effervescent layers with the diffusion of water through the outer swellable membrane layer. The system was found to float completely within 10 min. and approximately 80% remained floating over a period of 5 h irrespective of pH and viscosity of the test medium. Meanwhile, the drug was released.

An alternative mechanism of gas generation was developed as an osmotically controlled floating device, where gases with a boiling point < 37°C (e.g., cyclopentane, diethyl ether) can be incorporated in solidified or liquefied form into the systems. At physiological temperatures, the gases evaporate enabling the drug containing device to float. To enable the unit to exit from the stomach, the device contained a bioerodible plug that allowed the vapor to escape (Bashaw, 1976; Michaels, 1975; Micheals, 1974).

It has been observed that release kinetics for effervescent floating systems significantly deviate from the classical Higuchi model and approach zero-order kinetics systems (Chen and Hao, 1998; Hashim and Li Wan Po, 1987; Ichikawa et al., 1991b), which may be attributed to the air entrapped inside the matrix (Korsmeyer et al., 1983), acting as barrier to diffusion, and matrix relaxation (Chen and Hao, 1998). In contrast, non effervescent floating systems obey Higuchi model, indicating that drug release occurs via diffusion mechanism (Babu and Khar, 1990; Chen and Hao, 1998; Desai and Bolton, 1993; Khattar et al., 1990).

Floating dosage forms with an in-situ gas generating mechanism are expected to have greater buoyancy. However, the optimization of the drug release may alter the buoyancy and, therefore, it is sometimes necessary to separate the control of buoyancy from that of drug release kinetics during formulation optimization (Rouge et al., 1996).

Generally, effervescent systems suffer from the disadvantage not to float immediately after swallowing because the process of gas generation takes some time. Therefore, they could be cleared from the stomach before becoming effective. The performance of low-density, floating drug delivery systems is strongly dependent on the filling state of the stomach. Nevertheless, this approach can successfully prolong the gastric retention time (Talukder and Fassihi, 2004) and has already led to the production of pharmaceutical products, which are commercially available on the market (Singh and Kim, 2000).

1.2.4. Commercial Drug Delivery Systems with Gastric Retention

Even though gastric retentive systems have been in the focus of interest of many research groups for the last three decades, up to now only a few systems are available on the market. Obviously many obstacles have to be overcome to ensure a reliable function of the gastroretentive systems.

1.2.4.1. Commercial Floating Drug Delivery Systems

Madopar HBS®, an anti Parkinson's agent, is a commercially available product marketed by Hoffmann-LaRoche. It contains 100 mg levodopa and 25 mg benserazide, a peripheral dopa decarboxylase inhibitor. It consists of a gelatin capsule, designed to float on the surface of the gastric fluids. After the gelatin shell dissolves, a mucous body is formed that consists of the active drugs and other substances. The drugs diffuse from the hydrated boundary layers of the matrix at the desired rate (Ceballos-Baumann et al., 1990; Chouza et al., 1987; Erni and Held, 1987).

Valrease® is another floating capsule, marketed by Hoffmann-La Roche. It contains 15 mg diazepam, which is more soluble at low pH; therefore absorption is more desirable in the stomach. The drug components form a soft gelatinous mass in the stomach and are released gradually. The HBS system maximizes the dissolution of the drug by prolonging the gastric residence time (Pies, 1982).

Liquid Gaviscon®, a floating liquid alginate preparation, is used to suppress gastroesophageal reflux and alleviate the symptoms of heart burn. The formulation

consists of a mixture of alginate, which forms a gel of alginic acid, and a carbonate or bicarbonate component, evolving CO_2 upon reaction with the acidic content of the stomach. The formed gel entraps the CO_2 formed, and consequently floats on the stomach contents (Washington et al., 1986).

Topalkan® is a third generation aluminum magnesium antacid, which also contains alginic acid in its formula. It has antipeptic and protective effects with respect to the mucous membrane of the stomach and esophagus, and provides, together with magnesium salts, a floating layer of the preparation in the stomach (Degtiareva et al., 1994).

Almagate flotcoat® is another novel antacid formulation that confirms a higher antacid potency together with a prolonged gastric residence time and a safe as well as extended delivery of antacid drugs (Fabregas et al., 1994).

1.2.4.2. Commercial Size Increasing Drug Delivery Systems

The accuform technology of depomed is based on a unique blend of polymers with the API, which forms a gel like substance in the GI tract, which prevents the drug from passing through the pyloric opening and meanwhile releases the drug in a controlled manner. Two products are available in the market.

Glumetza®, a commercially available product by Depomed, Inc., Menlo Park, CA, USA, is a gastric retentive extended-release tablet formulation of 500 or 1000 mg metformin that provides effective, sustained and well-tolerated glycemic control with once daily administration (Schwartz et al., 2006; Schwartz et al., 2008).

Proquin® XR is another commercially available product by Depomed, based on the accuform technology. It is an antibiotic containing 500 mg ciprofloaxacin and is indiacted for for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of Escherichia coli and Klebsiella pneumonia (Fourcroy et al., 2005).

1.3. Polymers used in Extended Release Systems

Various pH independent polymers have been investigated in order to develop a drug delivery system, with instant floating activity and controlled drug release.

1.3.1. Polymers used in Matrix Tablets

1.3.1.1. Hypermellose or Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose **(Fig. 1)**, a non-ionic cellulose ether polymer, is an odorless and tasteless, white or creamy-white colored fibrous or granular powder, which is soluble in cold water, but insoluble in hot water. Cellulose ethers generally exhibit a lower degree of solubility at high temperatures, which can be used to obtain good dispersion of the polymer in hot water and faster dissolution when the temperature is lowered, forming a viscous colloidal solution (Lehmann, 1994). It is practically insoluble in chloroform, ethanol (95%), and ether (Rogers, 2009) and is widely used as a tablet binder, in film coating and as extended release matrix tablets (Chowhan, 1980; Dahl et al., 1990; Hogan, 1989; Shah et al., 1989; Wilson and Cuff, 1989).

The hydration rate of HPMC depends on the nature of the constituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropoxyl content. The viscosity of the aqueous solution increases by increasing the average molecular weight (MW) of the polymer, and varies from 15 to 100,000 cps. Most of HPMC viscosity grades have U.S. GRAS (generally recognized as safe) status (Buri and Doelker, 1980; Melia, 1991; Vazquez et al., 1992). HPMC polymers are non-toxic, have the capacity to accommodate high levels of drug loading, and are pH- independent (Amaral et al., 2001).

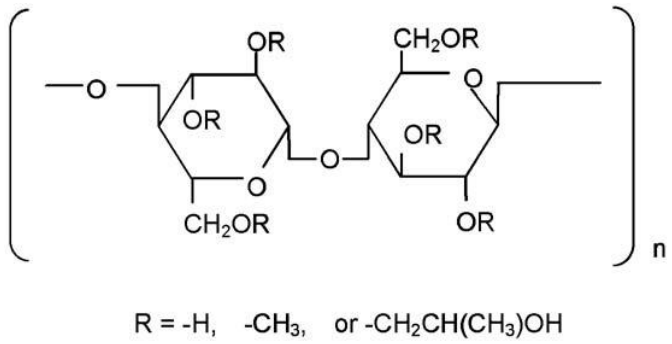


Fig. 1: *Chemical structure of Hydroxypropyl methylcellulose*

HPMC is the dominant hydrophilic carrier material used for the preparation of oral controlled DDS (Qiu and Zhang, 2000). HPMC provoked considerable interest to prolong drug release because it displays good compression characteristics and has adequate swelling properties that allow rapid formation of an external gel layer controlling the drug release (Rodrigues et al., 2000).

1.3.1.2. Carbomers or Carbopol

Carbopol or carbomer polymers **(Fig. 2)** are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose, allyl ethers of pentaerythritol or divinyl glycol. They contain between 52% and 68% carboxylic acid (COOH) groups calculated on the dry basis (Draganoiu et al., 2009). They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking. Carbopol polymers are formed from repeating units of acrylic acid.

Carbopol polymers were first prepared and patented in 1957 (Brown, 1957). Since then, a number of extended release tablet formulations, which involve carbopol matrices, have been developed (Cedillo-Ramirez et al., 2006; Li et al., 2002; Li et al., 2003; Nur and Zhang, 2000).

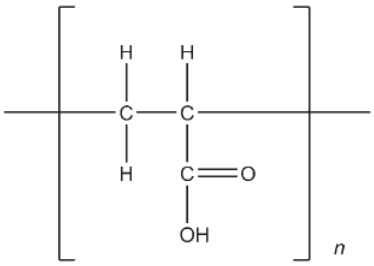


Fig. 2: *Chemical structure of an Acrylic acid monomer in carbopol*

Carbomers readily absorb water, get hydrated and swell. In addition to its hydrophilic nature, its cross-linked structure and its essentially insolubility in water makes Carbopol a potential candidate for use in controlled release drug delivery systems (Carnali and Naser, 1992; GarcíGonzález et al., 1994). In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers. Lightly crosslinked carbomers, with lower viscosity, are generally more efficient in controlling drug release than highly crosslinked carbomers, with a higher viscosity (Draganoiu et al., 2009).

1.3.1.3. Croscarmellose Sodium or Ac-Di-Sol

Ac-Di-Sol or croscarmellose sodium is an internally crosslinked polymer of carboxymethyl cellulose sodium. It occurs as an odorless, white or grayish white powder. It is insoluble in water, although it rapidly swells to 4- 8 times its original volume on contact with water (Guest, 2009). The cross-linking reduces water solubility while still allowing the material to swell (like a sponge) and absorb many times its weight in water. As a result, it provides superior drug dissolution and disintegration characteristics, thus improving bioavailability by bringing the APIs into better contact with body fluids.

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for granules, capsules (Botzolakis and Augsburger, 1988; Dahl et al., 1991) as well as tablets (Ferrero et al., 1997; Gordon et al., 1990; Gordon et al., 1993a; Gordon et al.,

1993b; Janet Roche et al., 1991; Khattab et al., 1993). In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized (Gordon et al., 1993a; Khattab et al., 1993). Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. At higher concentrations, croscarmellose sodium was also used as a sustained release tablet component (Hariharan et al., 1997).

1.3.2. Polymers for coating Multiparticulate Systems

1.3.2.1. Eudragit® polymers

Eudragit polymers, prepared by free-radical polymerization, are synthetic cationic, anionic or neutral polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as dry powder, aqueous dispersion, or as organic solution (Chang et al., 2009).

These polymers are widely used as film formers in application for functional pharmaceutical coatings for controlling the release of drugs (Chang and Hsiao, 1989; Chang et al., 1989; Pearnchob and Bodmeier, 2003). In addition, they are applied as matrix formers in granulation techniques as well as in direct compression (Evonik, 2009; Pereira de Souza et al., 2007).

Eudragit acrylic resins are harmless and inert compounds, not absorbed in the GIT and are resistant to body fluids. They stay for a limited time in the GIT, are excreted unchanged, and do not produce degradation products (Evonik, 2009).

1.3.2.1.1. *Eudragit® RL and RS*

Eudragit® RL and RS, also referred to as ammonio methacrylate copolymers **(Fig. 3)**, are copolymers synthesized from acrylic acid and methacrylic acid esters, with Eudragit® RL (Type A) having 10% of functional quaternary ammonium groups and Eudragit® RS (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and cause pH-independent permeability to the polymers. Both polymers are water-insoluble. Eudragit® RL films are freely permeable to water and other dissolved active substances, while films prepared from Eudragit® RS are only slightly permeable to water.

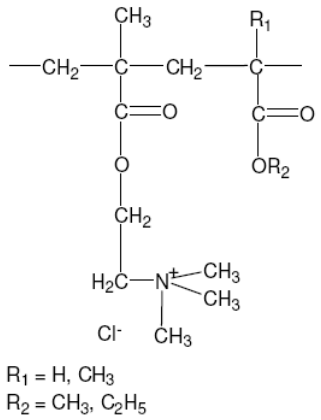


Fig. 3: *Chemical structure of Ammonio methacrylate copolymers*

Eudragit® RL 100 and RS 100 are granular in form and contain ≥ 97% of the dried weight content of the polymer.

Eudragit® RL 30 D and RS 30 D are 30% aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups (Chang et al., 2009).

The glass transition temperature (Tg) of Eudragit® RL and RS polymers are as high as 70°C and 65°C, respectively. While the minimum film formation temperature (MFT) of the aqueous dispersions Eudragit® RL 30 D and RS 30 D are 40°C and 45°C, respectively (Evonik, 2009). These polymers require the addition of a plasticizer, usually in the range of 5% to 30%, calculated on dry polymer mass, to reduce the MFT

of aqueous dispersion in order to ensure proper film formation and improve film properties (Chang et al., 1989; Chang et al., 2009; Skalsky and Petereit, 2008).

1.3.2.2. Aquacoat® ECD

Aquacoat® ECD is a commercially available ethylcellulose dispersion with 30% solids content, containing 27% ethylcellulose, with polymer droplets of around 200 nm and a viscosity of 150 cP, stabilized with sodium lauryl sulfate (SLS) (4% w/w of total solids), an anionic surfactant, and cetyl alcohol (9% w/w of total solids) (FMC, 2008).

Ethylcellulose **(Fig. 4)** is a water insoluble, at any pH, hydrophobic coating material (FMC, 2008; Siepmann et al., 2008) and due to its neutral side chains, it releases the drug in a pH-independent manner (Lehmann, 1994). It is often used for controlled release, taste masking and moisture barrier applications (FMC, 2008). It is non-toxic, non-allergenic, non-irritant and widely used in oral drug delivery devices as polymeric film former.

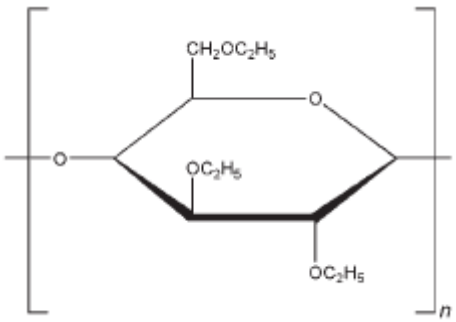


Fig. 4: *Chemical structure of Ethylcellulose*

Although EC is considered insoluble, it can take up water (Joshi and Wilson, 1993). This is because of hydrogen bonding with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer (Agrawal et al., 2003).

The high Tg of ethylcellulose (128°C) and MFT of Aquacoat® ECD (81°C) (Lippold et al., 1990) prevent coalescence and film formation of the particles during the coating process (Wagner and Bodmeier, 2003). Therefore, plasticizers are required to reduce the MFT below the coating temperature in order to enhance coalescence of the film (Lippold et al., 1990; Wesseling and Bodmeier, 1999).

The release mechanism from EC coated dosage forms has been investigated and there is increasing evidence that the drug is mainly released through micro cracks and water filled pores (Lecomte et al., 2004, , 2005).

1.3.2.3. Kollicoat® SR 30 D

Kollicoat® SR is a polyvinyl acetate **(Fig. 5)** polymer with an average molecular weight of 450.000. It is marketed as Kollicoat® SR 30 D, a ready to use aqueous dispersion composed of 27% poly(vinyl acetate) stabilized with 0.3% sodium lauryl sulphate and 2.7% povidone, which acts as a pore former (BASF, 2008).

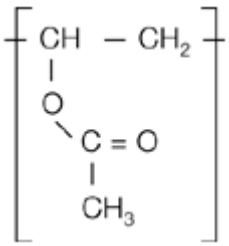


Fig. 5: *Chemical structure of Polyvinyl acetate*

Kollicoat® SR has exceptional sustained release characteristics for both water soluble and poorly water soluble drugs and provides drug release independent of pH and ionic strength of the release medium (Bordaweka et al., 2006; Dashevsky et al., 2004b; Dashevsky et al., 2005).

It is water insoluble, highly water permeable and has low MFT of 18°C and high tensile strength. Elongation at break is up to about 400% with an amount of 15% propylene glycol or 10% TEC as a plasticizer (BASF, 2008). Thus, compression of pellets without rupture of the polymer film is possible (Dashevsky et al., 2004a; Sawicki and Lunio, 2005).

Kollicoat® SR monograph is registered in the European Pharmacopoeia since April 2004. Though it represents a relatively new controlled release polymer on the market, since then it has been used in controlled drug delivery of some formulations (Dashevsky et al., 2004b; Dashevsky et al., 2005; Sawicki and Lunio, 2005; Shao et al., 2002). When in contact with the dissolution medium, PVP leaches out leaving pores for drug diffusion through the polymer film. Kollicoat® SR was also used as granulation agent due to its efficient binding characteristics (Flick and Kolter, 2003).

1.4. Research Objectives

The objective of this work was the development and investigation of floating drug delivery systems with an extended release profile. Particular goals were:

a) Preparation of floating single unit matrix tablets using different hydrophilic polymers with/without addition of sodium bicarbonate as effervescent agent;

b) Preparation of floating multiple unit pellets using the gas generation principle for various solubility drugs; and investigating the effect of polymer type on floating and drug release properties;

c) To provide a mechanistic understanding of the floating behavior from multiple unit pellets by water uptake and swelling studies;

d) Preparation of pH independent floating multiple unit pellets;

e) *In vitro* evaluation of the floating and drug release of the prepared systems

2. MATERIALS AND METHODS

2.1. Materials

Non-pareils 710-850 µm (Suglets sugar spheres NF, NP Pharm S.A., Bazainville, France), propranolol HCl, theophylline anhydrous (BASF SE, Ludwigshafen, Germany) and micronized carbamazepine (Fabrica Italiana Sintetici, Alto de Monte Vecchio, Italy) as model drugs, sodium hydrogen carbonate ($NaHCO_3$) (Merck KGaA, Darmstadt, Germany) and anhydrous citric acid (Jungbunzlauer AG, Wulzeshofen, Austria) as effervescenet agents, ethylcellulose aqueous dispersion (Aquacoat® ECD; FMC Biopolymers, Brussels, Belgium), polyvinyl acetate aqueous dispersion (Kollicoat® SR 30 D; BASF AG, Ludwigshafen, Germany), methacrylic copolymers with varying ratios of trimethylammonioethyl methacrylate as functional group, Type A and B (Eudragit® RL 30 D or Eudragit® RL 100 and Eudragit® RS 30 D respectively; Evonik Industries AG, Darmstadt, Germany), HPMC Type 2208 (Methocel® K15M Premium Grade; Colorcon Ltd., Orpington, UK), Carbopol 974P NF (Noveon Inc., Cleveland, OH, USA), croscarmellose sodium (Ac-Di-Sol®; FMC Biopolymer, Brussels, Belgium), triethyl citrate (TEC) (Morflex, Greensboro, NC, USA), talc (Luzenac Europe, Toulouse, France), hydroxypropyl methylcellulose (HPMC) (Methocel E5; Colorcon, Orpington, UK), polyethylene glycol 6000 (Lutrol E 6000, BASF AG, Ludwigshafen, Germany), magnesium stearate (Herwe Chemisch-technische Erzeugnisse GmbH, Sinsheim-Dühren, Germany) and silicon dioxide (Aerosil 200; Evonik Industries AG, Darmstadt, Germany) were used as received. All other reagents were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Single unit floating drug delivery systems

2.2.1.1. Tablet preparation

Tablets containing 15% propranolol HCl, 0.5% aerosil as glidant and 0.5% of magnesium stearate as lubricant were prepared by direct compression. Different ratios of polymer and sodium bicarbonate were used. Mixing of powders was carried out in a laboratory model turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 15 min., followed by the addition of magnesium stearate and aerosil and further mixed for 5 min. 400 mg of the mixture blend was weighed and fed manually into the die of an instrumented single punch tableting machine and directly compressed (Korsch EKO, Korsch Pressen GmbH, Berlin, Germany) to make one tablet. The hardness was kept constant (60- 80 N) and was measured with a hardness tester (PTB 311, Pharma Test, Hainburg, Germany).

2.2.1.2. Floating ability

The floating abilities of single tablets was determined in 500 ml prewarmed 0.1 N HCl, and shaken at 70 rpm, 37 ± 0.2°C for 18 h, using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH, Burgwedel, Germany) (n= 6). The floating lag time (time at which tablets start floating) and duration were measured by visual observation.

2.2.1.3. Drug release

The drug release from the propranolol HCl matrix tablets was investigated in a USP paddle apparatus (VK 700, Vankel Industries, Edison, NJ, USA), 900 ml of 0.1 N HCl (100 rpm, 37°C, n= 3). At predetermined time intervals, 3-ml samples were withdrawn and analyzed with UV spectrophotometry (UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA) at λ= 290 nm.

2.2.1.4. Medium uptake, mass loss and macroscopic examination

Single tablets were weighed ($weight_{initial}$), put into 500 ml prewarmed 0.1 N HCl, and shaken at 37 ± 0.2°C, 70 rpm for 18 h using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH, Burgwedel, Germany) (n= 3). At predetermined time intervals, the tablets were removed from the medium, blotted against a paper cloth to remove excess water and weighed ($weight_{wet}$). The tablets were oven-dried for 24 h at 105°C and additionally for 48 h in a desiccator and weighed again ($weight_{dry}$). Pictures of the dry tablets and at each time interval were taken under the light macroscope (Carl Zeiss, Inc., Beograd, Österreich) for characterization.

The medium uptake and mass loss were calculated as follows:

$$\text{Medium uptake / tablet weight } (mg/mg) = \frac{weight_{wet} - weight_{dry}}{weight_{initial}}$$

$$\text{Mass remaining / tablet weight } (mg/mg) = \frac{weight_{dry}}{weight_{initial}}$$

2.2.2. Multiple unit floating drug delivery systems

2.2.2.1. Preparation of the three layered pellet system

Drug loaded pellets were prepared by layering drug- binder suspensions in IPA: water (88: 12, w/w) for carbamazepine and theophylline and solution in ethanol: water (70: 30, w/w) for propranolol HCl using HPMC E5 as binder (10%, w/w, based on drug) onto drug free sugar pellets in a fluidized bed coater GPCG1 (Glatt Process Technology GmbH, Binzen, Germany) to achieve a 10% (for all drugs) or 50% (for carbamazepine) drug content based on the initial pellet weight. The layering conditions were, batch size: 900 g, inlet temperature: 38- 44°C (carbamazepine), 32- 36°C (theophylline) and 42- 46°C (propranolol HCl); product temperature: 32- 36°C (carbamazepine), 30- 32°C (theophylline) and 38- 42°C (propranolol HCl); air flow: 80- 90 m^3/h; nozzle diameter: 1.2 mm; spray pressure: 1.2 bar; spray rate: 9- 12 g/min (carbamazepine), 8- 10 g/min (theophylline and propranolol HCl); and final drying at 40°C for 15 minutes.

The drug loaded pellets were coated with $NaHCO_3$, as the gas generating agent, suspended in aqueous HPMC solution which was plasticized with Lutrol E 6000 (10%, w/w, based on the solids content of HPMC). On a dry solid basis, the ratios of $NaHCO_3$ to HPMC was 2:8 w/w, the solids content of coating suspension was kept constant at 12% w/w and coating was performed in a fluidized bed coater, Glatt GPCG-1 to a weight gain of 15%. The layering conditions were, batch size: 900 g; inlet temperature: 44- 48°C; product temperature: 36- 40°C; air flow: 80- 90 m^3/ h; nozzle diameter 1.2 mm; spray pressure: 1.2 bar; spray rate: 6- 6.5 g/min and final drying at 40°C for 15 min.

As topcoat, Eudragit® RL 30 D, RS 30 D or Kollicoat® SR 30 D were coated from an aqueous polymer dispersion, plasticized with 20% TEC (w/w, based on the total dry polymer weight of Eudragit® RL 30 D and Eudragit® RS 30 D and their combination) or 10% TEC (w/w, based on the dry Kollicoat® SR 30 D weight). 35% Talc (w/w, based on polymer content) was used as antitacking agent. The polymer content was adjusted to 15% (w/w) with purified water and the coating was done in a fluidized bed coater Mini Glatt (Glatt GmbH, Binzen, Germany) to a weight gain of 5- 20% (w/w). The coating

conditions were, batch size: 100 g; inlet temperature: 32- 34°C (Eudragit® RL 30 D: RS 30 D) and 34-38°C (Kollicoat® SR 30 D); product temperature: 28- 30°C; air flow: 0.2 bar; nozzle diameter 0.5 mm; spray pressure: 0.9 bar; spray rate: 1 g/min and final drying at 40°C for 15 min. 1% aerosil was added to the coated pellets, which were oven-cured at 60°C directly after the coating step using dry heat, with no controlled humidity for 2 h. The samples were put into a desiccator until further tested.

2.2.2.2. Drug layering and preparation of the extended release pellets

Propranolol HCl loaded pellets were prepared by layering drug- binder solution in ethanol: water (70: 30, w/w) using HPMC E5 as binder (10%, w/w, based on drug) onto drug free sugar pellets in a fluidized bed coater GPCG1 (Glatt Process Technology GmbH, Binzen, Germany) to achieve a 10, 30 or 50% drug content based on the initial pellet weight. The layering conditions were, batch size: 900 g, inlet temperature: 42-46°C; product temperature: 38- 42°C; air flow: 80- 90 m^3/h; nozzle diameter: 1.2 mm; spray pressure: 1.2 bar; spray rate: 8- 10 g/min; and final drying at 40°C for 15 minutes.

The propranolol HCl loaded pellets were further coated with an aqueous colloidal polymeric dispersion of Eudragit® RS 30 D, Kollicoat® SR 30 D or Aquacoat® ECD in a fluidized bed coater Glatt GPCG-1 to a predetermined weight gain. The dispersions were plasticized with 20% TEC (w/w, based on the dry Eudragit® RS 30 D weight), 10% TEC (w/w, based on the dry Kollicoat® SR 30 D weight) or 25% TEC (w/w, based on the dry Aquacoat® ECD weight). 35% Talc (w/w based on the dry polymer weight) was used as antitacking agent. The polymer content was adjusted to 15% (w/w) with purified water. The coating conditions were batch size: 900 g, inlet temperature: 38-42°C (Eudragit® RS 30 D) and 45°C (Kollicoat® SR 30 D or Aquacoat® ECD), product temperature: 30- 34°C (Eudragit® RS 30 D) and 35- 40°C (Kollicoat® SR 30 D or Aquacoat® ECD), air flow: 70-80 m^3/h, nozzle diameter 1.2 mm, spray pressure: 1.2 bar, spray rate: 8- 10 g/min and final drying at 40°C for 15 min. Samples of the coated pellets were oven-cured directly at 60°C after the coating step using dry heat, with no controlled humidity for 2 hours, after adding 1% aerosil and put into a desiccator until further tested.

2.2.2.3. Preparation of the modified multiple unit drug delivery system

The extended release uncured pellets were further coated with $NaHCO_3$ (15 or 20%, w/w, based on the initial pellet weight) and finally Eudragit® RL 30 D (to a predetermined weight gain) as top-coat, using the same procedure as previously mentioned. 1% aerosil was added to the coated pellets, which were oven-cured at 60°C directly after the coating step using dry heat, with no controlled humidity for 2 h. The samples were put into a desiccator until further tested.

2.2.2.4. Preparation of the pH independent multiple unit floating drug delivery system

The extended release cured pellets (10% Propranolol HCl coated with 15% Aquacoat® ECD) were coated with two effervescent layers, citric acid followed by $NaHCO_3$. Citric acid was dissolved in an HPC EXF (25%, w/w based on citric acid content) IPA solution, which was layered in a fluidized bed coater, STREA1 coater (Aeromatic AG, Muttenz, Switzerland) to a weight gain of 15% (w/w). The solids content of the coating solution was kept constant at 20% w/w. The layering conditions were, batch size: 900 g; inlet temperature: 48- 52°C; product temperature: 40- 44°C; air flow: 130 m^3/ h; nozzle diameter 1.2 mm; spray pressure: 1.2 bar; spray rate: 3- 3.5 g/min and final drying at 44°C for 15 min.

The second effervescent layer, $NaHCO_3$, was suspended in an HPC EXF solution (25%, w/w/ based on $NaHCO_3$ content) IPA solution and was layered in a fluidized bed coater, STREA1 coater to a weight gain of 20% (w/w). The solids content of the coating solution was kept constant at 15% w/w. The layering conditions were, batch size: 900 g; inlet temperature: 44- 48°C; product temperature: 36- 40°C; air flow: 80- 90 m^3/ h; nozzle diameter 1.2 mm; spray pressure: 1.2 bar; spray rate: 5.5- 6 g/min and final drying at 40°C for 15 min.

As topcoat, Eudragit® RL 100 was coated from an organic mixture of IPA-Acetone in the ratio 1:1, plasticized with 10% TEC (w/w, based on dry polymer weight). 35% Talc (w/w based on dry polymer weight) was used as antitacking agent. The solids content was adjusted to 12% (w/w) with purified water, and the coating was done in a fluidized

bed coater Mini Glatt to a predetermined weight gain. The coating conditions were, batch size: 100 g; inlet temperature: 25- 28°C; product temperature: 24- 26°C; air flow: 0.2 bar; nozzle diameter 0.5 mm; spray pressure: 0.9 bar; spray rate: 1.2 g/min and final drying at 40°C for 15 min. The coated pellets were put into a desiccator until further tested.

2.2.2.5. Floating ability

The floating abilities of the pellets was determined in 50 ml prewarmed 0.1 N, 0.01 N, 0.001 N HCl or deionized water at 70 rpm, 37 ± 0.2°C for 18 h, using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH, Burgwedel, Germany) (n= 2). One hundred pellets ($n_{initial}$) were placed in the medium; the number of floating pellets (n_t) over the tested time range was measured by visual observation. The percentage of floating pellets was calculated as follows:

$$\text{Floating pellets } (\%) = \frac{n_t}{n_{initial}} * 100$$

Or the floating lag time (time at which all pellets start floating) and the% floating pellets at 18 h was determined.

2.2.2.6. Drug release

The drug release from coated pellets was investigated in a USP paddle apparatus (VK 700, Vankel Industries, Edison, NJ, USA), 900 ml of 0.1 N HCl or deionized water (100 rpm, 37°C, *n*= 3). The weight of pellets used was equivalent to about 50 mg of propranolol HCl, and 20 mg for theophylline and carbamazepine. At predetermined time intervals, 3-ml samples were withdrawn and analyzed with UV spectrophotometry (UV-2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA), propranolol HCl, λ= 290 nm; theophylline, λ= 270 nm and carbamazepine, λ= 283 nm.

2.2.2.7. Medium uptake and mass loss of pellets

One hundred pellets were weighed ($weight_{initial}$), put into 50 ml prewarmed 0.1 N HCl, and shaken at 37 ± 0.2°C, 70 rpm for 18 h, using a shaker apparatus (GFL shaking incubator 3033; GFL GmbH, Burgwedel, Germany) (*n*= 2). The pellets were removed from the medium, dried using vacuum filtration to remove excess water and weighed ($weight_{wet}$). The pellets were oven-dried for 24 h at 105°C and additionally for 48 h in a desiccator and weighed till constant weight ($weight_{dry}$). The medium uptake and mass loss were calculated as follows:

$$\text{Medium uptake /pellet weight } (mg/mg) = \frac{weight_{wet} - weight_{dry}}{weight_{initial}}$$

$$\text{Mass remaining / pellet weight } (mg/mg) = \frac{weight_{dry}}{weight_{initial}}$$

2.2.2.8. Swelling studies and macroscopic examination

Pictures of the pellets were taken under the light macroscope (Carl Zeiss, Inc., Beograd, Österreich) using the image analyzing software (Inteq, Berlin, Germany) and their diameter ($d_{initial}$) was measured. The pellets were then placed into 50 ml prewarmed 0.1 N HCl, and shaken at 37 ± 0.2°C, 70 rpm for 18 h using a shaker apparatus (GFL shaking incubator 3033; GFL mbH, Burgwedel, Germany) (*n*= 2). The pellets were removed from the medium at predetermined time points and pictures of the swollen pellets were taken under the macroscope and their diameter (d_{wet}) was measured.

$$\text{Swelling } (\%) = \frac{d_{wet} - d_{initial}}{d_{initial}} * 100$$

2.2.2.9. Density calculation

The density (ρ_t) was calculated from the weight (w_t= $w_{initial}$ or w_{wet}) and diameter (d_t= $d_{initial}$ or d_{wet}) at each time point, by the following equation:

$$\rho_t = \frac{w_t}{V_t} = \frac{w_t}{1/6\pi d_t^3}$$

2.2.2.10. Stability studies

To assess the formulation stability, stability studies were performed for 3 months. The cured drug-loaded pellets were weighed and stored in 10 ml open glass vials. Stability studies were performed under ambient temperature at 25 ± 2°C/ 0% RH; 40°C/ 0% RH, in a desiccator put in an oven and according to the ICH guideline for accelerated conditions at 40°C/ 75% RH in a climatic chamber. At each time interval, the samples were weighed and analyzed for their floating and release behavior.

3. RESULTS AND DISCUSSION

3.1. Development and in vitro evalua
tion of single unit floating drug delivery systems

3.1.1. Introduction

Numerous oral extended DDS have been developed to prolong drug release. Since the majority of drugs are preferentially absorbed in the upper part of the small intestine (Singh and Kim, 2000), the real challenge in the development of an extended release DDS lies mainly in prolonging the residence of the dosage form in the stomach or upper part of the small intestine until all the drug is completely released in the desired time period (Deshpande et al., 1996; Hwang et al., 1998).

An option for the preparation of floating oral dosage forms is described by the development of floating matrix tablets. A matrix device consists of drug dispersed homogenously throughout a polymer matrix. There are two major types of materials used in the preparation of matrix devices (Qiu and Zhang, 2000; Venkatraman et al., 2000):

1. Hyrophobic carriers either as digestible base, e.g., fatty compounds, glycerides, glyceryltristearate, fatty alcohols, fatty acids or waxes; or nondigestible base (insoluble plastics), e.g., methylacrylate, methylmethacrylate, polyvinyl chloride, polyethylene or ethyl cellulose (Ding et al., 2000);
2. Hydrophilic polymers, e.g. methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, xanthan gum, polyethylene oxide and carbopols.

Matrix devices offer several advantages relative to other extended release dose forms:

- Ease of manufacture, since the dosage form is prepared with a single manufacturing step
- Versatility, effectiveness and low cost
- Can be made to release high molecular weight compounds

- As the drug is dispersed homogeneously throughout the polymeric matrix, accidental leakage of the total drug component is less likely to occur, although

occasionally, cracking of the matrix material can cause unwanted release, since the drug is dispersed in the matrix system.

Challenges of matrix systems:

- The remaining matrix should be removed after the drug has been completely released to avoid accumulation following multiple administrations.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/ or a decrease in effective area at the diffusion front (Qiu and Zhang, 2000). However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order (Jantzen and Robinson, 2002).

The principle of floating from hydrophilic single unit matrices is based on the fact that the matrix begins to swell and forms a gel layer when in contact with gastric fluid. The formed gel layer decreases the tablet density and controls the drug release by diffusion through the matrix. The swelling boundary moves towards the dry core, maintaining hydration and buoyancy of the system (Hwang et al., 1998; Reddy and Murthy, 2002). A drawback lies in the variability of buoyancy, depending on the air in the matrix void (porosity) during the compression step (Bardonnet et al., 2006). This can be overcome by the incorporation of gas forming agents in the matrix for e.g. sodium bicarbonate, to increase the tablets floating strength.

This study aimed to evaluate the floating and drug release behavior of directly compressed hydrophilic matrices (HPMC, Carbopol and Ac-Di-Sol) for the development of single unit floating drug delivery systems.

3.1.2. Results and discussion

HPMC matrix tablets floated after 40-45 min in 0.1 N HCl **(Table 1)**. When HPMC matrix hydrates, a swollen gel-like structure **(Fig. 6A)** was formed that resulted in the decrease in tablet density.

Table 1: *Polymer and sodium bicarbonate composition of tablets, floating lag time and floating duration*

HPMC K15M (%)	Carbopol 974P (%)	Ac-Di-Sol (%)	$NaHCO_3$ (%)	Floating lag time (min)	Floating duration (h)
84				**40-45**	**> 18**
65			**19**	**20-25**	**> 18**
55			**29**	**3-5**	**> 18**
42	**42**			**-**	**-**
56	**28**			**-**	**-**
28	**56**			**-**	**-**
32.5	**32.5**		**19**	**< 1**	**> 18**
	65		**19**	**< 1**	**> 18**
	55		**29**	**< 1**	**> 18**
42		**42**		**> 60**	**> 18**
56		**28**		**> 60**	**> 18**
28		**56**		**> 60**	**> 18**
32.5		**32.5**	**19**	**< 1**	**> 18**

Loss of floating ability was shown when a combination of HPMC and carbopol, in varying ratios, were used as matrix carrier **(Table 1)**. Higher moisture absorption was reported for carbopol compared to HPMC, which may have resulted in increased initial

tablet density (Li et al., 2003). The HPMC- Carbopol matrices showed sponge-like structure and high swelling tendency, which may make them a good candidate for swelling gastroretentive drug delivery systems **(Fig. 6B)**. More swelling was observed when the Carbopol portion in the matrix was increased **(Fig. 6B)**.

Moreover, the floating lag time increased when a combination of HPMC and Ac-Di-Sol, in varying ratios, was used as a matrix carrier (> 60 min). This may be the time taken for tablet hydration and gel formation **(Table 1)**. HPMC-Ac-Di-Sol matrices showed higher erosion especially with increasing the Ac-Di-Sol polymer portion in the tablet **(Fig. 6C)**.

The incorporation of $NaHCO_3$ in the matrix caused a reduction of floating lag time in all tablets. Floating lag time of HPMC matrix tablets decreased to 25 and 5 min when 19% and 29% $NaHCO_3$ was included **(Table 1)**. However, with $NaHCO_3$, until stable buoyancy was achieved the matrices began an up and down movement, attributed to rapid changes in CO_2 production and loss, leading to changes in matrix density. This may be the time needed for the HPMC matrix to form the gel layer capable of entrapping the formed CO_2. The HPMC- $NaHCO_3$ matrices showed a swollen gel-like structure, with entrapped CO_2 **(Fig. 6A)**, which improved the floating ability of the tablet.

In case of carbopol, HPMC-Carbopol and HPMC-Ac-Di-Sol matrix, they exhibited instant floating and more than 18 hour floating duration after $NaHCO_3$ was added **(Table 1)**. This was due to CO_2 formation in the presence of acidic medium, which was entrapped inside the hydrated matrix and caused a decrease in the tablet density.

The addition of carbopol to HPMC matrices did not change the drug release at the initial phase (< 6 h), but slowed down the release rate at the later phase **(Fig. 7A)**. HPMC matrices were smaller than HPMC- Carbopol, indicating more swelling than erosion at 18 h in the presence of carbopol **(Fig. 6A vs B)**. This may be due to more polymer erosion from HPMC matrices alone, which decreased the diffusion path length thus faster release was observed. Drug release from HPMC- Carbopol was independent on the carbopol amount **(Fig 7A)**. Varying carbopol amount showed slightly different medium uptake, increasing with increasing the carbopol portion, but similar mass loss

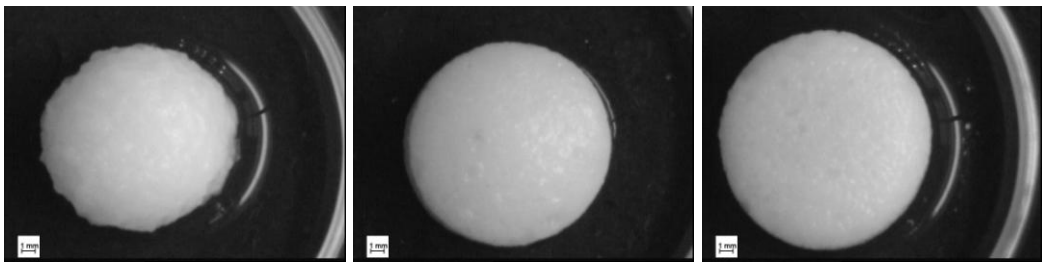
was observed **(Fig 8A and B)**. This may explain the similar drug release profiles **(Fig 7A)**.

(A) HPMC: $NaHCO_3$

84:0 65:19 55:29

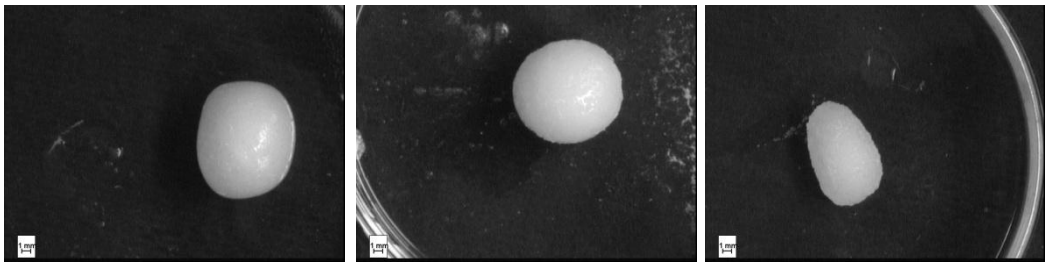
(B) HPMC: Carbopol

56:28 42:42 28:56



(C) HPMC: Ac-Di-Sol

56:28 42:42 28:56



(D) HPMC: Carbopol: Ac-Di-Sol: $NaHCO_3$

32.5:32.5:0:19 32.5:0:32.5:19

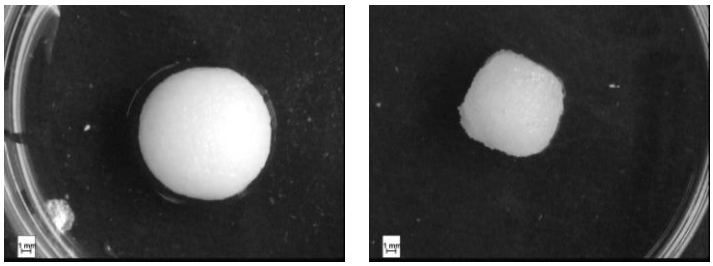


Fig. 6: *Macroscopic examination of (A) HPMC: $NaHCO_3$, (B) HPMC: Carbopol, (C) HPMC: Ac-Di-Sol and (D) HPMC: Carbopol: Ac-Di-Sol: $NaHCO_3$ tablets at 18 h in 0.1 N HCl*

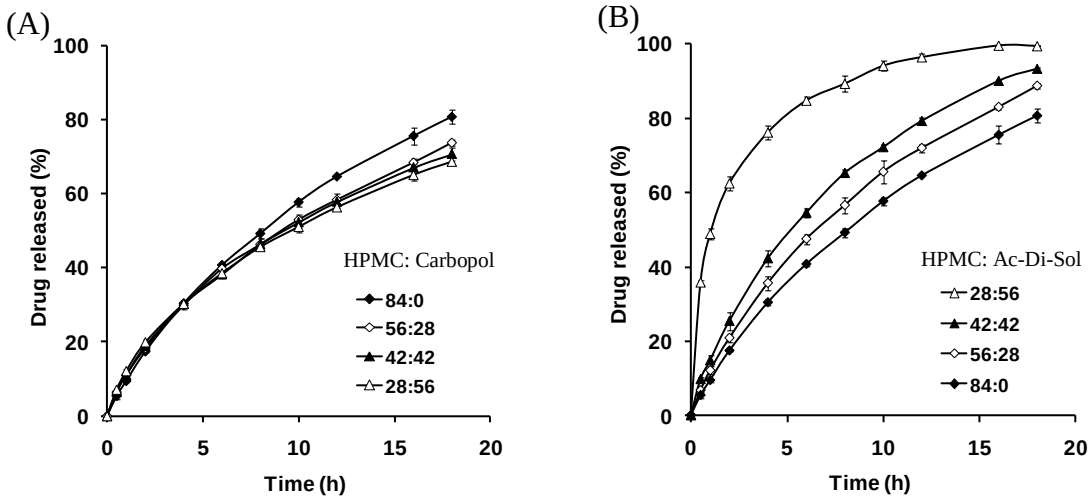


Fig. 7: *Effect of varying polymer on drug release from Propranolol HCl tablet (A) HPMC: Carbopol, (B) HPMC: Ac-Di-Sol*

Ac-Di-Sol is a high water absorption agent, which is normally used as a disintegrant. It formed a gel in high concentration, thus could be used for controlled drug release. On the contrary to HPMC- Carbopol, the drug release from HPMC-Ac-Di-Sol was dependent on the Ac-Di-Sol portion in the matrix **(Fig. 7B)**. Medium uptake and mass loss increased with increasing the amount of Ac-Di-Sol **(Fig. 9A and B)**, indicating higher erosion of the Ac-Di-Sol containing matrices, which contributed to the increase in drug release.

On adding $NaHCO_3$ to HPMC matrices in varying ratios the drug release was almost similar **(Fig. 10A)**. This is because, once the tablet hydrates and the gel layer of HPMC is formed, there appears to be no difference in release rate from the tablets, where the hydration and gel formation is the rate limiting step. Lower medium uptake after 8 h and increased mass loss was observed **(Fig. 11)**. This correlates well with the lower polymer amount in the matrix, leading to decreased tablet hydration. The dissolution of $NaHCO_3$ and its conversion to CO_2, along with drug release and polymer erosion, increased the mass loss from $NaHCO_3$ containing tablets.

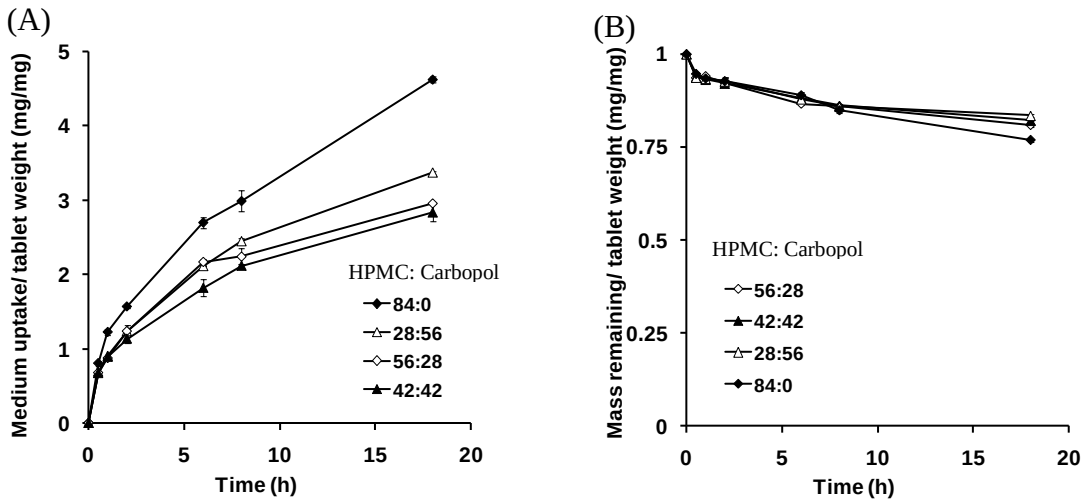


Fig. 8: *Effect of HPMC: Carbopol ratio on (A) medium uptake and (B) mass remaining from Propranolol HCl tablets*

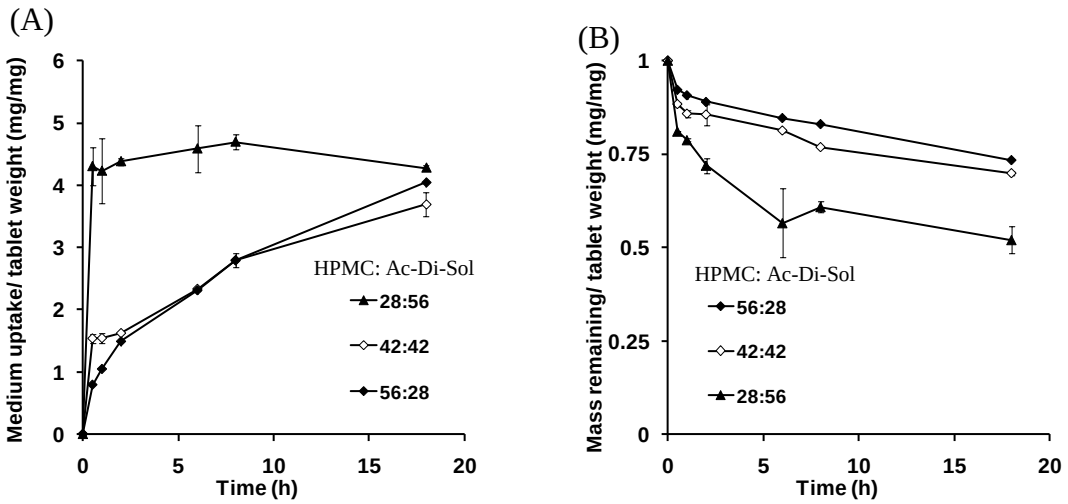


Fig. 9: *Effect of HPMC: Ac-Di-Sol ratio on (A) medium uptake and (B) mass remaining from Propranolol HCl tablets*

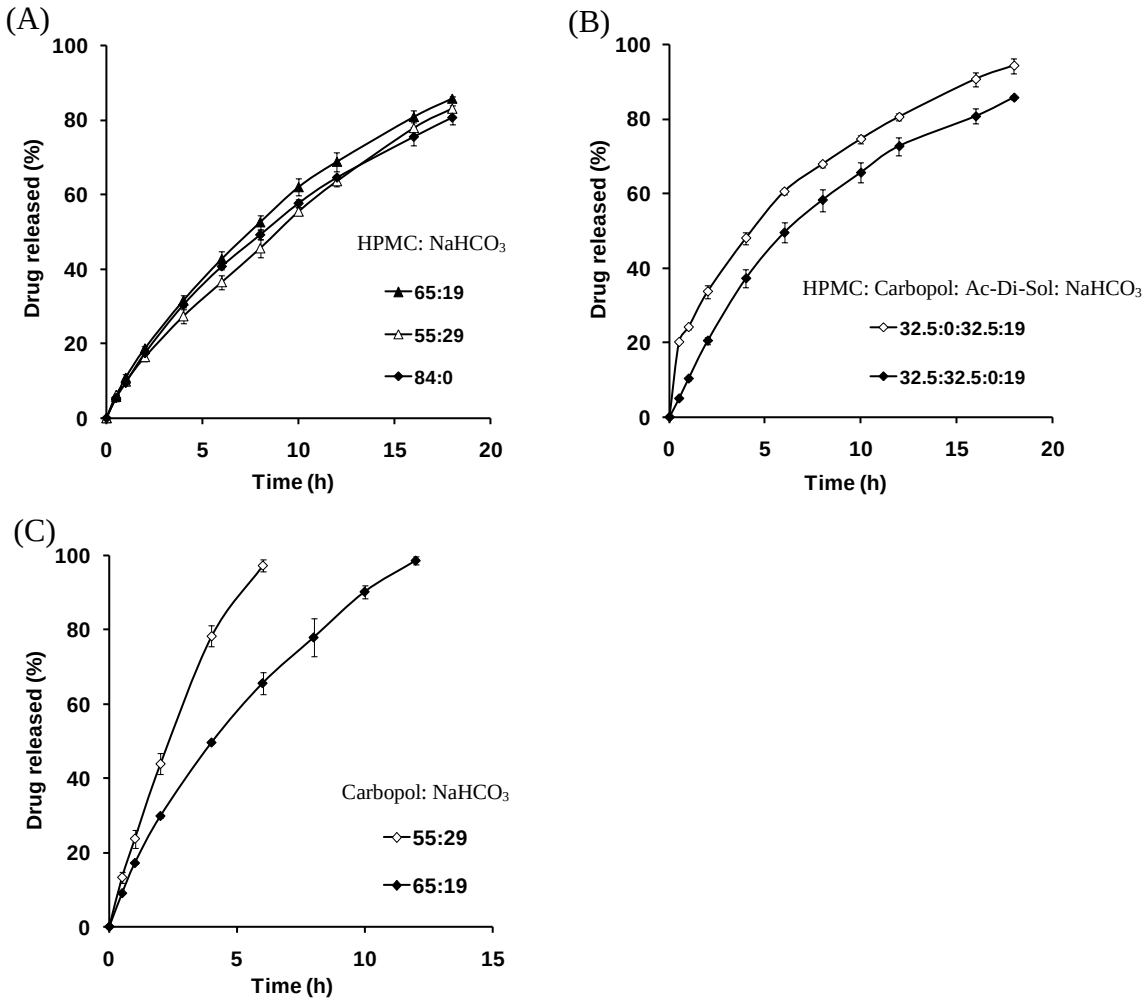


Fig. 10: *Effect of varying polymer and sodium bicarbonate ratios on drug release from Propranolol HCl tablets (A) HPMC: $NaHCO_3$, (B) Carbopol: $NaHCO_3$ and (C) HPMC: Carbopol: Ac-Di-Sol: $NaHCO_3$*

In the presence of $NaHCO_3$, HPMC- Ac-Di-Sol matrix tablets had a faster drug release compared to HPMC- Carbopol matrix tablets **(Fig. 10B)**, which was due to higher and faster hydration and erosion of Ac-Di-Sol than carbopol **(Fig. 6D and 12)**.

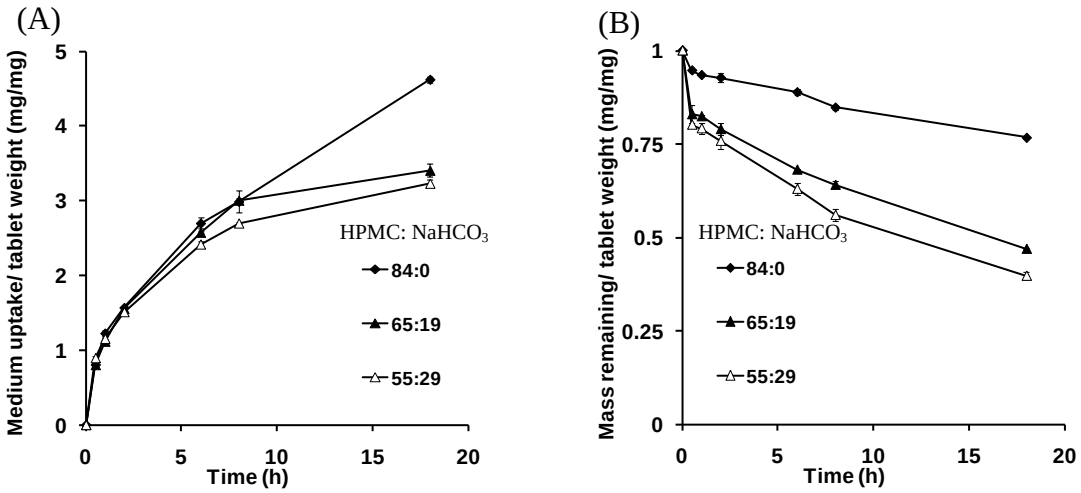


Fig. 11: *Effect of HPMC: $NaHCO_3$ ratio on (A) medium uptake and (B) mass remaining from Propranolol HCl tablets*

As expected, increasing the amount of carbopol in Carbopol- $NaHCO_3$ matrix tablets from 55% to 65%, and consequently decreasing $NaHCO_3$ from 29% to 19% decreased the drug release; 100% drug release was achieved in 12 h instead of 6 h **(Fig. 10C)**. This was due to the higher polymer portion in the matrix, which was reflected as higher maximum amount of medium uptake and lower mass loss from the tablet **(Fig. 13)**. Due to the increased hydration, swelling and uncoiling of the carbopol polymer, complete erosion of carbopol-$NaHCO_3$ tablets occurred. The complete erosion would avoid accumulation of the tablet following multiple administrations.

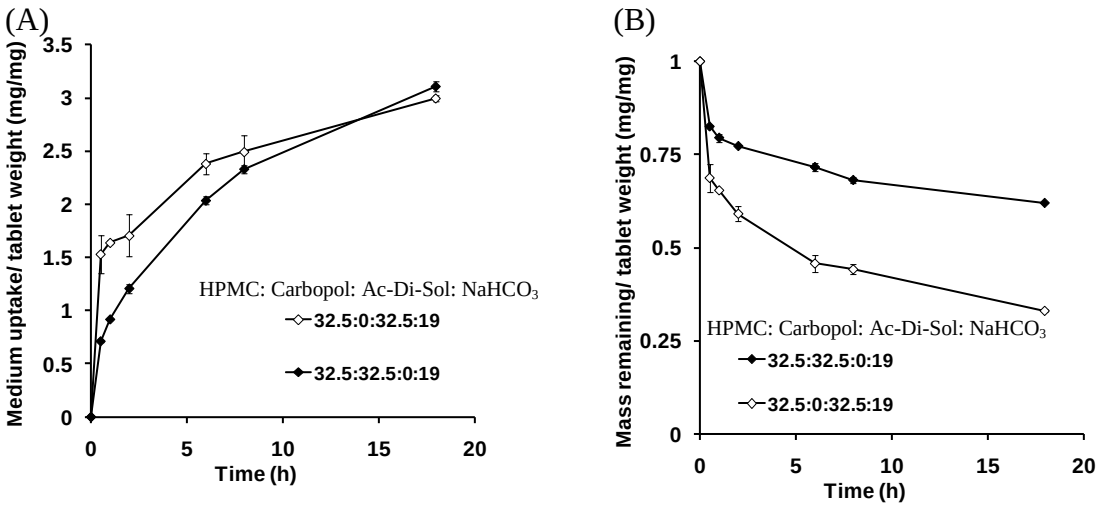


Fig. 12: *Effect of HPMC: Carbopol: Ac-Di-Sol: $NaHCO_3$ ratio on (A) medium uptake and (B) mass remaining from Propranolol HCl tablets*

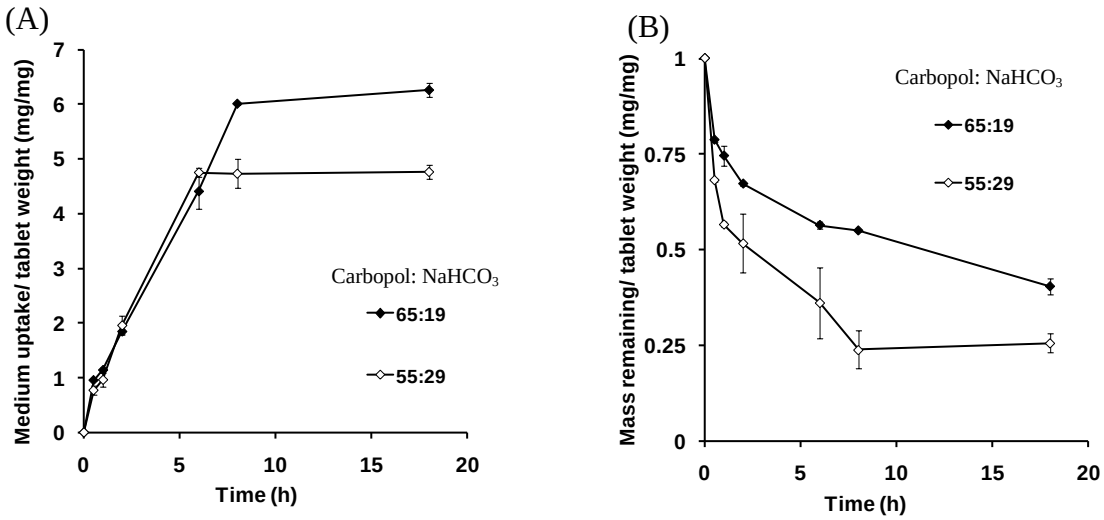


Fig. 13: *Effect of Carbopol: $NaHCO_3$ ratio on (A) medium uptake and (B) mass remaining from Propranolol HCl tablets*

For the analysis of the drug release mechanism, the data obtained from the dissolution studies were analyzed according to the semiemperical equation **(1)** proposed by Korsmeyer et al. (Korsmeyer et al., 1983).

$$M_t / M_\infty = kt^n \qquad \textbf{(1)}$$

where (M_t/M_∞) represents the percentage of drug released at time t, k is a constant incorporating geometric and structural characteristics and n is an exponent which indicates the drug release mechanism.

For cylindrical shapes, Fickian diffusion is related to n = 0.45, whereas n = 0.89 indicates case II transport (zero order or time dependent drug release) and n > 0.89 super case II transport. Values of n between 0.45 and 0.89 identify anomalous (non-Fickian) diffusion, corresponding to coupled diffusion and polymer relaxation (Ritger and Peppas, 1987). In practice, drug release from polymeric matrices will not solely be attributed to one mechanism. Therefore, the application of the Korsmeyer-Peppas model on DDS of interest provides information regarding the prevalent mechanism of drug release.

As the Korsmeyer-Peppas model is often valid for cumulative drug release up to ~ 60%, the data used for the analysis were limited to this range. To identify the drug release mechanism, n values for the different formulations were calculated using equation **(1)**. The coefficient of determination r^2 was used as an indicator for the fitting of the considered model.

The release of Propranolol HCl from various polymer matrices fits well with the Korsmeyer-Peppas model. The release exponent n exhibits values between 0.45 and 0.89 **(Table 2)**, indicating a drug release mechanism which is governed by anomalous (non-Fickian) diffusion. A change in drug release mechanism to Fickian diffusion was observed for the HPMC: Ac-Di-Sol: $NaHCO_3$ matrices in the ratios 28:56:0 and 32.5:32.5:19. This may be because Ac-Di-Sol was the dominant polymer causing this shift in drug release mechanism.

Table 2: *Kinetic parameters based on Korsmeyer-Peppas (power law) equation (1) for Propranolol HCl matrix tablets (k = release kinetic constant; n = release exponent; r² = coefficient of determination).*

HPMC: Carbopol: Ac-Di-Sol: $NaHCO_3$	**k (h^{-1})**	**n**	**r^2**
84: 0: 0: 0	0.9819	0.7978	0.9983
65: 0: 0: 19	1.0187	0.7849	0.9985
55: 0: 0: 29	0.9998	0.7304	0.9993
42: 42: 0: 0	1.0476	0.6809	0.9974
56: 28: 0: 0	1.0401	0.6942	0.9976
28: 56: 0: 0	1.0768	0.6442	0.9963
32.5: 32.5: 0: 19	1.0034	0.8914	0.9933
0: 65: 0: 19	1.2163	0.7743	0.9961
0: 55: 0: 29	1.3785	0.8584	0.9998
42: 0: 42: 0	1.1889	0.7018	0.9986
56: 0: 28: 0	1.0733	0.7724	0.9986
28: 0: 56: 0	1.6794	0.402	0.9954
32.5: 0: 32.5: 19	1.4111	0.451	0.9849

3.1.3. Conclusion

While the addition of carbopol and Ac-Di-Sol to pure HPMC matrices was found to compromise the floating properties of HPMC, carbopol might provide other gastric retentive mechanisms to maintain the delivery system in the GI tract. The drug release of HPMC was similar at the initial phase, and decreased at the late stage, when carbopol was added to the matrix and was independent of the carbopol amount. This was due to more swelling than erosion from carbopol containing matrices. On the other hand, the addition of Ac-Di-Sol increased the drug release because erosion from the matrix was higher. When $NaHCO_3$ was added to carbopol, HPMC- carbopol and HPMC- Ac-Di-Sol matrices, instant floating and more than 18 hour floating duration was achieved, with varying drug release profiles. For the carbopol- $NaHCO_3$ matrices, extended drug release, followed by complete erosion of the matrix was accomplished, which would avoid accumulation following multiple administrations.

3.2. Development of extended release multiple unit effervescent floating drug delivery systems for drugs with differing solubility

3.2.1. Introduction

Gastroretentive dosage forms are interesting extended release delivery systems for drugs with a narrow window of absorption in the upper intestine (Davis, 2005; Rouge et al., 1996; Sato et al., 2004), for drugs with pH-dependent solubility (Jain et al., 2005; Singh and Kim, 2000), for drugs degraded by higher pH intestinal fluids (Badve et al., 2007; Whitehead et al., 2000) or for drugs with local action in the proximal part of the GI tract, such as antibiotic administration for *Helicobacter pylori* in the treatment of peptic ulcer (Moes, 1993; Murata et al., 2000; Yang et al., 1999).

Several approaches to prolong gastric retention have been investigated: Magnetic systems (Fujimori et al., 1995), high density systems (Rouge et al., 1998), mucoadhesive systems (Bravo-Osuna et al., 2007; Jackson et al., 2000), swelling (Chen et al., 2000; Shalaby et al., 1992) and expanding systems (Gröning et al., 2007; Kagan et al., 2006; Klausner et al., 2003) and floating systems (Atyabi et al., 1996a; Hamdani et al., 2006b; Krögel and Bodmeier, 1999; Li et al., 2003; Streubel et al., 2002).

Floating systems are either based on an inherently low density or on effervescence. Non-effervescent systems have their inherent low density due to the entrapment of air, as in the formation of low density hollow microspheres (Badve et al., 2007; Iannuccelli et al., 1998; Joseph et al., 2002; Kawashima et al., 1991), incorporation of low density material (sponges) (Streubel et al., 2002, , 2003a) or due to swelling (Dennis, 1992; Sheth, 1978). The effervescent systems, on the other hand, have an initially high density, which decreases upon contact with the acidic environment due to CO_2 generation (Choi et al., 2002; Ichikawa et al., 1991; Sungthongjeen et al., 2008). This is achieved by the incorporation of effervescent components such as sodium bicarbonate or sodium carbonate, and additionally citric or tartaric acid (Rubinstein and Friend, 1994).

Besides frequently investigated single unit dosage forms, which have a high variability of GI transit time due to their all-or-nothing emptying process (Streubel et al., 2003b; Talukder and Fassihi, 2004), multiple unit floating systems have been developed to overcome this problem due to their gradual emptying from the stomach (Bulgarelli et al., 2000), as well as reducing the risk of dose dumping (Iannuccelli et al., 1998). Multiple unit effervescent systems utilizing ion exchange resins beads (Atyabi et al., 1996a, 1996b), matrix minitablets (Goole et al., 2008a; Goole et al., 2008b; Goole et al., 2007; Meka et al., 2008), as well as pellets (Sungthongjeen et al., 2006) have been previously developed.

In the present study, floating reservoir type pellets based on CO_2 formation were developed for various solubility drugs, characterized in vitro and their stability under various conditions was evaluated**.**

3.2.2. Results and Discussion

A floating pellet system based on CO_2 formation should rapidly float for extended time periods and release the drug in a controlled fashion during this time period. In this study, a three-layer pellet system was prepared by layering sugar cores with drug, followed by layering with $NaHCO_3$ as the CO_2-source and finally followed by topcoating with a polymeric film **(Fig. 14A**). Ideally, the system should quickly take up acidic gastric juice to rapidly develop CO_2 to be trapped within the coated pellets in order to induce floating and then release the drug slowly during the floating time period. The top coating should thus fulfill two functions, namely first entrapping the CO_2, which is rapidly generated upon contact with acidic gastric fluids to maintain floating and second, releasing the drug slowly over an extended time period.

In a coated pellet system, increasing the medium uptake will increase the pellet weight and also increase the dissolved CO_2, which facilitates its diffusion and escape from the system.

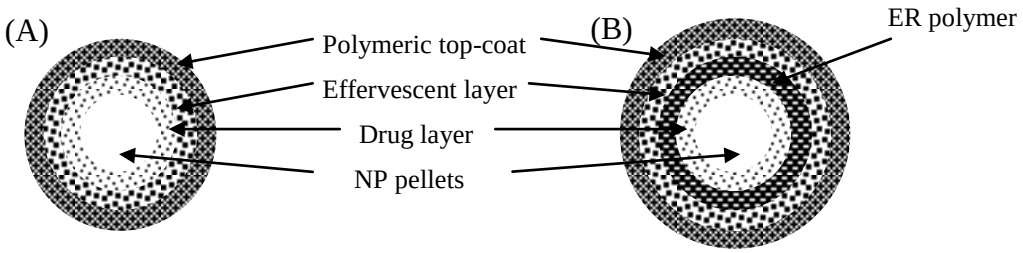


Fig. 14: *Schematic representation of (A) three layered system composed of NP pellets layered with drug, $NaHCO_3$ and topcoated with a polymeric film and (B) modified system composed of extended release pellets (NP pellets layered with drug and extended release polymer), layered with $NaHCO_3$ and topcoated with Eudragit® RL 30 D*

Therefore, for the floating system to be effective, the top-coat should have an initially high water permeability to rapidly initiate the effervescent reaction and the floating process, and be water-insoluble to stay intact and entrap CO_2. Moreover the polymeric coating should have a certain flexibility in the wet state to withstand the expansion pressure due to the generated CO_2 gas and to avoid rupturing (Krögel and Bodmeier, 1999). In addition, the pellets should have a negligible increase in medium uptake following the CO_2 formation in order to maintain floating.

For extended gastric residence, rapid floating and long floating duration are desired. In this study, formulations were considered effective with floating lag times ≤ 10 min and a percentage (%) of floating pellets > 75% for at least 18 h or until complete drug release.

Three water-insoluble polymers in the form of aqueous polymer dispersions were investigated as top-coatings: polyvinyl acetate (Kollicoat® SR 30 D) and two cationic methacrylic copolymers (Eudragit® RL 30 D and RS 30 D) alone or in combination. Eudragit® RL 30 D has twice the number of quaternary ammonium groups than Eudragit® RS 30 D and is thus more hydrophilic and permeable.

The process of floating for pellets with the three polymer coatings was followed by macroscopic examination **(Fig. 15)**. After permeation of the release medium, CO_2 formed because of the effervescent reaction between the dissolved $NaHCO_3$ and the

acid in the medium, and the pellets started to float. The process of medium penetration and CO_2 formation was very fast for Eudragit® RL 30 D pellets due to its hydrophilic nature and high permeability (≤ 2 min). On the other hand, for Eudragit® RS 30 D and Kollicoat® SR 30 D pellets the process of polymer hydration, permeation and CO_2 formation took much longer, ~ 2 h and 1 h, respectively until pellets started floating. Further medium uptake not only increased pellet weight, but also dissolved the formed CO_2 and lead to its escape from the pellets. This was seen as a decrease in the size or disappearance of the CO_2 bubble.

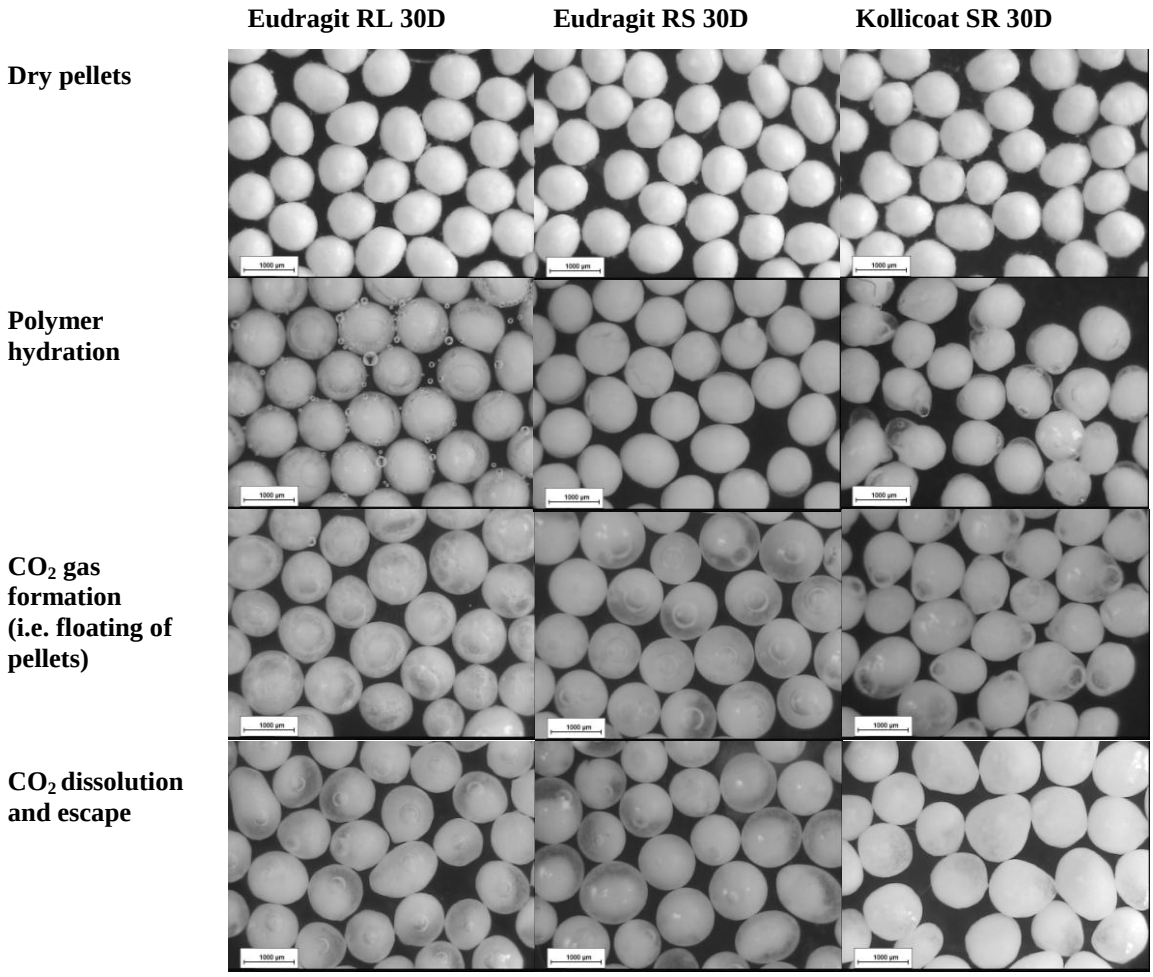


Fig. 15: *Macroscopic examination of the floating process with pellets coated with the three polymer coatings*

Eudragit® RL 30 D resulted in excellent floating but poor extended release **(Fig. 16A)**. The floating lag time was ≤ 2 min and the % floating pellets at 18 h was ≥ 85% for all coating levels. However, the drug was released completely already by the first sampling point (30 min). This was due to the high solubility of propranolol HCl and the high permeability of Eudragit® RL 30 D, initiating rapidly not only the effervescent reaction but also the drug release.

The less permeable Eudragit® RS 30 D **(Fig. 16B)** and Kollicoat® SR 30 D **(Fig. 16C)** had longer floating lag times - floating started at ~ 2 and 1 h, respectively - and had a maximum percentage of floating of only 45% and 80% at 8 and 4 h, respectively. In accordance with their lower permeability, the release of propranolol HCl was extended **(Fig. 16B and C)**.

Unfortunately, the desired combination of rapid, extended floating and extended drug release could not be obtained with this system design and the three top coating polymers with propranolol HCl.

The initial rate of medium penetration and swelling was lower for Eudragit® RS 30 D- and Kollicoat® SR 30 D- coated pellets when compared to Eudragit® RL 30 D **(Fig. 17A and B)**. This explained the longer floating and release lag time. The higher swelling of Eudragit® RS 30 D and Kollicoat® SR 30 D **(Fig. 17B)** was mainly due to medium uptake at the later stage **(Fig. 17A)**, which increased the pellet weight, dissolved the formed CO_2 and lead to sinking.

The mass loss correlated well with the drug release results and was in the order of Eudragit® RL 30 D >> Eudragit® RS 30 > Kollicoat® SR 30 D **(Fig. 17C)**.

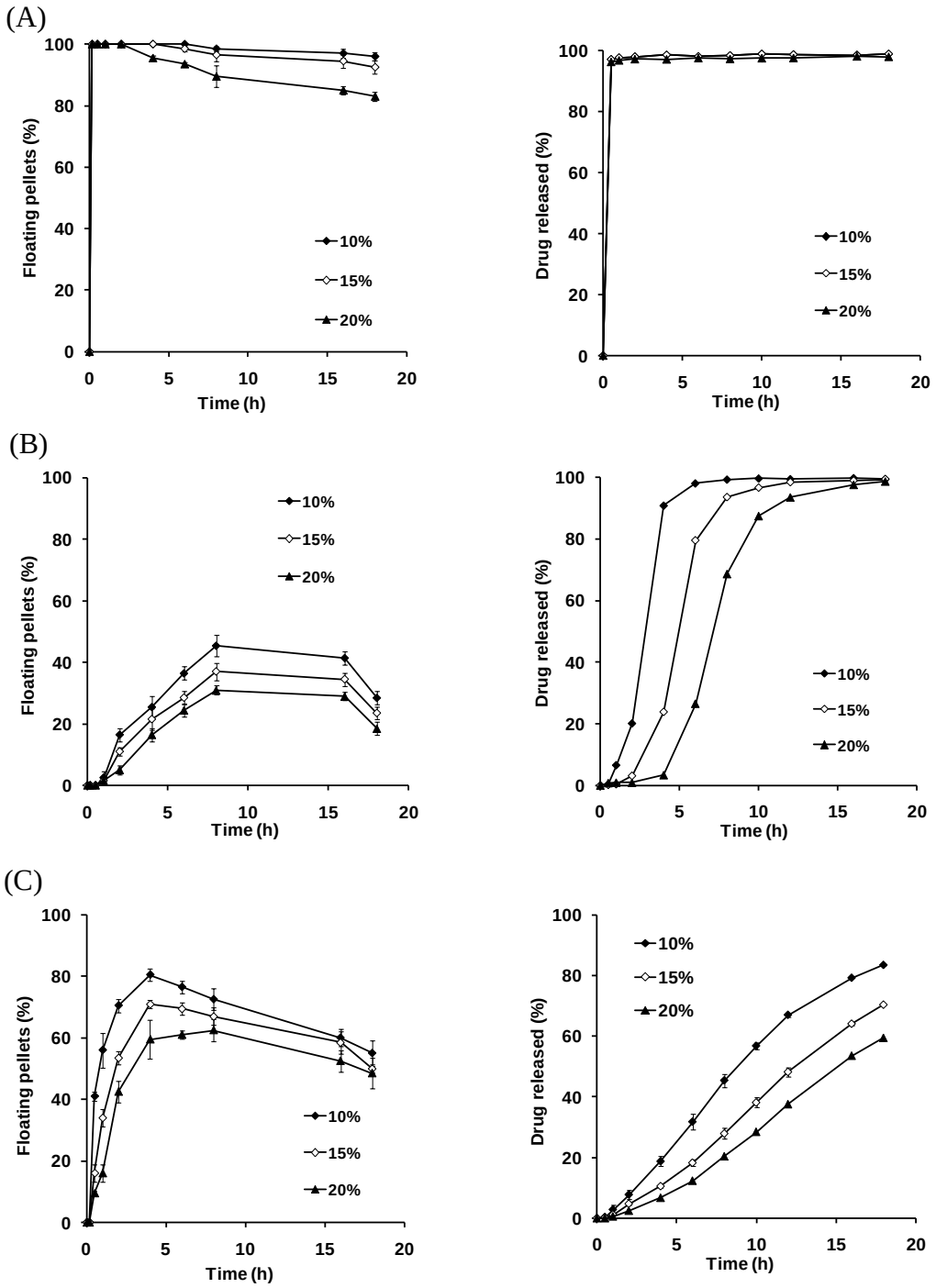


Fig. 16: *Effect of polymer type and coating level on the floating properties and drug release from (A) Eudragit® RL 30 D, (B) Eudragit® RS 30 D and (C) Kollicoat® SR 30 D coated propranolol HCl pellets (10% propranolol HCl, 15% $NaHCO_3$, and polymeric top-coating)*

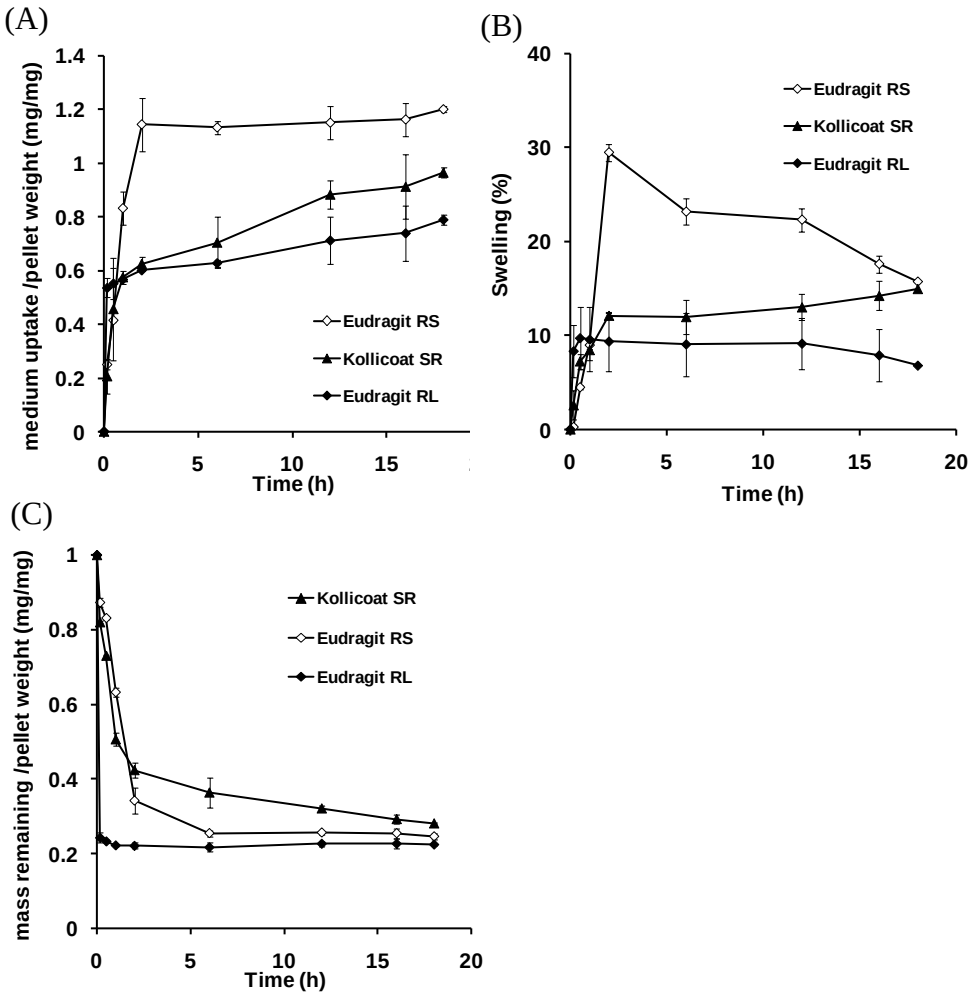


Fig. 17: *Effect of polymer type on (A) medium uptake, (B) swelling and (C) mass loss of 10% polymer coated propranolol HCl pellets (10% Propranolol HCl, 15% $NaHCO_3$)*

Next, drugs with lower water solubility; namely theophylline a sparingly soluble drug, and carbamazepine a practically insoluble drug, were investigated using Eudragit® RL 30 D as top-coating at a drug loading of 10%. Theophylline **(Fig. 18B)**, and carbamazepine (data not shown) had similar floating properties to propranolol HCl **(Fig. 18A)** (floating lag time and % floating at 18 h ≤ 2 min and ≥ 85%, respectively).

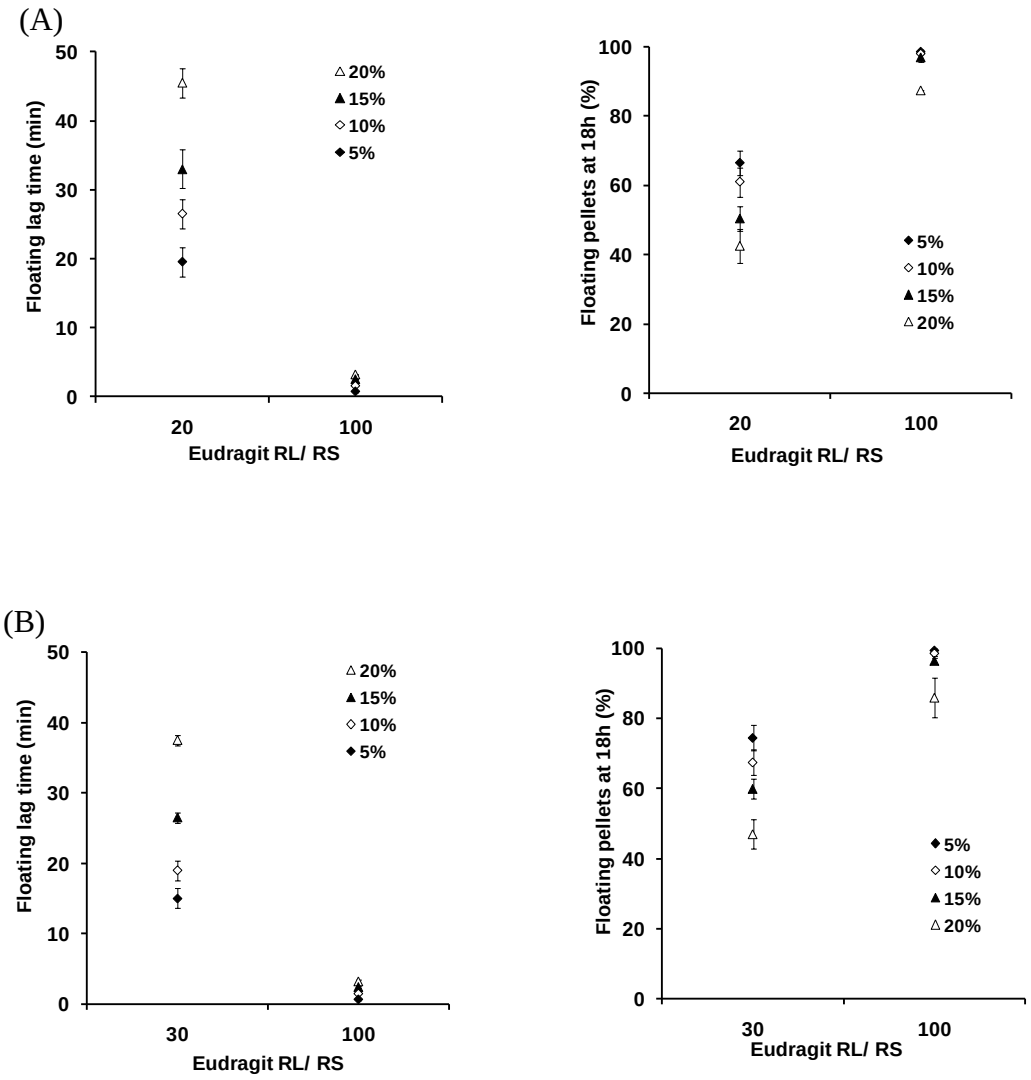


Fig. 18: *Effect of Eudragit® RL/RS 30 D ratio and coating level on the floating lag time and the % floating pellets at 18 h, from (A) 10% Propranolol HCl and (B) 10% Theophylline, and 15% $NaHCO_3$ layered pellets*

Unfortunately, extended drug release could still not be achieved, even for carbamazepine (< 4 h) (data not shown). In addition, a combination of Eudragit® RS/RL 30 D was investigated as top-coating for 10% drug loading of propranolol HCl or theophylline. Longer floating lag times > 15 min. and lower % floating at 18 h were obtained **(Fig. 18A and B)**. Moreover, the drug was released completely in ≤ 1.5 h (data not shown).

Due to the low aqueous solubility of carbamazepine, a higher drug loading (50%) was used to extend its drug release. Simultaneously a combination of Eudragit® RS/RL 30 D was investigated as top-coating to reduce the permeability of the coating. Efficient floating and acceptable release profiles could be obtained over a wide range of Eudragit® RL/RS 30 D ratios. As expected, increasing the amount of the less permeable Eudragit® RS 30 D decreased the release of carbamazepine **(Fig. 19)**, increased the floating lag time (because of the slower medium permeation caused by the higher Eudragit® RS 30 D portion in the topcoat) and decreased the % floating at 18 h **(Fig. 20)**. Above 60% Eudragit® RL 30 D, the medium penetrated rapidly to initiate the effervescent reaction, resulting in short floating lag times ≤ 7 min and high % floating at 18 h (< 70%), even at the highest coating level. Lower ratios of Eudragit® RL/RS 30 D showed a longer floating lag time of >10 min and a lower % floating at 18 h **(Fig. 20)**, due to lower initial pellet density.

Thus, this three-layer multiple unit system could be used for low solubility drugs at high loading, where the poor solubility of the drug contributed to the extended release.

In order to obtain good floating and extended release properties also for water-soluble drugs, a modification of the system was necessary.

This was achieved by separating the floating and release "functions" of the polymer coating into two separate coatings of different composition. Extended release pellets of propranolol HCl were coated with the less permeable Eudragit® RS 30 D, then layered with $NaHCO_3$ and finally topcoated with the permeable Eudragit® RL 30 D **(Fig. 14B)**. The inner Eudragit® RS 30 D coating was thus responsible for the extended release and the outer Eudragit® RL 30 D for the floating.

The floating lag time (≤ 3min) was not negatively affected by the inner Eudragit® RS 30 D coating, due to the fast medium permeation across the outer Eudragit® RL 30 D coating and rapid formation of CO_2. In contrast, the % floating at 18 h decreased with this system design **(Fig. 21A vs. 16A)**. This may be attributed to the increased pellet weight and density, due to multiple coatings.

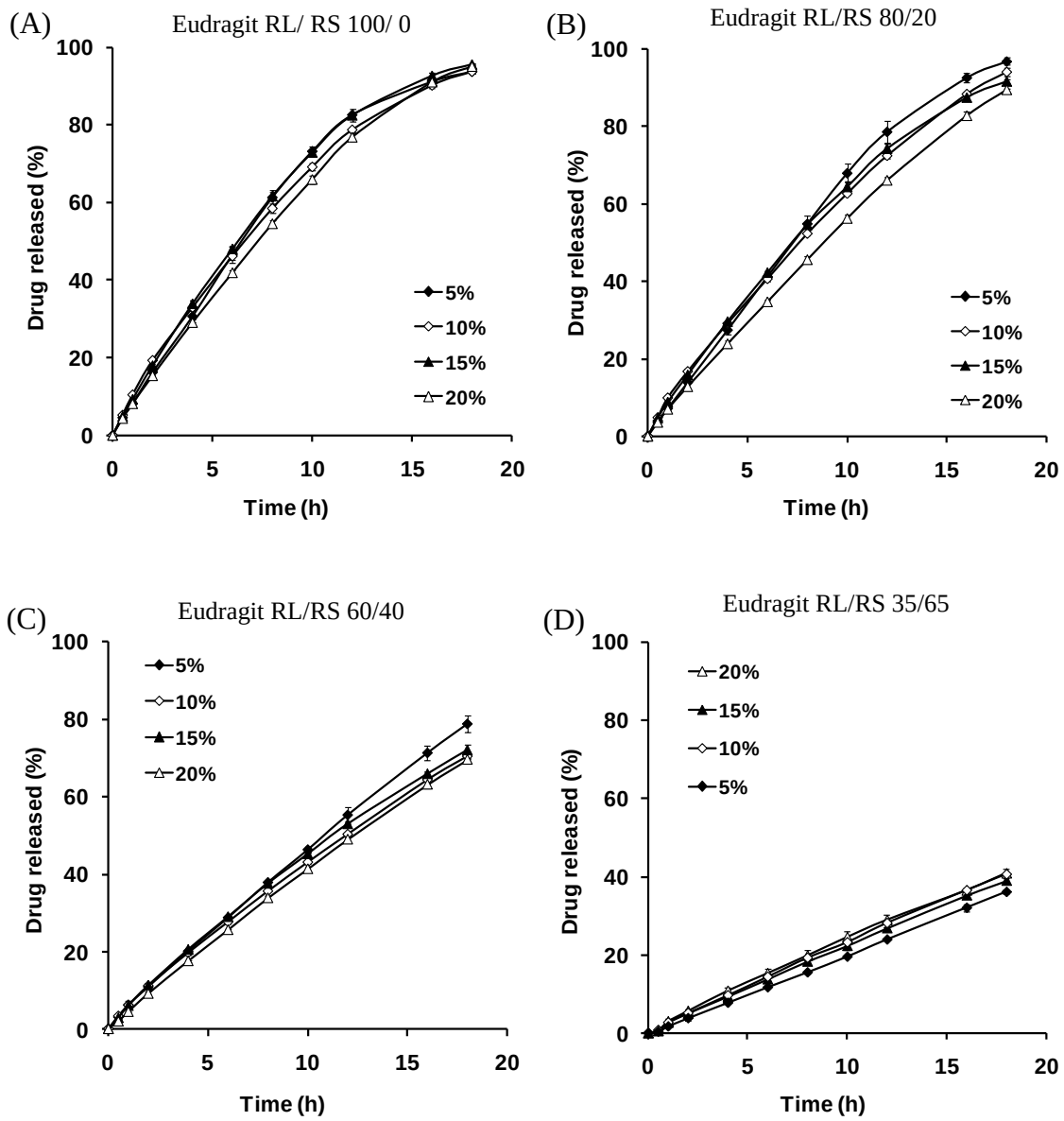


Fig. 19: *Effect of Eudragit® RL/ RS 30 D coating level on the drug release from 50% carbamazepine and 15% $NaHCO_3$ layered pellets*

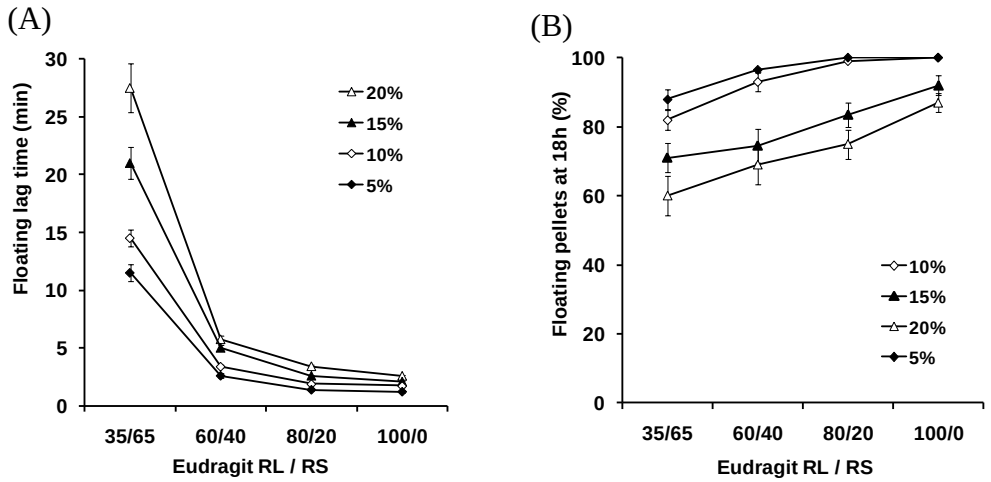


Fig. 20: *Effect of Eudragit® RL/ RS 30 D ratio and coating level on (A) floating lag time and (B) % floating pellets at 18 h, from 50% carbamazepine and 15% $NaHCO_3$ layered pellets*

Increasing the amount of $NaHCO_3$ from 15% to 20% w/w did not affect the floating lag time (≤ 3min) **(Fig. 21B)**, but improved the % floating at 18 h, because of the higher CO_2 generation. In addition, increasing the Eudragit® RL 30 D coating level increased the % floating at 18 h. This could be attributed to the better CO_2 entrapment by the formation of a thicker coating resisting rupture due to the increased internal pressure.

Coating the extended release Eudragit® RS 30 D pellets with the $NaHCO_3$ layer and Eudragit® RL 30 D top-coating resulted in an increase in drug release when compared to the pure extended release pellets **(Fig. 22A)**. This could potentially be due to an anion exchange mechanism between the chloride ions in the Eudragit® RS moiety and the $NaHCO_3$ causing an increase in the polymer permeability (Bodmeier et al., 1996).

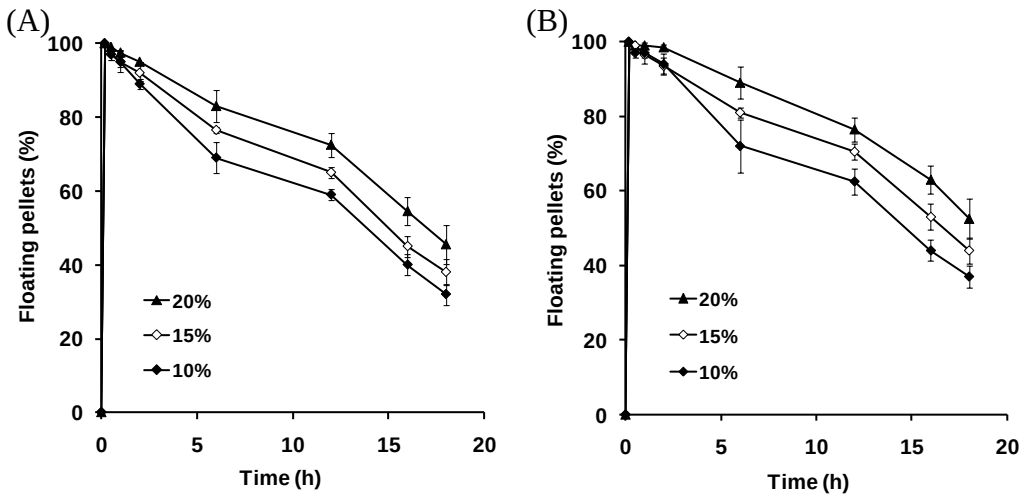


Fig. 21: *Effect of Eudragit® RL 30 D coating level on the floating properties from (A) 15% and (B) 20% $NaHCO_3$ layered propranolol HCl layered extended release pellets (10% propranolol HCl, 20% Eudragit® RS 30 D)*

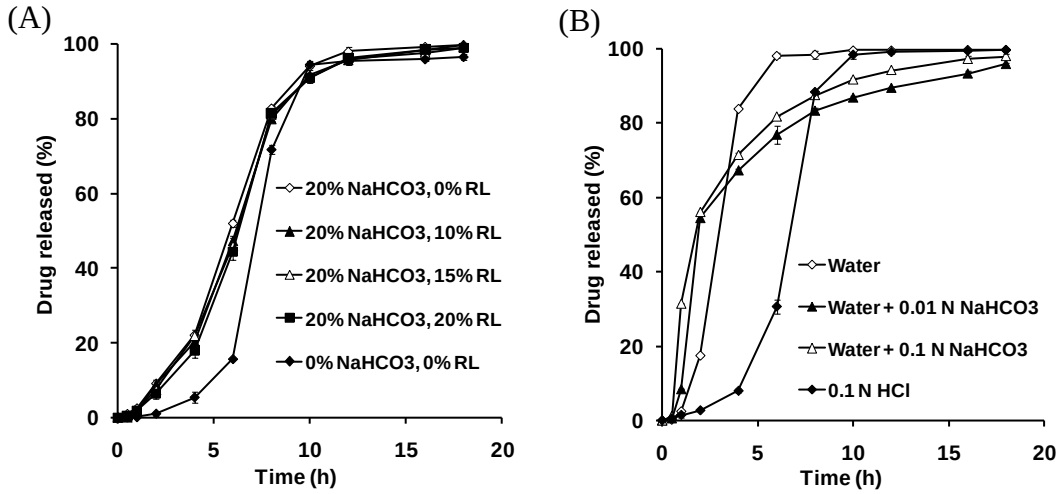


Fig. 22: *(A) Effect of the floating layers (20% $NaHCO_3$ and Eudragit® RL topcoat) on the drug release from extended release pellets (10% Propranolol HCl, 20% Eudragit® RS 30 D) and (B) effect of the release media on the extended release pellets*

A faster drug release was obtained for the extended release pellets in water compared to in 0.1 N HCl, suggesting a pH-dependent drug release behavior. This may be due to the cationic nature of Eudragit® RS as well as the pH-dependent solubility of propranolol HCl. The addition of $NaHCO_3$ to the water medium caused a change in the shape of the release curve **(Fig. 22B)**, indicating a different release mechanism, which confirms a possible interaction between the Eudragit® RS polymer and $NaHCO_3$.

Fast medium penetration of the modified system **(Fig. 23A)**, due to the fast hydration of the hydrophilic Eudragit® RL 30 D outer membrane, resulted in quick initiation of the effervescent reaction which was reflected as instant floating of the pellets **(Fig. 21B)**. This was followed by an increase in medium uptake **(Fig. 23A)** which corresponded to the hydration of the internal Eudragit® RS 30 D polymer (extended release pellets) **(Fig. 23A)** and beginning of the drug release **(Fig. 22A)**. The increased medium uptake of the modified system, resulting from the medium uptake and hydration of the extended release pellets, increased the pellet weight and caused more CO_2 to be dissolved and escape.

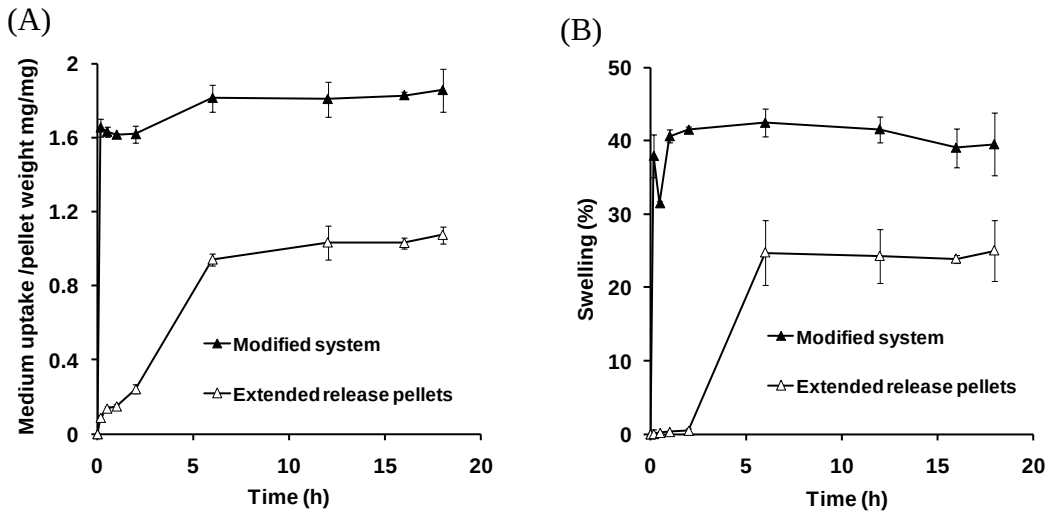


Fig. 23: *(A) Water uptake and (B) swelling from the extended release pellets composed of 10% Propranolol HCl and 20% Eudragit® RS 30 D alone and the modified system of extended release pellets coated with 20% $NaHCO_3$ and 20% Eudragit® RL 30 D*

The further swelling of the modified system **(Fig. 23B)** was mainly due to medium uptake of the extended release pellets **(Fig. 23A)**, which increased the pellet weight, dissolved the formed CO_2 and lead to sinking.

For stability studies, both systems were stored at 25°C/ 0% RH, 40°C/ 0% RH and 40°C/ 75% RH for 3 months. After storage, the floating behavior and in vitro drug release were studied.

The drug release of the three-layered system was not affected by the different storage conditions, indicating that neither heat nor humidity affected the permeability of the Eudragit® RL 30 D polymeric membrane **(Fig. 24A)**. An increase in drug release was observed for the extended release pellets **(Fig. 24B)** and the modified system **(Fig. 24C)** at 40°C/ 75% RH. A possibility of instability of methacrylate films has been previously mentioned (Petereit and Weisbrod, 1999), which could be a result of physical changes. More often the changes in drug release rate are a result of a change in film porosity or tortuosity, which could alter the diffusion coefficient.

The extended release pellets became very sticky and were hard to separate from each other at 40°C/ 75% RH. This might indicate migration of the plasticizer from the polymeric film during storage, leading to the formation of molecular-scale channels within the films, which would result in increased film permeability, and hence drug release (Wurster et al., 2007).

The floating ability was not affected at 25 and 40°C/ 0% RH **(Table 3)**. At 40°C/ 75% RH the floating ability decreased over time until lost completely at 3 months **(Table 3)**. This was attributed to the migration of $NaHCO_3$ through the polymeric coating in the presence of humidity, which was observed as effervescence in 0.1 N HCl **(Fig. 25)**. Therefore, the system should be kept under dry conditions or at low relative humidity. The effect of humidity might also be reduced by applying moisture-protective aqueous polymer coatings, like Eudragit® EPO and Opadry AMB coatings (Bley et al., 2009a, 2009b), in order to reduce the moisture uptake rates during storage time.

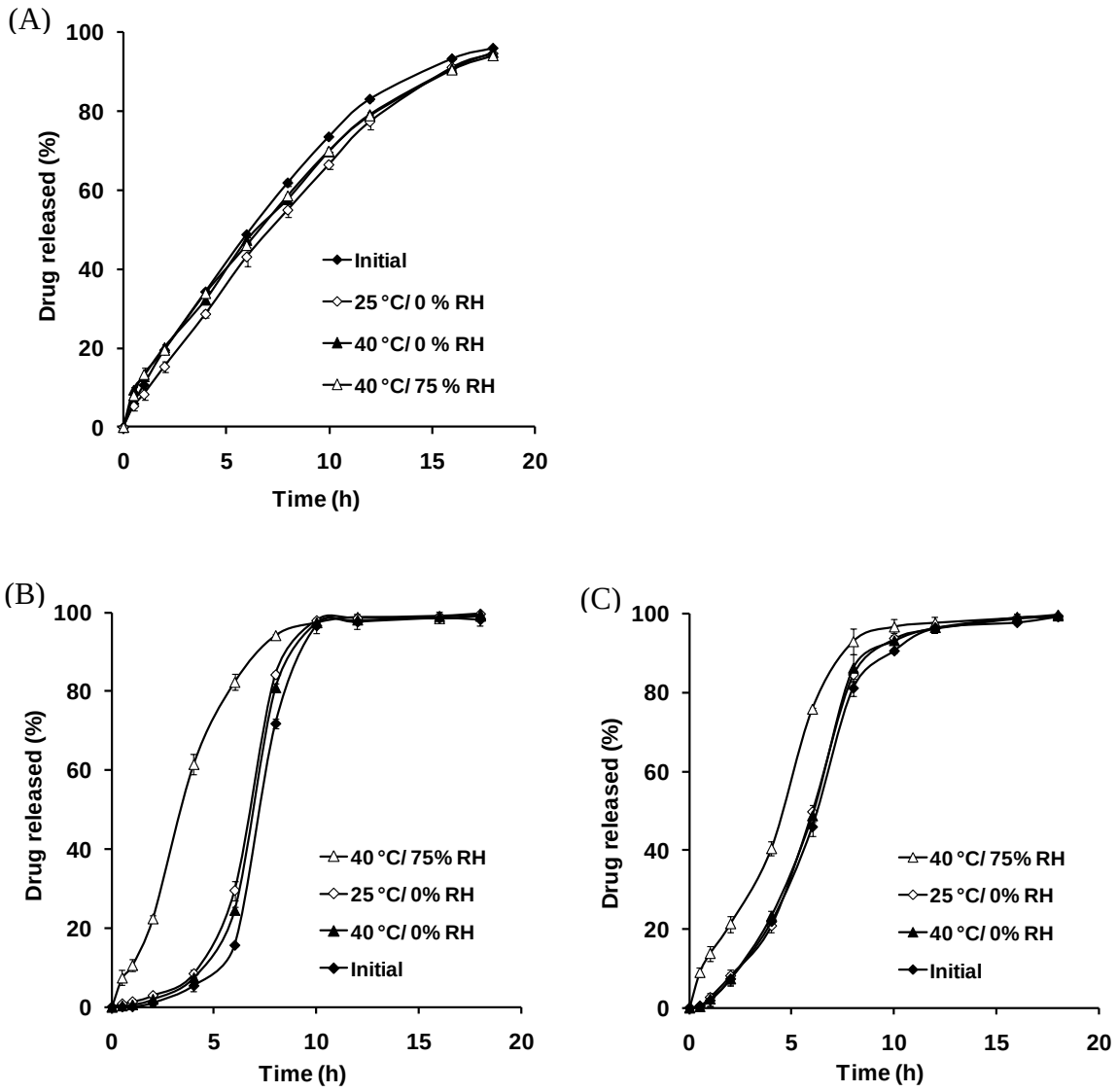


Fig. 24: *Effect of storage condition on drug release from (A) 50% carbamazepine loaded pellets coated with 15% $NaHCO_3$ and topcoated with 10% Eudragit® RL 30 D, (B) 10% Propranolol HCl loaded extended release pellets coated with 20% Eudragit® RS 30 D and (C) modified system where extended release pellets were layered with 20% $NaHCO_3$ and topcoated with 20% Eudragit® RL 30 D*

Table 3: *Effect of storage condition (3months) on floating lag time and % floating pellets*

Formulation	Storage condition (°C /% RH)	Floating lag time (min)	Floating pellets at 18 h (%)
Three-layered system	**25°C/ 0% RH**	**1.75 ± 0.35**	**96 ± 1.4**
(50% carbamazepine, 15% $NaHCO_3$ and 10% Eudragit® RL30 D)	**40°C/ 0% RH**	**1.75 ± 0.35**	**95.5 ± 2.1**
	40°C/ 75% RH	**No floating**	-
Modified system	**25°C/ 0% RH**	**1.75 ± 0.35**	**53.5 ± 2.1**
(10% propranolol HCl, 20% Eudragit® RS 30 D, 20% $NaHCO_3$ and 20% Eudragit® RL 30 D)	**40°C/ 0% RH**	**1.75 ± 0.35**	**52.5 ± 2.1**
	40°C/ 75% RH	**No floating**	-

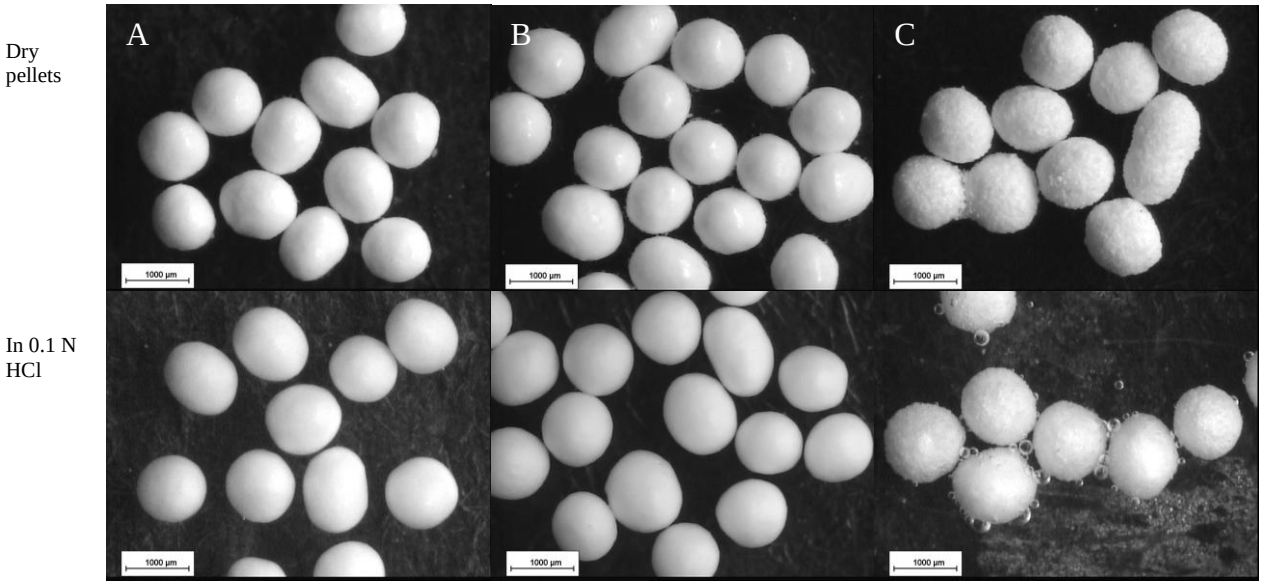


Fig. 25: *Macroscopic examination of stored pellets - dry (top) and in 0.1 N HCl (bottom) at (A) 25°C/ 0% RH, (B) 40°C/ 0% RH,(C) 40°C/ 75% RH*

3.2.3. Conclusion

The purpose of this study was the preparation and evaluation of extended release multiple unit floating drug delivery systems based on CO_2 formation having rapid and extended floating properties and good control over the release of drugs with differing solubilities. Two pellet systems were prepared by fluidized bed layering/coating techniques and evaluated by floating, drug release, medium uptake and swelling studies in 0.1 N HCl. The first system consisted of drug layered sugar cores, $NaHCO_3$-layer and a polymeric top-coating, which ideally controlled both the floating and release properties. The second, modified system consisted of extended release pellets coated with a $NaHCO_3$ layer and water-insoluble, but highly permeable and flexible Eudragit RL coating. Stability testing was performed at different conditions and the drug release and floating ability were examined. Coating with highly permeable Eudragit® RL 30 D was essential for sufficient medium penetration, a prerequisite for CO_2 formation, and had high CO_2 entrapment efficiency. Floating was maintained over a wide range of Eudragit® RL/ RS combination. An extended release profile from the first system could be achieved only for low solubility high dose drugs, due to coating with highly

permeable Eudragit® RL 30 D. For high solubility drugs, separating the floating and release "functions" was necessary. Extended release pellets were used to achieve better drug control, while maintaining the systems' floating properties by using Eudragit® RL 30 D as top-coat. Loss of floating ability was observed in the presence of humidity, due to $NaHCO_3$ migration, thus formulations should be stored under dry condition. In addition, plasticizer migration from the polymeric coating occurred with Eudragit® RS 30 D extended release pellets in the presence of humidity, leading to an increased drug release after storage. Extended release multiple unit drug delivery systems, with fast and efficient floating activity, for drugs with varying solubility were developed. The system was unstable under humidity and therefore, should be stored under dry conditions.

3.3. Effect of type of extended release pellets on floating properties for the preparation of a pH independent multiple unit floating drug delivery system

3.3.1. Introduction

Modified release (MR) oral delivery systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients and patient compliance, as well as reducing side effects (Eisen et al., 1990; Getsios et al., 2004). MR delivery systems are most commonly used for 1) delayed-release (e.g., by using an enteric coating); 2) extended-release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile release) and 4) site-specific or timed release (e.g., for colonic delivery or gastric retention).

Different methods and techniques have been used in the manufacture of oral modified release dosage forms, which are divided into single and multiple unit drug delivery systems. Multiple unit drug delivery systems offer many advantages over single unit systems as they lower the probability of dose dumping, are better distributed and are less likely to cause local irritation, as well as providing less inter- and intra-subject variability (Rouge et al., 1997) and better statistical assurance of drug release (Rao and Murthy, 2002; Tang et al., 2005). Accordingly, they have been used extensively as gastroretentive floating systems to control the transport of dosage forms in the digestive tract; e.g. in the form of porous and hollow microspheres (Badve et al., 2007; Joseph et al., 2002; Kawashima et al., 1991; Sato et al., 2004; Streubel et al., 2002), ion exchange resin beads (Atyabi et al., 1996a, 1996b; Murata et al., 2000; Whitehead et al., 1998), matrix minitablets (Goole et al., 2007; Rouge et al., 1997) as well as pellets (Hamdani et al., 2006a; Hamdani et al., 2006b; Sungthongjeen et al., 2006).

Floating systems are useful for drugs with a narrow window of absorption (Davis, 2005; Rouge et al., 1996), drugs with pH dependent solubility (Jain et al., 2005; Singh and Kim, 2000), drugs which degrade in the alkaline environment (Badve et al., 2007; Whitehead et al., 2000), or drugs with local action in the proximal part of the GI tract,

such as antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer (Moes, 1993; Murata et al., 2000; Yang et al., 1999).

Floating dosage forms with an in-situ gas generating mechanism are expected to have greater buoyancy. However, the optimization of the drug release may alter the buoyancy and, therefore, it is sometimes necessary to separate the control of buoyancy from that of drug release kinetics during formulation optimization (Rouge et al., 1996).

Most multiple unit floating drug delivery systems that are based on gas generation contain only $NaHCO_3$, and require acidic conditions for the effervescent reaction to occur and floating to take place. When the environmental pH increases, CO_2 generated will not be enough to initiate and maintain floating. Therefore it would be preferable to have a system that would float independent of the pH of the medium.

A multiple unit pH- independent floating system, based on gas generation, has been previously developed (Ichikawa et al., 1991). The system consisted of sustained release seeds surrounded by a double effervescent layer composed of $NaHCO_3$ and tartaric acid, and coated with a swellable membrane layer to trap the CO_2 formed and maintain floating. All units floated within 10 min and ~ 80% remained floating over a period of 5 h, irrespective of the pH of the medium.

The purpose of this study was to evaluate the influence of the type of extended release pellets on the floating properties from a multiple unit system, where floating and release are independent of each other, by separation of their "functional" layers. Another purpose was the preparation of a pH independent floating drug delivery system and its in vitro evaluation.

3.3.2. Results and Discussion

An ideal effervescent extended release floating system requires rapid CO_2 formation. The formed CO_2 should be entrapped well in order to maintain floating for extended time periods. In addition to floating, extended drug release is required. For drugs with high solubility, both "functions" have to be independent of each other for better control.

Floating multiple unit drug delivery systems, composed of extended release (ER) pellets, layered with $NaHCO_3$, and topcoated with Eudragit® RL 30 D, were prepared. Eudragit® RL 30 D was used to permit quick medium penetration and entrap the formed CO_2, while the type of extended release polymer controlled the drug release.

Increasing the polymer thickness from pellets coated with Aquacoat® ECD from 2.9 to 5.7 mg/cm^2 had no major effect on the % swelling at 18 h from the pellets **(Fig. 26)**, due to low permeability, brittleness and rigidity (Bodmeier and Paeratakul, 1994), leading to low polymer hydration and permeation. Increasing the polymer thickness (coating level) from pellets coated with Kollicoat® SR 30 D, on the other hand, increased the % swelling at 18 h, due to its increased mechanical properties, elasticity and flexibility by the thicker coating, leading to more hydration and permeation.

Therefore, five extended release pellets (2.9, 4.3 and 5.7 mg/cm^2 Kollicoat® SR 30 D, and 4.3 and 5.7 mg/cm^2 Aquacoat® ECD pellets) loaded with 10% propranolol HCl w/w were used to prepare floating pellets and were further investigated **(Table 4)**.

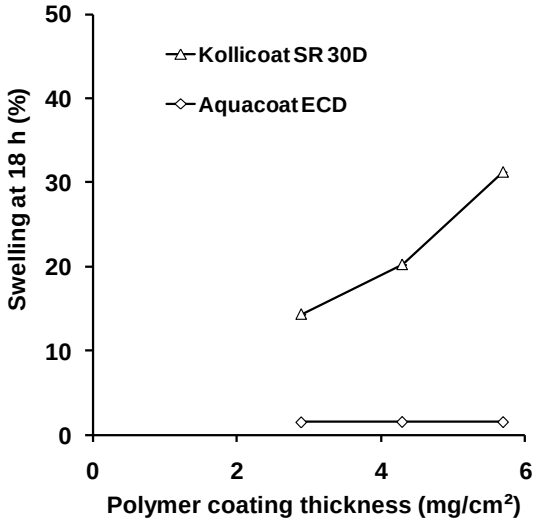


Fig. 26: *Effect of type and coating thickness of* extended release *polymer on swelling from 10% loaded propranolol HCl pellets*

Table 4: *Composition of the pellet layers (quantities given in % w/w of initial pellet weight, unless otherwise stated)*

Propranolol HCl loading (%)	**ER polymer**	**ER polymer coating**		**Type of effervescent agent (%)**		**Outer top-coat**
		Coating level (%)	**Thickness (mg/cm^2)**			
10	Kollicoat SR 30D	10	2.9	$NaHCO_3$ (20)		Eudragit RL 30 D
10	Kollicoat SR 30D	15	4.3	$NaHCO_3$ (20)		Eudragit RL 30 D
10	Kollicoat SR 30D	20	5.7	$NaHCO_3$ (20)		Eudragit RL 30 D
30	Kollicoat SR 30D	20	5.8	$NaHCO_3$ (20)		Eudragit RL 30 D
50	Kollicoat SR 30D	20	5.9	$NaHCO_3$ (20)		Eudragit RL 30 D
10	Aquacoat ECD	15	4.3	$NaHCO_3$ (20)		Eudragit RL 30 D
10	Aquacoat ECD	20	5.7	$NaHCO_3$ (20)		Eudragit RL 30 D
10	Aquacoat ECD	15	4.3	Citric acid (15)	$NaHCO_3$ (20)	Eudragit RL 100 (organic)

In 0.1 N HCl, the floating lag time from all pellet formulations was between 1.5 and 3 min. **(Fig. 27 and 28)**, accordingly, the type and thickness of the extended release polymer had no effect on the initiation of floating, which was only affected by the outer Eudragit® RL 30 D top-coat.

Increasing the outer Eudragit® RL 30 D membrane thickness, on the other hand, increased the % floating from all pellets. This was attributed to increased CO_2 entrapment efficiency, avoiding pellet rupture due to expansion; by the thicker and hence, more flexible polymer coat **(Fig. 27 and 28)**.

In addition, increasing the coating thickness of Kollicoat® SR 30 D (ER) pellets from 2.9 to 5.7 mg/cm^2 decreased the % floating pellets at 18 h **(Fig. 27)** from 87% to 56%, respectively (at the lowest Eudragit® RL 30 D thickness). This may be due to the flexible mechanical properties of Kollicoat® SR 30 D. Although medium permeates slower with thicker coatings, reflected as longer lag time in the drug release **(Fig. 27)**, the total amount of medium uptake is more. This is due to the increased mechanical properties of the higher polymer thickness, leading to more hydration and medium permeation. This increase in medium uptake increased the pellet weight and lead to more CO_2 dissolution and escape and hence, more sinking of pellets.

Interestingly, this was not the case for Aquacoat® ECD pellets, where increasing the polymer thickness, had no major effect on the % floating pellets at 18 h **(Fig. 28)**. This behavior could be attributed to the lower permeability and brittle mechanical properties of Aquacoat® ECD.

In 0.01 and 0.001 N HCl the pellets did not float, due to less CO_2 formed (less acidic medium), which was not enough to initiate floating (Data not shown). The initiation of floating thus depends on the acidity of the medium. Therefore, developing a system that floats independent of the pH, will reduce inter- and intra- gastric variability, and hence, initiate floating under the changing pH of the stomach.

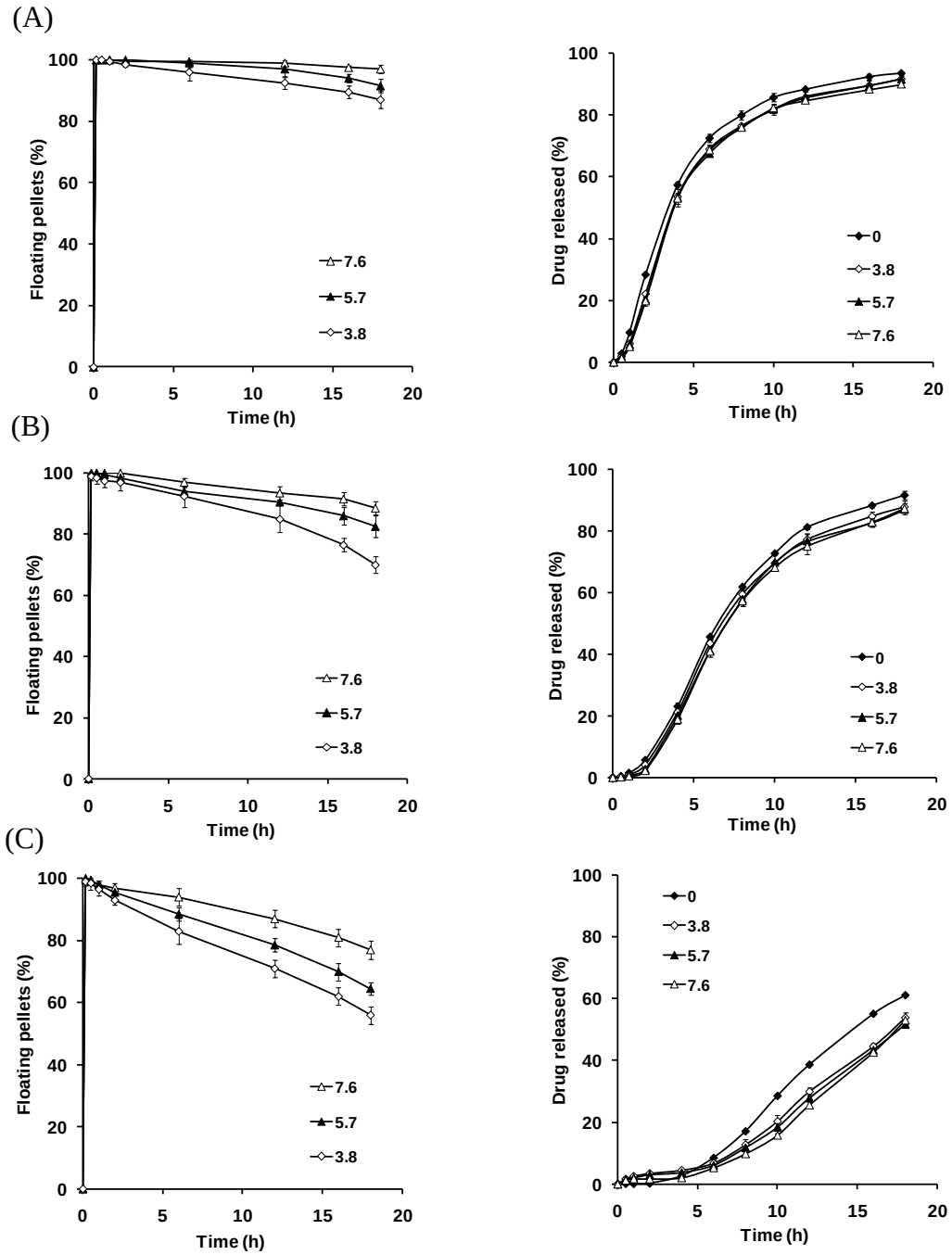


Fig. 27: *Effect of Eudragit RL coating thickness (mg/cm^2) on floating and drug release from (A) 2.9 mg/cm^2 Kollicoat SR, (B) 4.3 mg/cm^2 Kollicoat SR and (C) 5.7 mg/cm^2 Kollicoat SR coated propranolol HCl pellets (10% propranolol HCl, ER polymer, 20% $NaHCO_3$ and Eudragit RL 30 D as top-coat)*

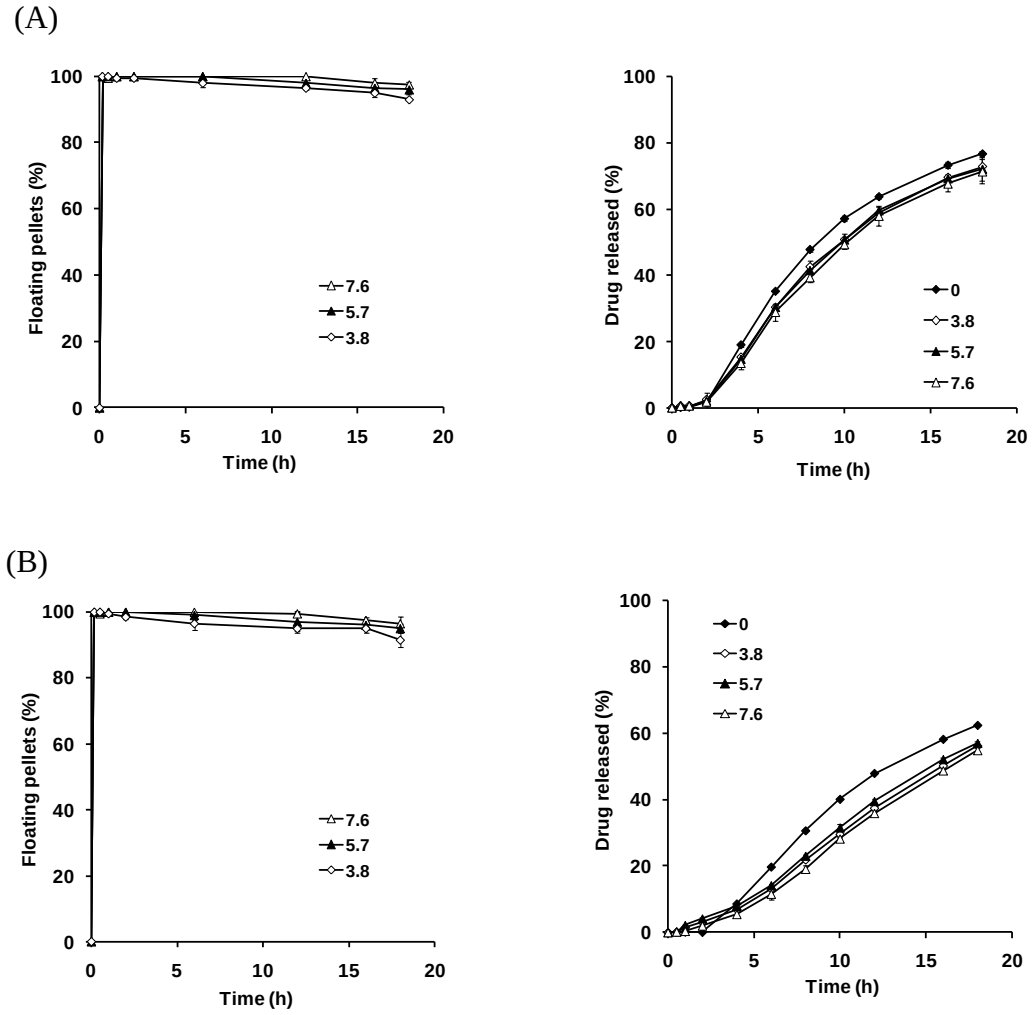


Fig. 28: *Effect of Eudragit RL coating thickness (mg/cm^2) on floating and drug release from (A) 4.3 mg/cm^2 Aquacoat and (B) 5.7 mg/cm^2 Aquacoat coated propranolol HCl pellets (10% propranolol HCl, ER polymer, 20% $NaHCO_3$ and Eudragit RL 30 D as top-coat)*

As expected, increasing the ER polymer thickness decreased the drug release from propranolol HCl coated pellets **(Fig. 27 and 28)**. The "floating layers" ($NaHCO_3$ and Eudragit RL 30 D top-coat) caused a slight decrease in the drug release from all formulations, due to the additional diffusion path. The "floating layers" had thus a minor effect on the drug release, which was mainly controlled by the extended release polymer.

The process of floating was followed by macroscopic examination **(Fig. 29)**: After permeation of the release medium, CO_2 formed because of the effervescent reaction between the dissolved $NaHCO_3$ and the acid in the medium, and the pellets started to rapidly float in ≤ 2 min **(Fig. 29 B)**. As the internal extended release polymer became hydrated, the medium uptake caused more swelling of pellets **(Fig. 29 C)**. Further medium uptake not only increased pellet weight, but also dissolved the formed CO_2 and lead to its escape from the pellets. This was seen as a decrease in the size or disappearance of the CO_2 bubble **(Fig. 29 D)**.

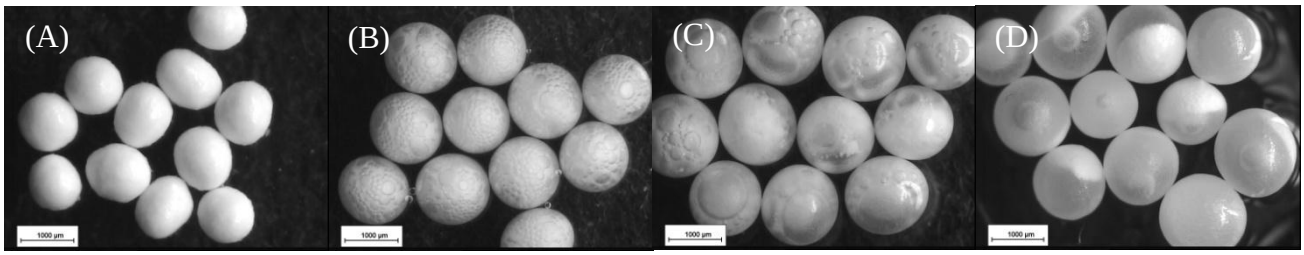


Fig. 29: *The floating process, (A) Dry pellets,(B) Outer polymer hydration, water penetration through polymer membrane and CO_2 formation, (C) Swelling of pellets due to CO_2 formation and medium uptake, (D) higher medium uptake causing CO_2 dissolution and escape*

Fast medium penetration of the floating pellets of both extended release pellets at 5.7 *mg/cm*^{2} coating thickness was observed **(Fig. 30)**, due to the fast hydration of the hydrophilic Eudragit® RL 30 D top-cot. This resulted in quick initiation of the effervescent reaction and hence, floating. This was followed by a variable increase in medium uptake, corresponding to the permeability of the internal extended release polymer, where higher medium uptake from Kollicoat® SR 30 D coated extended release pellets compared to Aquacoat® ECD pellets was observed. The increased medium uptake of the floating system in case of "Kollicoat® SR 30 D" pellets resulted in increased pellet weight and more CO_2 dissolution and escape. This was reflected on the floating abilities of pellets, showing lower % floating for "Kollicoat® SR 30 D" containing pellets compared to "Aquacoat® ECD" containing pellets **(Fig. 27C vs 28B)**.

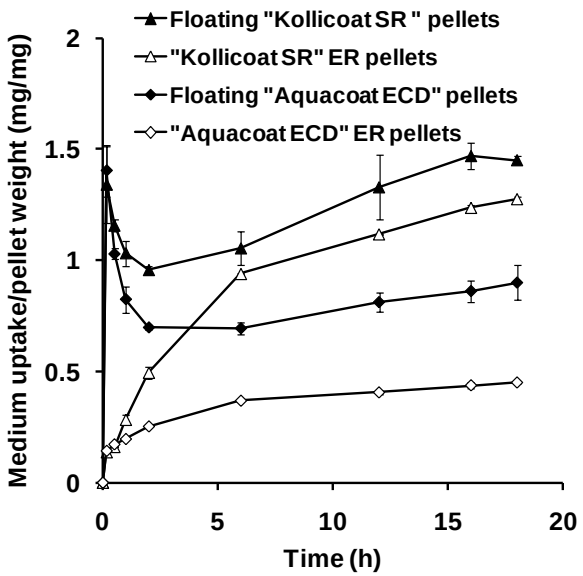


Fig. 30: *Effect of extended release (ER) pellets (10% propranolol HCl and 5.7 mg/cm^2 polymer coating) and extended release pellets layered with 20% $NaHCO_3$ and topcoated with 7.6 mg/cm^2 Eudragit RL 30 D (floating pellets) on water (medium) uptake*

Based on these results, the rate of medium penetration through the outer polymeric membrane determines the floating lag time of pellets, where the HCl in the medium reacts with the dissolved $NaHCO_3$ and initiates CO_2 formation. After all $NaHCO_3$ has been consumed in the reaction, further medium penetration, determined by the type and thickness of the extended release polymer, will cause a further increase in pellet weight as well as increased dissolution and escape of the formed CO_2 and hence negatively affect the floating behavior.

The average initial apparent density of the floating pellets containing 5.7 *mg/cm^2* Kollicoat® SR 30 D was 1.3 mg/cm^3 which decreased to 0.95 mg/cm^3 at 10 min. **(Fig. 31)**, due to CO_2 formation, after which there was a gradual increase in density reaching and 0.98 mg/cm^3 and 1.03 mg/cm^3 at 6 and 12 h respectively. This density was slightly higher than the density of the medium (dotted line) leading to sinking. On the other hand, the floating pellets containing 5.7 *mg/cm^2* Aquacoat® ECD started with a higher

initial apparent density of 1.42 mg/cm^3, which decreased to 0.98 and 0.82 mg/cm^3 at 10 min. and 6 h, respectively. At 12 h it only increased to 0.91 mg/cm^3, which was less than the density of the medium and hence, floating was maintained.

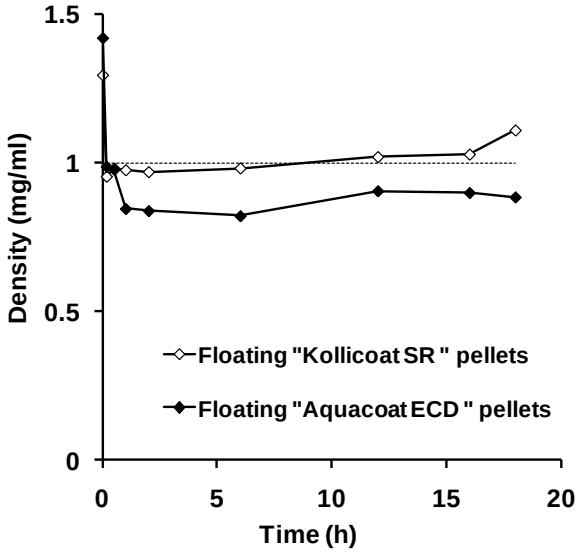


Fig. 31: *Effect of ER polymer type (5.7 mg/cm^2 thickness) on density from 7.6 mg/cm^2 coated Eudragit RL pellets*

In addition, extended release pellets with three drug loadings, 10, 30 and 50% w/w and coated with 20% Kollicoat® SR 30 D **(Table 4)** were investigated.

There was no effect on the floating lag time (1.5- 3 min) with increasing drug loading, from all Eudragit® RL 30 D coating thickness (mg/cm^2). On the other hand, increasing the drug loading, from 10 to 50%, increased the % floating pellets at 18 h from 59 to 84%, respectively (at the same Eudragit® RL 30 D thickness) **(Fig. 32)** despite the thicker Kollicoat® SR 30 D coating (5.7 to 5.9 mg/cm^2 respectively) **(Table 4)**, and hence higher medium uptake. This may either be due to a salting out effect of CO_2 by the higher amount of drug dissolved in the medium, an increased volume to weight ratio of the higher drug loaded pellets or due to higher amount of $NaHCO_3$ involved.

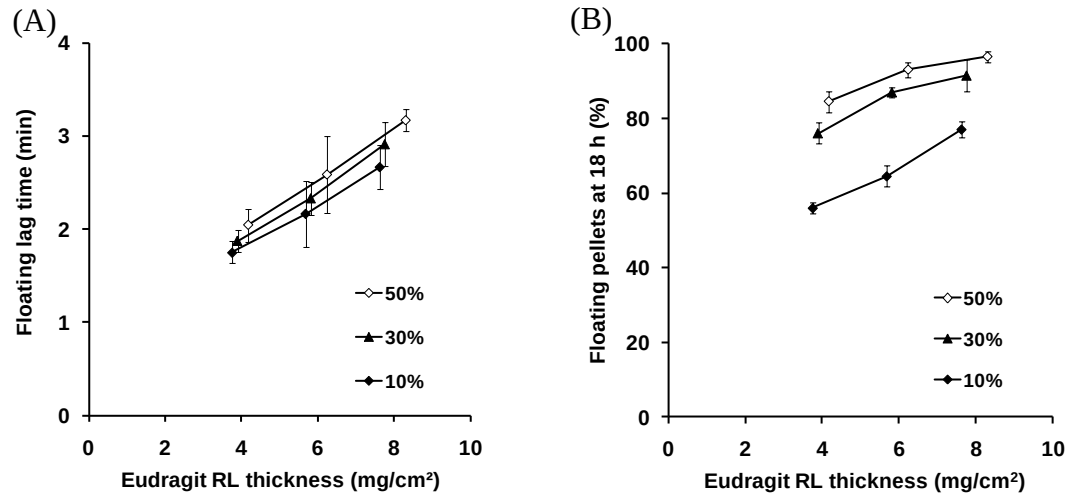


Fig. 32: *Effect of propranolol HCl loading and Eudragit RL coating thickness on (A) floating lag time and (B) % floating pellets at 18 h from floating pellets coated with 20% Kollicoat SR 30D and subsequent floating layers*

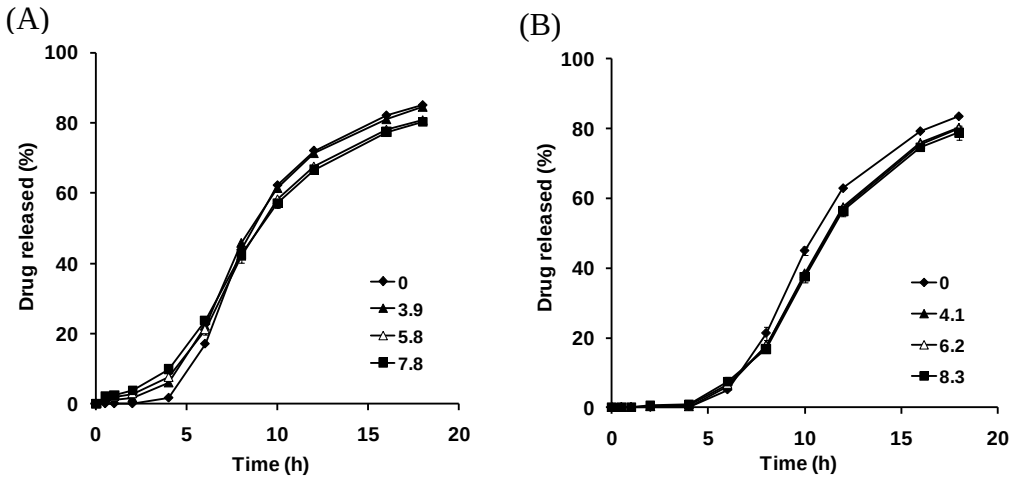


Fig. 33: *Effect of* $NaHCO_3$ *layer and Eudragit RL coating thickness (mg/cm^2) on drug release from (A) 30% and (B) 50% drug loaded pellets coated with 20% Kollicoat SR 30 D and subsequent floating layers*

The "floating layers" slightly decreased the drug release from all drug loadings **(Fig. 27C and 33)**, due to the increased diffusion path.

For stability studies, the pellets were stored at 25°C/ 0% RH, 40°C/ 0% RH and 40°C/ 75% RH for 3 months. After storage, the drug release was examined.

A decrease in drug release with a burst was observed for "Aquacoat® ECD" extended release pellets and the floating pellets **(Fig. 34 A and B)**, at 40°C/ 75% RH. This may be due to further polymer particle coalescence and continuous film formation during humidity storage and drug migration, respectively, as reported many times in the literature (Koerber et al., 2009).

In case of "Kollicoat® SR 30 D" extended release pellets a slight decrease in drug release was observed at 25°C/ 0% RH and 40°C/ 0% RH, which became more prominent by humidity curing **(Fig. 34 C).** This again could be attributed to further polymer particle coalescence and continuous film formation during storage (Shao et al., 2002). On the other hand, the effect of storage has declined in case of thermal and humidity storage for "Kollicoat® SR 30 D" floating pellets **(Fig. 34 D)**, which may be because the floating layers acted as barrier from moisture to the extended release pellets, leading to incomplete film formation. The problem of instability of the ER pellets could be overcome by the use of organic coating, where upon complete solvent evaporation, a continuous polymeric film is formed (Lehmann, 1997; Wesseling and Bodmeier, 1999).

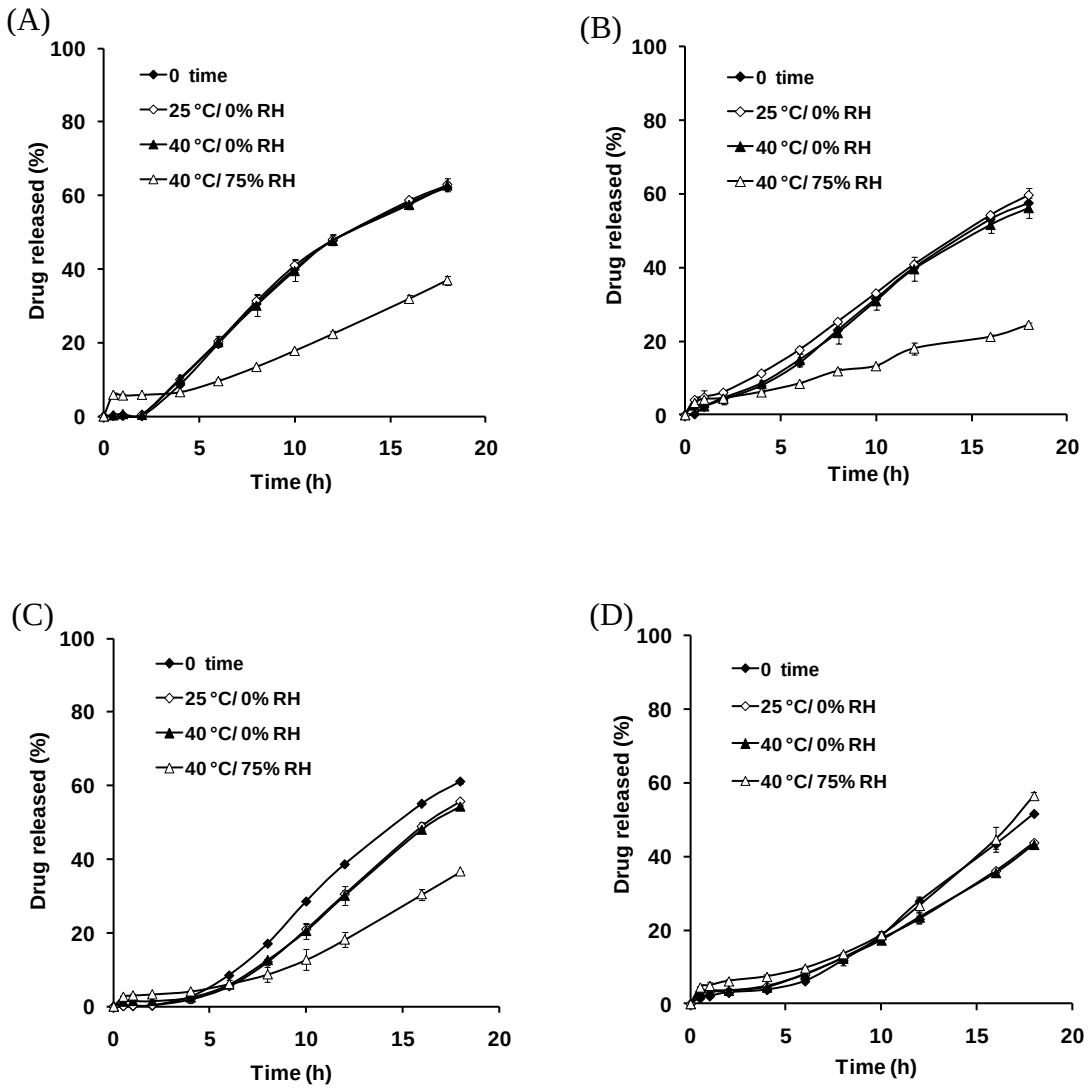


Fig. 34: *Effect of storage condition on drug release from (A) 10% Propranolol HCl loaded ER pellets coated with 5.7 mg/cm^2 Aquacoat® ECD, (B) "Aquacoat® ECD" floating pellets (ER pellets layered with 20% $NaHCO_3$ and topcoated with 7.6 mg/cm^2 Eudragit® RL 30 D), (C) 10% Propranolol HCl loaded extended release pellets coated with 5.7 mg/cm^2 Kollicoat® SR 30 D and (D) "Kollicoat® SR 30 D" floating pellets (ER pellets layered with 20% $NaHCO_3$ and topcoated with 7.6 mg/cm^2 Eudragit® RL 30 D)*

Extended release pellets loaded with 10% Propranolol HCl and coated with 4.3 *mg/cm^2* Aquacoat® ECD, were further used for preparation of the pH independent system **(Table 4)**. These had optimum drug release and could achieve excellent floating after layering with the floating layers **(Fig. 28A)**. Citric acid was chosen for this formulation,

being the most commonly used acid for the effervescent reactions, and having high solubility and acid strength.

Since the presence of acids (or acid salts) in the medium or in the dosage form may cause a change in the permeability and swelling kinetics of the cationic polymethyl methacrylate copolymers, due to an exchange reaction between the chloride moiety in the polymer and the anion present in the acid (Bodmeier et al., 1996; Narisawa et al., 1994). Therefore, citric acid was layered first, followed by $NaHCO_3$ layer, to prevent direct contact between citric acid and Eudragit® RL 100 top-coat.

The floating layers were coated from organic solution for citric acid or suspension for $NaHCO_3$ and Eudragit® RL 100, due to the hygroscopic nature of citric acid, to minimize its sticking tendency during the coating process and to prevent premature CO_2 formation (effervescent reaction), between citric acid and $NaHCO_3$ during the coating process.

The floating lag time was < 5 min in 0.1 N HCl and in water, which was slightly higher than from the aqueous coated pellets due to the tougher and less permeable film coatings form organic coating compared to aqueous coating (Lecomte et al., 2004). The % floating at 18h was similar in both media and was only slightly affected by the additional citric acid layer **(Fig. 35 A and B)**.

In addition, the drug release was similar in both media and was only slightly affected by the floating layers **(Fig. 35 A and B)**, showing a pH independent drug release from the floating pellets.

The similar floating and release pattern of the pellets in both media could be attributed to their similar swelling behavior in both media **(Fig. 36)**.

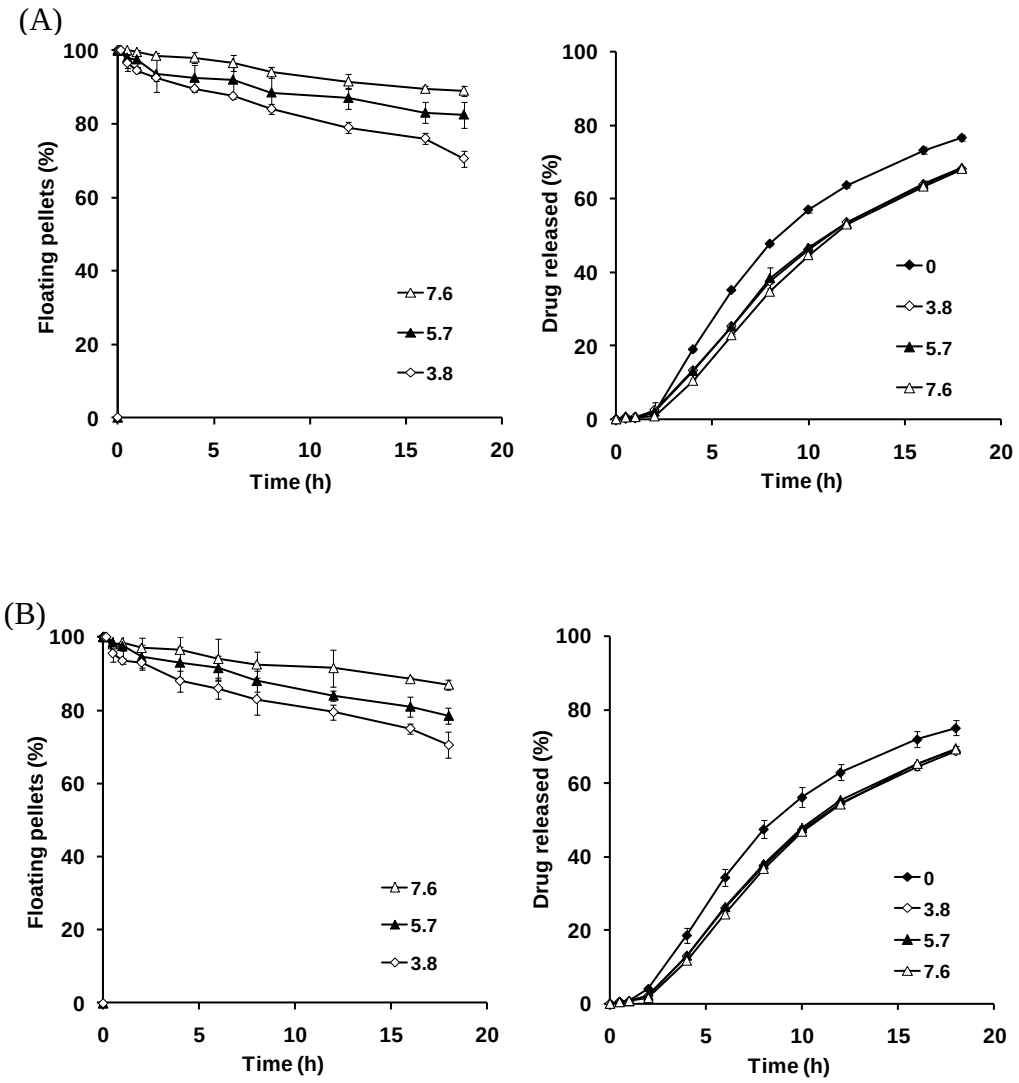


Fig. 35: *Effect of release medium and Eudragit RL coating thickness (mg/cm^2) on floating and drug release on the pH independent floating pellets in (A) 0.1 N HCl and (B) Water*

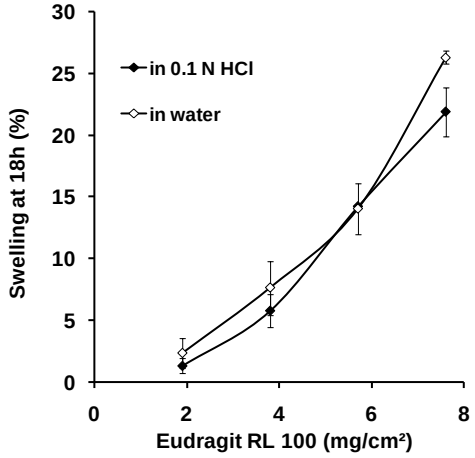


Fig. 36: *Effect of release medium on swelling from pH independent floating pellets*

3.3.3. Conclusion

The purpose of this study was to evaluate the influence of various types of extended release pellets on the floating properties of a multiple unit drug delivery system as a preformulation study for the development of a pH independent floating system. The pellets were prepared by fluidized bed layering/coating techniques and evaluated for their floating and drug release behavior. The pellets consisted of extended release pellets coated with $NaHCO_3$-layer and the water insoluble, highly permeable and flexible Eudragit® RL 30 D top-coating. Kollicoat® SR 30 D and Aquacoat® ECD extended release pellets with varying thickness were investigated. To prepare the pH independent floating system, citric acid was layered below the $NaHCO_3$-layer, and topcoated with an organic Eudragit® RL 100. Increasing the thickness of Kollicoat® SR 30 D coated pellets decreased the floating properties, due to higher medium uptake and swelling which increased pellet weight and lead to more CO_2 dissolution and escape. Aquacoat® ECD, on the other hand, is more lipophilic and brittle, therefore had less medium uptake and maintained good floating properties independent of the ER polymer thickness. In addition, increasing the drug loading improved the floating properties, either due to the salting out effect of the dissolved CO_2 by the higher amount of drug or a higher amount

of CO_2 formed. The pH independent system floated completely in different media, with similar drug release. The medium uptake of the extended release pellets has a big influence on the pellets' floating properties and has to be taken in consideration when designing a coated floating pellet system. A pH independent floating system has been developed using Aquacoat® ECD extended release pellets. The system showed excellent floating properties coupled with extended release in different media.

4. SUMMARY

4.1 Single unit floating drug delivery systems

Gastroretentive dosage forms are useful extended release delivery systems for drugs with a narrow window of absorption in the upper intestine, for drugs with pH-dependent solubility, for drugs degraded by higher pH or for drugs with local action in the proximal part of the GI tract. Gastric retention can be achieved by the use of floating systems, which are either based on an inherently low density or on effervescence.

This study aimed to evaluate the floating and release behavior of directly compressed hydrophilic matrices (HPMC, Carbopol and Ac-Di-Sol) to develop floating single unit drug delivery systems.

Despite the floating ability of HPMC matrices, as a result of swelling and gel formation of the hydrophilic matrix, the addition of $NaHCO_3$ to the matrix was essential to ensure rapid floating. Similar drug release profiles were obtained with varying ratios of HPMC: $NaHCO_3$ in the investigated range. This is because hydration and gel formation of the matrix were rate limiting.

By addition of carbopol to HPMC matrices no floating was observed. This may be due to higher moisture absorption properties of carbopol leading to increased initial tablet density. The initial phase of drug release was unchanged, but slower rate at the later phase was observed. This was due to decreased matrix erosion in the presence of carbopol. Furthermore, the drug release from HPMC-carbopol was independent on the carbopol amount in the investigated ratio. When Ac-Di-Sol was added to HPMC, the floating lag time increased. This may be the time needed for tablet hydration and gel formation. On the contrary to HPMC-carbopol matrices, the drug release from HPMC-Ac-Di-Sol matrices increased with increasing Ac-Di-Sol portion in the matrix. This was due to higher erosion of the Ac-Di-Sol containing matrices.

By addition of $NaHCO_3$ to carbopol, HPMC- carbopol and HPMC- Ac-Di-Sol matrices, instant floating was obtained. This was due to rapid CO_2 formation in the presence of acidic medium, which decreased the tablet density. Drug release was faster from HPMC- Ac-Di-Sol compared to HPMC- carbopol matrix tablets in the presence of $NaHCO_3$. This was due to higher hydration and erosion of Ac-Di-Sol than carbopol. Increasing the amount of carbopol in matrices containing only Carbopol and $NaHCO_3$

decreased the drug release. This was due to more polymer portion in the matrix. Furthermore, complete erosion from Carbopol -$NaHCO_3$ matrices was achieved, which would avoid accumulation following multiple administrations.

The release from the different matrices followed the Korsmeyer-Peppas model and was governed by anomalous (non-Fickian) diffusion. A change in drug release mechanism to Fickian diffusion was observed for matrices with Ac-Di-Sol as the dominant polymer or with Ac-Di-Sol in the presence of $NaHCO_3$.

In conclusion, rapid floating with long duration was obtained from hydrophilic matrices in the presence of $NaHCO_3$. Flexible drug release profiles could be obtained with varying the polymer ratios. Furthermore, tablet erosion was achieved after complete drug release with Carbopol -$NaHCO_3$ matrices.

4.2 Multiple unit floating drug delivery systems

The objective of this study was the preparation and in vitro evaluation of extended release multiple unit floating drug delivery systems based on CO_2 formation (effervescence) for drugs with different solubilities and to provide a mechanistic understanding of the floating behavior from such a system.

A floating pellet system based on effervescence should quickly take up acidic gastric juice to rapidly develop CO_2 in order to induce floating. The pellets should thus be coated to efficiently entrap the formed CO_2 for extended time periods and control the drug release.

Firstly, the system was composed of drug layered sugar cores, $NaHCO_3$-layer and an aqueous polymeric top-coating which should ideally control both floating and release properties.

The high permeability of Eudragit® RL 30 D resulted in rapid floating and long floating duration (due to the efficient CO_2 entrapment), but poor control over the drug release (no retardation), except for low solubility high dose drugs (carbamazepine). A wide range of drug release could be achieved when using a combination of Eudragit® RL/RS, where the portion of Eudragit® RS should not exceed 40% to maintain the good floating

properties. Coating with the less permeable Kollicoat® SR 30 D resulted in extended drug release, but the floating lag time was too long.

Modification of the system, by separating the floating and release "functions" of the polymer coating into two separate coatings, was necessary in order to obtain good floating and extended drug release for water-soluble drugs (propranolol HCl). Extended release pellets (drug layered sugar cores, coated with different aqueous polymeric dispersions of Eudragit® RS 30 D, Kollicoat® SR 30 D or Aquacoat® ECD), were layered with $NaHCO_3$ and finally topcoated with the permeable Eudragit® RL 30 D. The inner polymer was thus responsible for the extended drug release and the outer Eudragit® RL for controlling the floating.

The floating lag time was short and was not affected by the inner extended release polymer coating, due to the fast medium permeation across the outer Eudragit® RL coating. In contrast, the floating duration was strongly affected by the type or coating thickness of the extended release polymer. This was mainly attributed to the different medium uptake by the extended release pellets. Increasing the medium uptake also increased dissolution of the formed CO_2 and its escape. This has lead to increasing the pellet density and hence sinking of the pellets. For example, Aquacoat ECD, a more lipophilic and brittle polymer, had low medium uptake. As a result, long floating duration, irrespective of the polymers' thickness could be obtained. The more hydrophilic polymers (Eudragit® RS 30 D and Kollicoat® SR 30 D) had high medium uptake, leading to increased pellet weight and density, and therefore, had shorter floating duration. Furthermore, lower coating thickness of a more hydrophilic and flexible polymer (Kollicoat® SR 30 D) resulted in longer floating. This may be attributed to lower medium uptake. In addition, increasing the drug loading of the water-soluble drugs increased the floating duration.

Floating was not changed upon storage at 25 °C/ 0 % RH and 40 °C/ 0 % RH for 3 months, whereas the floating ability was lost on humidity storage at 40 °C/ 75 % RH. This was due to the migration of $NaHCO_3$ through the polymeric coating observed by macroscopic examination. Therefore, CO_2 based floating drug delivery systems should be stored under dry conditions or topcoated with a moisture protective coat. In addition, an increase in drug release from Eudragit® RS 30 D coated pellets was attributed to a physical change in the film properties, which may be due to plasticizer migration from

the polymeric coating. On the contrary, a decrease in drug release from Aquacoat® ECD or Kollicoat® SR 30 D coated pellets may be due to further polymer particle coalescence upon storage.

On increasing the pH of the medium, less CO_2 was formed, which was not enough to initiate floating. Therefore, a pH-independent floating system was developed by using a combination of citric acid and $NaHCO_3$ as the effervescent agents. Organic coating of the effervescent layers and outer polymeric Eudragit® RL 100 was necessary in order to avoid premature CO_2 formation during the coating process. The system showed extended drug release, as well as excellent floating properties independent of the pH of the medium.

In conclusion, the key parameters affecting floating have been identified. Multiple unit floating drug delivery systems for drugs with different solubilities and flexible release profiles have been successfully developed, which should be stored in dry conditions to avoid loss of floating ability. By the addition of citric acid layer, pH-independent floating from the multiple unit drug delivery systems was achieved.

5. ZUSAMMENFASSUNG

5.1 Schwimmende „single unit“ Arzneistoffgabesysteme

Gastroretentive Darreichungsformen sind nützliche Retardarzneiformen für Arzneistoffe mit einem engen Resorptionsfenster im oberen Darm, oder mit pH-abhängiger Löslichkeit, oder für Arzneistoffe, die bei höheren pH-Wert abgebaut werden oder lokal im proximalen Teil des GI-Traktes wirken. Magenretention kann durch den Einsatz schwimmender Systeme auf der Basis einer geringen Dichte oder Gasbildung erreicht werden.

Das Ziel dieser Studie war das Schwimm- und Freisetzungsverhalten direkt komprimierter hydrophiler einzeldosierter Matrices (HPMC, Carbopol und Ac-Di-Sol) zu untersuchen, um schwimmende Arzneistoffabgabesysteme zu entwickeln.

Trotz der Schwimmfähigkeit von HPMC Matrizen als Folge der Quellung und Gelbildung der hydrophilen Matrices, war die Zugabe von $NaHCO_3$ notwendig zur Sicherstellung des schnellen Aufschwimmens. Ähnliche Freisetzungsprofilen wurden mit unterschiedlichen Anteilen von HPMC: $NaHCO_3$ im untersuchten Bereich erhalten. Dies liegt daran, dass Hydratation und Gelbildung der Matrix geschwindigkeitsbestimmend waren.

Die Zugabe von Carbopol zu HPMC Matrizen ergab kein Schwimmen. Die höhere Feuchtigkeitsaufnahme von Carbopol führte zu einer erhöhten Dichte der Tablette. Die Anfangsphase der Freisetzung war unverändert, aber langsamer in der späteren Phase. Dies war aufgrund der verringerten Matrix-Erosion in Anwesenheit von Carbopol. Des Weiteren war die Freisetzung von HPMC-Carbopol unabhängig von Carbopol Menge. Wenn Ac-Di-Sol zu HPMC hinzugefügt wurde, erhöhte sich die Zeitverzögerung bis zum Aufschwimmen aufgrund der langsameren Hydratation und Gelbildung. Im Gegensatz zu HPMC-Carbopol Matrizen, wurde die Freisetzung mit Ac-Di-Sol wegen einer schnelleren Erosion beschleunigt.

Durch Zugabe von $NaHCO_3$ zu Carbopol, HPMC-Carbopol und HPMC-Ac-Di-Sol-Matrizen, wurde sofortiges Aufschwimmen erreicht. Dies war wegen der raschen CO_2-Bildung im sauren Medium, so dass die Tablette ihre Dichte verringerte. Die Freisetzung war schneller aus HPMC-Ac-Di-Sol im Vergleich zu HPMC-Carbopol Tabletten mit $NaHCO_3$ wegen der höheren Medium-Aufnahme und Erosion von Ac-Di-

Sol. Die Erhöhung von Carbopol in Carbopol- $NaHCO_3$-Matrizen verringerte die Wirkstoff-Freisetzung. Darüber hinaus wurde eine komplette Erosion von Carbopol-$NaHCO_3$-Matrizen erreicht; dies vermeidet Akkumulation nach mehrfacher Gabe.

Die Freisetzung aus den verschiedenen Matrices folgte dem Korsmeyer Peppas-Modell und wurde von anomalen (non-Fickian) Diffusion gesteuert. Eine Änderung in dem Wirkstoffabgabemechanismus zu Fickian Diffusion wurde für Matrizen mit hohen Ac-Di-Sol Anteil oder mit Ac-Di-Sol in Gegenwart von $NaHCO_3$ beobachtet.

Schnell schwimmende hydrophile Matrizen mit einer langen Schwimmdauer wurden erhalten. Flexible Profile der Wirkstoffabgabe wurden mit Variationen des Polymer-Verhältnisses erreicht. Darüber hinaus wurde eine vollständige Erosion nach der Wirkstofffreisetzung mit Carbopol - $NaHCO_3$ Matrizen erreicht.

5.2 Schwimmende „multiple unit“ Arzneistoffgabesysteme

Die Ziele dieser Studien waren die Herstellung von „multiple unit“ Schwimmretardarzneiformen auf Basis von CO_2-Bildung (Aufbrausen) für Arzenistoffe mit unterschiedlichen Löslichkeiten und die Klärung einen mechanistischen Überblick über das Schwimmverhalten eines solchen Systems.

Ein schwimmendes Pellet-System sollte rasch sauren Magensaft aufnehmen um schnell CO_2 zu bilden und zu schwimmen. Die Pellets sollten damit beschichtet werden, um das gebildete CO_2 für längere Zeiträume zu behalten und die Freisetzung der Wirkstoffe zu kontrollieren.

Das System ist aus arzneistoff-beladenen Kernen, einer $NaHCO_3$-Schicht und einer wässrigen Polymertop-Beschichtung zusammengesetzt. Diese Top-Beschichtung sollte idealerweise das Schwimm-und Wirkstofffreigabeverhalten kontrollieren.

Die hohe Permeabilität von Eudragit® RL 30 D führte zu schnellem und langem Aufschwimmen (aufgrund des effizienten CO_2 Rückhaltens), aber zu einer schlechten Kontrolle über die Wirkstoffabgabe (keine Verzögerung) mit Ausnahme von wasserunlöslichen, hochdosierten Arzneistoffen (Carbamazepin). Eine breite Palette von Wirkstoffabgabe konnte durch eine Kombination von Eudragit® RL / RS erreicht

werden, wobei der Anteil von Eudragit® RS 40% nicht überschreiten soll, um die guten Schwimmeigenschaften zu bewahren. Beschichtung mit dem weniger durchlässigen Kollicoat® SR 30 D verlängerte die Wirkstofffreisetzung, aber das Aufschwimmen dauerte zu lange.

Eine Änderung des Systems durch die Trennung der Schwimm-und Freisetzungs "Funktionen" der Polymerschicht in zwei getrennte Schichten war notwendig, um das Aufschwimmen zu bewahren und eine Retardierung der Wirkstoffabgabe für wasserlösliche Arzneistoffe (Propranolol HCl) zu erhalten. Retardierende Pellets (arzneistoff-beladene Kerne mit unterschiedlichen wässrigen Polymerdispersionen von Eudragit® RS 30 D, Kollicoat® SR 30 D oder Aquacoat® ECD überzogen), wurden mit $NaHCO_3$- und schließlich mit der durchlässigen Eudragit® RL 30 D überzogen. Das innere retardierende Polymer war damit zuständig für die verzögerte Freisetzung und das äußere Eudragit® RL für das Aufschwimmen.

Die Zeitverzögerung des Aufschwimmens war kurz und wurde nicht durch die innere retardierende Polymer-Beschichtung beeinflusst. Im Gegensatz dazu war die Schwimmdauer stark von der Art des retardierenden Polymeren abhängig. Die zunehmende Medium-Aufnahme erhöhte die Löslichkeit des gebildeten CO_2 und seine Diffusion. Dies führte zu einer erhöhten Pellet-Dichte und zum Absinken der Pellets. Zum Beispiel, Aquacoat® ECD, ein lipophiles Polymer, hatte eine geringe Medium-Aufnahme. Das führte zu langem Schwimmen, unabhängig von der Polymerschichtdicke. Die mehr hydrophilen Polymere (Eudragit® RS 30 D und Kollicoat® SR 30 D) hatten eine hohe Medium-Aufnahme, was zu erhöhten Pelletgewicht und Dichte führte, und daher zu einer kürzeren Schwimmdauer. Eine höhere Arzneistoffbeladung der wasserlöslichen Arzneistoffe erhöhte die Schwimmdauer.

Das Aufschwimmen war unabhängig von der Lagerung bei 25 ° C / 0% RH und 40 ° C / 0% RH über 3 Monate, während die schwimmenden Fähigkeit bei Lagerung bei 40 ° C / 75% RH verloren gingen. Dies war aufgrund der Migration von $NaHCO_3$ durch die polymere Beschichtung hervorgerufen. Daher sollten die CO_2-basierte schwimmenden Arzneistoffgabesysteme unter trockenen Bedingungen gelagert werden oder mit einer Schutzschicht überzogen werden. Darüber hinaus erhöhte sich die Wirkstofffreisetzung aus Eudragit® RS 30 D- überzogenen Pellets aufgrund der Migration des

Weichmachers. Eine Abnahme der Freisetzung von mit Aquacoat® ECD oder Kollicoat® SR 30 D überzogenen Pellets wurde durch die weitere Koaleszenz der Polymerpartikel während der Lagerung hervorgerufen.

Durch Erhöhung des pH-Wert des Mediums wurde nicht mehr ausreichend CO_2 zum Aufschwimmen gebildet. Daher wurde ein pH-unabhängiges Schwimm-System durch eine Kombination von Zitronensäure und $NaHCO_3$ entwickelt. Eine organische Beschichtung der Brause-Schichten und äußeren polymer Schichten Eudragit® RL 100 war notwendig, um eine vorzeitige CO_2-Bildung zu verhindern. Das System zeigte eine verlängerte Freisetzung, sowie hervorragende Schwimmeigenschaften, unabhängig vom pH-Wert des Mediums.

Die wichtigsten Parameter, die das Aufschwimmen beeinflussen, wurden identifiziert. Schwimmende „multiple unit“ Arzneistofffreigabesysteme für Arzneistoffe mit unterschiedlichen Löslichkeiten und variablen Freisetzungs-Profilen wurden erfolgreich entwickelt. Durch die Zugabe einer Zitronensäure-Schicht wurde ein pH-unabhängiges System entwickelt.

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7. PUBLICATIONS AND PRESENTATIONS

7.1. Publications

El Samaligy, S., Bodmeier, R., Development and in vitro evaluation of single unit floating drug delivery systems. (In preparation)

El Samaligy, S., Bodmeier, R., Development of extended release multiple unit effervescent floating drug delivery systems for drugs with differing solubility. (In preparation)

El Samaligy, S., Bodmeier, R., Effect of type of extended release pellets on floating properties for the preparation of a pH independent multiple unit floating drug delivery system. (In preparation)

7.2. Presentations

El Samaligy, S., Bodmeier, R. (2008), Multiple unit floating drug delivery systems, 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, PBP, Barcelona, Spain, #209.

8. CURRICULUM VITAE

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