INVESTIGATION OF BILAYER MATRIX TABLET FOR BIPHASIC DELIVERY OF LORATADINE AND PSEUDOEPHEDRINE

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UNIVERSITI SAINS MALAYSIA

2011

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by

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Thesis submitted in fulfillment of the requirement for the degree of Doctor of Philosophy

June 2011

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and appreciation to my supervisor Professor Dr. Peh Kok Khiang for all his continuous guidance, constant effort and patience in providing invaluable ideas, guidance, encouragement and the exceptional role he has played in making this project a reality. Big thanks to my co-supervisor Associate Professor Dr. Yvonne Tze Fung Tan for her invaluable advice, guidance and her great patience in guiding me as a novice researcher.

I would like to thank Associate Professor Dr. Syed Azhar Syed Sulaiman, Dean of the School of Pharmaceutical Sciences, for giving me the opportunity to carry out this study in the School of Pharmaceutical Sciences, Universiti Sains Malaysia. I am most grateful and enormously indebted to my wife Aruna, two daughters Anoushka and Tanishka and my family for their love, support and encouragement during this period. They provided a lot of inspiration and zeal for me to work hard.

My sincere thanks to Institute of Postgraduate Studies for helping me during my stay here. I would like to thank IPS, USM for providing financial assistance during my course. I would also like to thank Universiti Sains Malaysia for giving me the opportunity and providing me with all the necessary facilities that made my study possible. Last but not the least, my warmest appreciation to Mr. Chuah, Shamshuddin, Rahim, Rizal, Yousuf and Ibrahim for their help in the laboratory. I would also like to thank other staff members of the School of Pharmaceutical Sciences, Universiti Sains Malaysia, who helped me in one way or another either directly or indirectly throughout my research and my stay here.

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LIST OF ABBREVIATION & SYMBOLS

%	Percent
ºC	Degree centigrade
ANOVA	Analysis of variance
AUC	Area under curve
C_{std}	Concentration of standard solution
C_{SS},	Concentration steady state
CDDS	Controlled Drug Delivery System
CV	Coefficient of variation
DDS	Drug Delivery System
FDA	Food and Drug Administration
FMDDS	Floating matrix drug delivery system
HPLC	High performance liquid chromatography
HPMC	Hydroxy Propyl Methylcellulose
ICH	International conference on harmonization
LOD	Limit of detection
LOQ	Limit of quantification
Mg	Milligram
ng/mL	Nanogram / milliliter
MW	Molecular weight
RPM	Rotation per minute
SD	Standard deviation
SPSS	Statistical procedures for social science
T	Tailing factor
$T_{50\%}$	Time for 50% of drug release
$T_{75\%}$	Time for 75% of drug release
T_{max}	Time to reach maximum plasma concentration
USP DI	United States Pharmacopoeia Drug Information
UV	Ultra violet
$W_{0.05}$	Width of peak at 5% height
µg/mL	Microgram per milliliter
µL	Microliter
kN	Kilo Newton

LIST OF PRESENTATIONS

1 **Krishna Murthy Bhavanasi**, Kok Khiang Peh and Yvonne Tze Fung Tan. "Release of Loratadine and Pseudoephedrine from Bilayer Matrix Tablet: Evaluation and comparison of Hydrophilic Polymers" Proceedings of the 57th Indian Pharmaceutical Congress Scientific Conference, Hyderabad, India (2005).

2 **Krishna Murthy Bhavanasi**, Kok Khiang Peh and Yvonne Tze Fung Tan, Anand Swarup K.R.L. "Simultaneous determination of loratadine and desloratadine in plasma by high performance liquid chromatography method with fluorescence detection" Proceedings of the 57th Indian Pharmaceutical Congress Scientific Conference, Hyderabad, India, (2005).

3 **Krishna Murthy Bhavanasi**, Kok Khiang Peh and Yvonne Tze Fung Tan. "Simultaneous determination of pseudoephedrine and loratadine by high performance liquid chromatography method in pharmaceutical dosage forms" Proceedings of the 4th UiTM-MPS Pharmacy Scientific Conference, Kuala Lumpur, (2004).

4 **Krishna Murthy Bhavanasi**, Kok Khiang Peh and Yvonne Tze Fung Tan. "Optimisation of floating matrix tablets and in-vitro evaluation of their gastric residence time" Proceedings of the 4th UiTM-MPS Pharmacy Scientific Conference, Kuala Lumpur, (2004).

5 **Krishna Murthy Bhavanasi**, Kok Khiang Peh and Yvonne Tze Fung Tan. "Design and evaluation of novel formulation for bimodal drug release" Proceedings of the MPS Pharmacy Scientific conference, at Sunway Lagoon Convention Centre Kuala Lumpur, (2003).

PENYELIDIKAN TABLET MATRIKS DUA-LAPIS UNTUK PENGHANTARAN DUA FASA LORATADIN DAN PSEUDOEFEDRIN

ABSTRAK

Pengambilan drug secara oral lebih digemari kerana ia mudah, komplians pesakit tinggi, keadaan pengeluaran yang kurang ketat dan kos yang lebih rendah. Sudah menjadi kebiasaan dengan dua atau lebih drug terkandung dalam satu bentuk dos untuk indikasi yang berlainan. Dalam kajian ini, rekabentuk tablet matriks yang berlainan diuji keupayaan mereka mengubahsuai pelepasan drug terutamanya dalam penghantaran lebih daripada satu drug dengan kadar berlainan. Kajian bermula dengan penyediaan tablet matriks "press coated" dan sistem "monolithic" yang dilengkapi dengan ciri-ciri terapung, menggunakan parasetamol sebagai satu drug model. Seterusnya, untuk mencapai profil penghantaran drug dua fasa, tablet matriks "press coated" dan dua-lapis diuji, sekali lagi menggunakan parasetamol sebagai drug model. Peningkatan kandungan hidroksipropil metilselulosa dan gam xantan pada tahap 40% mampu mengawal pelepasan drug sehingga 12 jam. Pada kepekatan polimer yang sama, profil pelepasan drug tablet matriks dua-lapis dan "press coated" adalah setara. Lebih daripada 50% drug dilepaskan dalam satu 1 jam diikuti dengan pelepasan yang perlahan dalam satu tempoh panjang bergantung pada kandungan dan jenis polimer yang digunakan. Kedua-dua sistem dinilai lebih lanjut untuk pelepasan dua fasa loratadin dan pseudoefedrin, dibandingkan dengan tablet Clarinase®. Profil pelepasan loratadin dan pseudoefedrin daripada tablet matriks "press coated" dan dua-lapis dibandingkan dengan tablet Clarinase® untuk kesetaraan. Tablet matriks dua-lapis lebih disukai dan dipilih untuk kajian in vivo

dengan menggunakan arnab. Sebelum kajian in vivo, kaedah HPLC telah dibangunkan dan divalidasi untuk mengesan pseudoefedrin dan loratadin dalam plasma arnab. Formulasi F19 telah digunakan untuk kajian in vivo. Keputusan yang didapati menunjukkan kadar dan jumlah yang diserap untuk loratadin dan pseudoefedrin tablet matriks dua-lapis F19 setanding dengan tablet Clarinase®. Pendek kata, sistem tablet matriks dua-lapis boleh digunakan sebagai satu sistem penghantaran drug alternatif untuk penghantaran dua fasa dua drug dengan keterlarutan yang berlainan.

INVESTIGATION OF BILAYER MATRIX TABLET FOR BIPHASIC DELIVERY OF LORATADINE AND PSEUDOEPHEDRINE

ABSTRACT

The oral route of administration is often preferred due to its convenience, high patient compliance, less stringent production conditions, and lower costs. It has become common to incorporate two or more drugs in a single dosage form, for different indications. In the present study, different designs of matrix tablet systems were examined for their ability in modifying the drug release especially for the delivery of more than one drug at different release rates. The study commenced with the preparation of press coated matrix tablets and a conventional monolithic system with floating features, using paracetamol as a model drug. Subsequently, to achieve biphasic drug delivery profiles, the press coated and bilayered matrix tablet systems were examined, again using paracetamol as a model drug. An increase in hydroxypropyl methylcellulose and xanthan gum at 40% level was able to sustain the drug release for 12 hr. At similar polymer concentration, the drug release profiles of bilayer and press coated tablets were comparable. More than 50% of drug was released within 1 hour followed by a slow drug release over an extended period of time dependent on the content and types of polymer used. The two systems were further evaluated for biphasic delivery of loratadine and pseudoephedrine, in comparison with Clarinase® tablets. The release profiles of loratadine and pseudoephedrine from the press coated and bilayer matrix tablet were compared with those of Clarinase® tablets to establish similarity. The bilayer matrix tablet was preferred and selected for in vivo study using rabbits. Prior to the in vivo study,

HPLC method was developed and validated for the determination of pseudoephedrine and loratadine in rabbit plasma. Formulation containing hypromellose and sodium carboxymethyl cellulose (F19) was used for in vivo study. The results obtained show that the rate and extent of absorption of loratadine and pseudoephedrine of studied bilayer matrix tablets were comparable with those of Clarinase® tablets. In short, the bilayer matrix tablet system could be used as an alternative drug delivery system for biphasic delivery of two drugs with different solubility.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 ORAL DRUG DELIVERY SYSTEM

The oral delivery system is the most common route of drug administration due to the ease of administration and widespread acceptance by patients. However, this system has limitations (Jain, 2008) :

(i) Drugs taken orally for systemic effects have variable absorption rates and serum concentrations which may be unpredictable.

(ii) The high acid content and ubiquitous digestive enzymes of the digestive tract can degrade some of the drugs before they reach the site of absorption into bloodstream;

(iii) Many macromolecules and polar compounds cannot effectively traverse the epithelial membrane in the small intestine to reach the bloodstream.

(iv) Many drugs become insoluble at the low pH levels encountered in the digestive tract. Since only soluble drugs can be absorbed into the bloodstream, the transition of the drugs to the insoluble form can significantly reduce the bioavailability.

(v) Some drugs are inactivated by the first pass metabolism in the liver on its way to the systemic circulation.

(vi) Some drugs irritate the gastrointestinal mucosa.

(vii) Oral route may not be suitable for drugs targeted to specific organs.

Hence, several improvements have taken place by development of sustained and controlled release form of oral drug delivery system to improve their action (Jain, 2008).

1.2 EXTENDED RELEASE ORAL DRUG DELIVERY

The United States Pharmacopoeia (USP, 2010) defines the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms". One class of modified-release dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow release (SR)" and "long-acting (LA)" have been used synonymously with "extended release". The commercial products in this category are often designated by suffixes such as CR, CD (controlled delivery), ER, LA, PD (programmed or prolonged delivery), Retard, SA (slow-acting), SR, TD (timed delivery), TR (timed release), XL and XR (extended release) (Tiwari and Rajabi-Siahboomi, 2008). The rationale for development of an extended-release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition and providing an opportunity for pharmaceutical companies to manage product life-cycle (Tiwari and Rajabi-Siahboomi, 2008).

1.3 GASTRORETENTIVE DOSAGE FORMS

The real challenge in the development of oral controlled-release drug delivery systems is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely

released at the desired period of time (Prajapati et al., 2008). Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time (Sauzet et al., 2009). Indeed, gastric drug retention has received significant interest in the past few decades. The gastroretentive dosage forms are classified into high density systems (Hwang et al., 1998), floating systems (Xu et al., 2006), expandable systems (Deshpande et al., 1996), superporous hydrogels (Chen et al., 2000), mucoadhesive or bioadhesive systems (Chavanpatil et al., 2006) and magnetic systems (Gröning et al., 1998).

The stomach anatomy and physiology constrain are the parameters to be considered in the development of gastric retentive dosage forms, probably the two most important features are their size and density (Bardonnet et al., 2006). Size is especially important in designing indigestible solid dosage forms (single unit systems). The human pyloric diameter is 12 ± 7mm (Timmermans and Moes, 1993). It is open while the stomach is in a fasting state. The first mouthful thus passes directly into the duodenum, triggering closure of the pyloric sphincter. The pylorus then sorts the gastric contents, large particles being carried away by retrograde flow to the center of the stomach. Solids are evacuated by the pylorus slowly and regularly. Finally, indigestible materials, including solid pharmaceutical dosage forms, are evacuated by a interdigestive migration myoelectric complex peristaltic wave. Particles with diameter < 7 mm are efficiently evacuated, and it is generally accepted that a diameter > 15 mm is necessary for useful prolongation of retention especially during the fasting state. Chance determines whether a single unit system is lost during a particular gastric emptying, so high variability in gastrointestinal transit time is a major drawback of these systems. However, density determines the location

of the system in the stomach. Systems with density lower than gastric content can float to the surface, while high-density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus (Bardonnet et al., 2006). In addition, the molecular weight and the lipophilicity of the active agent, depending on its ionization state are also important parameters. Gastric secretion is an aqueous isotonic solution containing H^+, Na^+, K^+, Cl^-, HCO_3^-, mucus, intrinsic factor, pepsinogen and gastric lipase. The gastro-duodenal lumen pH approaches 2, while the layer immediately adjacent to the epithelium is almost neutral pH 7 (Frieri et al., 1995, Goddard and Logan, 2003, Schreiber et al., 2004). This pH gradient, which helps protect the mucous membrane from digestion by the acid-dependent pepsin, is maintained by the secretion of HCO_3^- and mucus (Frieri et al., 1995). Gastric mucus is an approximately 5% aqueous solution of glycoproteins with molecular weight $> 10^6$ Da. Its electrical charge is determined by the presence of sialic acid ($pK_a \sim$ 2.6) (Larhed et al., 1997). Mucus and HCO_3^- are produced by the epithelial cells, the mucous neck cells of gastric glands and the Brunner's duodenal glands. The layer of mucus varies in thickness between 100 (Jordan et al., 1998, Newton et al., 1998, Newton et al., 2000) and 200 μm (Gu et al., 1988) according to the gastric location. Mucus ensures lubrication of solid particles, and its gelatinous consistency enables retention of water and HCO_3^- close to the epithelium. The gastric mucus layer acts as a sacrificial physical barrier against luminal pepsin, which digests the surface of the mucus gel to soluble mucin. The continuity and almost constant thickness of the mucus gel layer observed in vivo is evidence that mucus secretion balances the losses by peptic digestion and mechanical erosion. Diffusion of drugs through the mucus to the epithelium is dependent on their size. It was shown that gastric mucus was more permeable to metronidazole (171 Da) than amoxicillin (365.4 Da) (Shah et al., 1999).

It was demonstrated that charge decreased diffusion of a drug but lipophilicity was the most important physicochemical parameter: a high lipophilicity reducing diffusion across the very hydrophilic mucus layer (Bardonnet et al., 2006).

1.3.1 High-density delivery systems

Gastric contents have a density close to water (≈1.004 g/cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach (Figure 1.1) where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time (Clarke et al., 1993, Bardonnet et al., 2006).

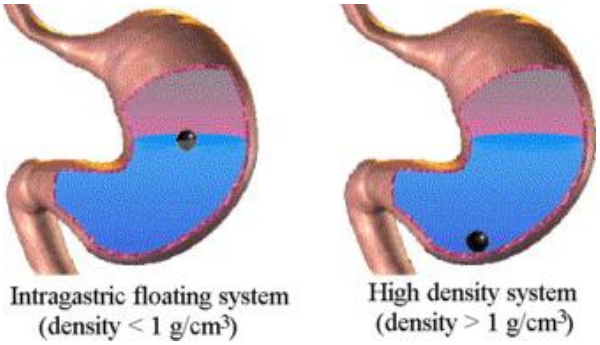

Figure 1.1: Schematic localization of an intragastric floating system and high-density system in the stomach (adapted from Bardonnet et al., 2006).

1.3.2 Floating delivery systems

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy (Singh and Kim, 2000, Saito et al., 2003).

1.3.2 (a) Hydrodynamically balanced systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most commonly used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageenans or alginic acid are also used (Reddy and Murthy, 2002). The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Reddy and Murthy, 2002) (Figure 1.2).

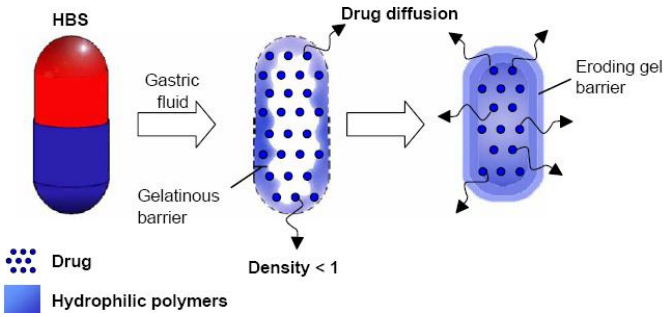

Figure 1.2: Hydrodynamically balanced system (HBS): The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier (adapted from Hwang et al., 1998).

Incorporation of fatty excipients gives low-density formulations, reduces water penetration and decreases the erosion. Madopar LP®, which is fabricated based on this system, was marketed by Roche during the 1980s (Jansen and Meerwaldtt, 1990). The main drawback is the passivity of the operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence the characteristics and amount of polymer (Hwang et al., 1998). Effective drug delivery depends on the balance of drug loading and the effect of polymer on its

release profile. A variety of strategies has been employed to improve efficacies of the floating HBS (Reddy and Murthy, 2002). Some investigators developed bilayer formulations in which one layer conferred the buoyancy and the other controlled the drug release. A bilayer formulation of misoprostol against gastric ulcers was produced (Oth et al., 1992). Both layers contained swellable polymers and only one contained drug (Figure 1.3a) so that buoyancy and drug release could be optimized independently. They observed a mean gastric residence time >3 h after a single meal (breakfast) and >10 h after a succession of meals. A bioadhesive floating system was formulated by coating tablets with Carbopol or a synthetic bioadhesive cross-linked polymer of methacrylic and acrylic acids (Chitnis et al., 1991). Finally, Krogel and Bodmeier (1999a) designed an impermeable polypropylene cylinder, 10–15 mm long, sealed on both sides by a matrix of hydrophilic polymer (HPMC) containing the drug. Air entrapped in the core of the cylinder provided the buoyancy (Figure 1.3b).

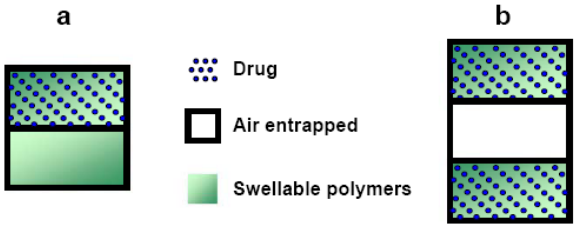

Figure 1.3: Hydrodynamically balanced systems (adapted from Bardonnet et al. (2006)).

1.3.2 (b) Gas-generating systems

Floatability can also be achieved by generation of gas bubbles. CO_2 can be generated in-situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

In single unit systems, such as capsules (Chen and Hao, 1998) or tablets (Baumgartner et al., 2000, Xu and Groves, 2001), effervescent substances are incorporated in the hydrophilic polymer, and CO_2 bubbles are trapped in the swollen matrix (Figure 1.4a). In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h (Baumgartner et al., 2000). In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h (Baumgartner et al., 2000). Bilayer or multilayer systems have also been designed (Krögel and Bodmeier, 1999b, Yang et al., 1999, Ozdemir et al., 2000, Wei et al., 2001). Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers (Figure 1.4b). Further refinements involve the coating of the matrix with a polymer which is permeable to water, but not to CO_2 (Krögel and Bodmeier, 1999b) (Figure 1.4c). The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer.

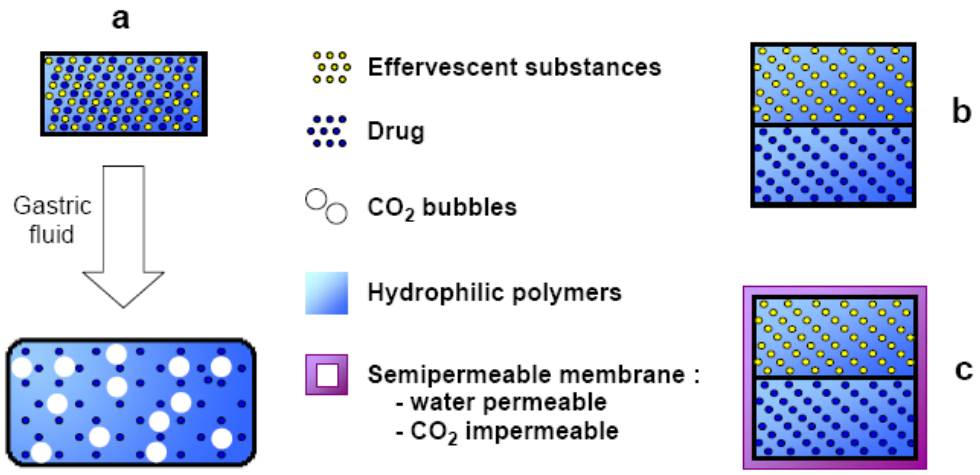

Figure 1.4: Gas-generating systems. (a) Schematic monolayer drug delivery system. Bilayer gas-generating systems, (b) without semipermeable membrane; (c) with semipermeable membrane.

It is essential that the multiple unit systems remain dispersed and suspended individually in the gastric fluid and not agglomerate into a mass floating at the top of

the stomach (Hou et al., 2003). Ichikawa et al. (1991b) reported a double-layered coated system in the form of granules, comprising of an inner effervescent layer (bicarbonate and tartaric acid) and an outer swellable membrane (polyvinyl acetate and shellac). The system floated completely within 10 min and ~80% remained floating over a period of 5 h. In-vivo studies were carried out in beagle dogs and humans in the fed state using granules loaded with barium sulphate as a radio-opaque marker. Most floated in the stomach within 10 min and remained so for at least 3 h as observed by X-ray photography (Ichikawa et al., 1991a) (Figure 1.5).

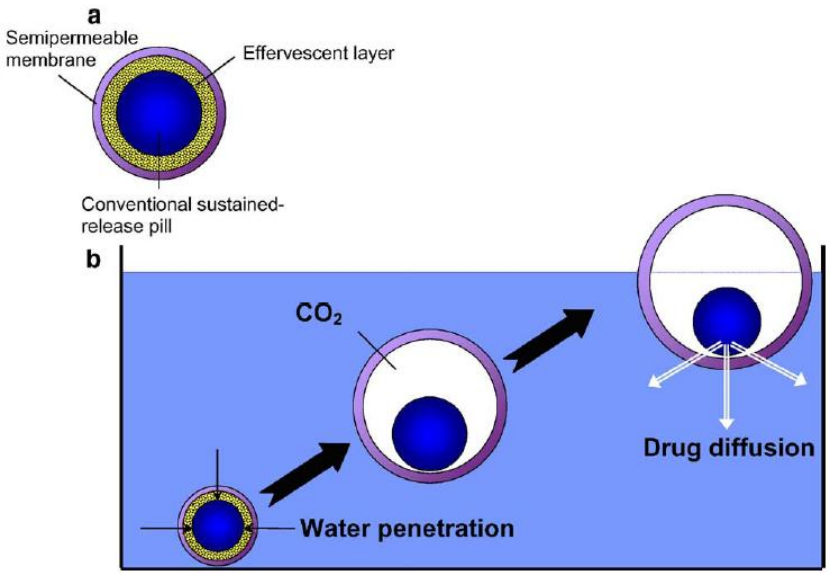

Figure 1.5: (a) Schematic representation of ‘‘floating pill’’. (b) The penetration of water into effervescent layer leads to a CO_2 generation and makes the system float (adapted from Ichikawa et al., 1991a).

Atyabi et al. (1996a) developed microparticles loaded with theophylline and bicarbonate (Atyabi et al., 1996a). The ion-exchange resin beads were coated with a semipermeable membrane. CO_2 was released on contact with the acid gastric juice (Atyabi et al., 1996b). The microparticles exhibited in vitro floating times of over 24 h. Studies in human volunteers using gamma-scintigraphy showed a prolonged residence time for coated beads (40% to 65% of the dose remained in the upper

stomach 3 h after a light breakfast) compared to control (no uncoated beads remained in the stomach after 3 h).

1.3.2 (c) Raft-forming systems

For raft-forming system, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid (Figure 1.6). Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. As raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment (Fabregas et al., 1994, Havelund et al., 1997) as with Liquid Gaviscon® (GlaxoSmithkline).

Figure 1.6: Schematic illustration of the barrier formed by a raft-forming system (adapted from Fabregas et al., 1994).

1.3.2 (d) Low-density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm^3) with immediate buoyancy

have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘micro-balloons’’ because of the low-density core (Kawashima et al., 1992, Jayanthi et al., 1995, Sato et al., 2003, Sato et al., 2004a, Sato et al., 2004b) (Figure 1.7a).

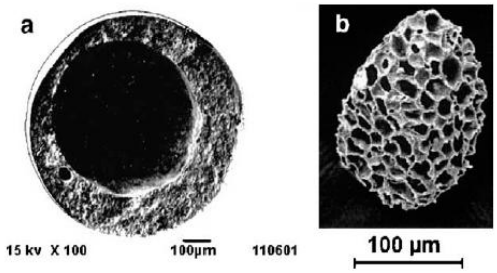

Figure 1.7: (a) Microballoons (adapted from Sato et al., 2003) and (b) foam-particles (adapted from Streubel et al., 2002).

Generally, the techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion/evaporation methods. Polycarbonate, Eudragit S®, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used (Reddy and Murthy, 2002).

An emulsion–solvent diffusion method was used to prepare hollow microspheres loaded with drug (ibuprofen) in their outer polymer shells. They dissolved the drug and an enteric acrylic polymer (Eudragit S®) in an ethanol/dichloromethane solution. This mixture was added into a stirred aqueous solution of polyvinyl alcohol (0.75% w/v) to obtain an o/w emulsion. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in the microspheres. In-vitro study showed that the “microballoons” floated for >12 h on acidic dissolution medium containing surfactant (Kawashima et al., 1992). Thanoo et al. (1993) prepared polycarbonate microspheres loaded with aspirin, griseofulvin and

p-nitroaniline, by a solvent evaporation technique. Electron microscopy revealed spherical and hollow microspheres. A high drug loading (>50%) was achieved and the microspheres floated on simulated gastric and intestinal fluids (Thanoo et al., 1993). Stithit et al. (1998) used a novel emulsion–solvent evaporation process to obtain microspheres containing theophylline. The drug–polymer (cellulose acetate butyrate and Eudragit® RL 100 at 1:1) dispersions are pressurized under CO_2, which dissolves within them and forms bubbles upon the release of the pressure, giving microspheres with round cavities enclosed in the dispersed drug polymer droplets**.** They float for more than 24 h in pH 1.2 and 7.5 buffers (Stithit et al., 1998). Streubel et al. (2002) prepared foam-based floating microparticles consisting of polypropylene foam powder, drug (chlorpheniramine maleate, diltiazem-HCl, theophylline or verapamil-HCl) and polymer (Eudragit RS® or polymethyl methacrylate), by soaking the microporous foam carrier with an organic solution of drug and polymer, followed by drying. The mixture was poured into an organic liquid (ethanol or methylene chloride) forming a suspension. The polypropylene foam particles acted like microsponges, absorbing the organic liquid, and becoming free-flowing, low-density microparticles following solvent evaporation (Figure 1.7b). Good in-vitro buoyancy was observed in most cases and a broad variety of drug release patterns could be achieved by varying drug loading and type of polymer. More than 77% or 98% of particles floated for at least 8 h depending on the polymer type (Eudragit RS® or polymethyl methacrylate) and initial drug loading of the system (10% or 23%) (Streubel et al., 2002). Based on a similar approach, the same group developed a single unit floating system, consisting of low-density polypropylene foam powder, matrix-forming polymers (HPMC, polyacrylates,

sodium alginate, corn starch, carrageenan, agar, guar gum, arabic gum), drug and filler (Figure 1.8).

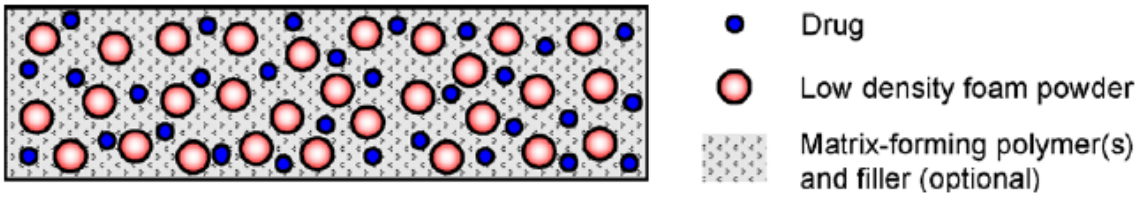

Figure 1.8: Schematic presentation of the structure of the low-density, floating matrix tablets (adapted from Streubel et al., 2003).

All the tablets remained floating for at least 8 h in 0.1M HCl at 37 ºC. The release rate could effectively be modified by varying the matrix-forming polymer/foam powder ratio, the initial drug loading, the tablet geometry (radius and height), the type of matrix-forming polymer, the use of polymer blends and the addition of water soluble or insoluble fillers (such as lactose or microcrystalline cellulose) (Streubel et al., 2003).

Talukder and Fassihi (2004) developed a multiple unit system based on cross-linked beads. They were prepared using Ca^{2+} and low methoxylated pectin (anionic polysaccharide), or Ca^{2+}, low methoxylated pectin and sodium alginate. Riboflavin, tetracycline and methotrexate were used as model drugs and drying was performed using two methods—air convection oven at 40 ºC for 6 h and freeze drying. Confocal laser microscopy revealed hollow spaces inside the freeze dried beads, which allowed them to remain buoyant over 12 h in buffer of pH 1.5, while the air-dried beads sank. Calcium–pectinate–alginate beads released their contents at relatively faster rates than did calcium–pectinate beads (100% vs. 50% in 10 h) (Talukder and Fassihi, 2004). Presently, hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple unit

systems and good floating properties. However, like all floating systems, their efficacy is dependent on the presence of enough liquid in the stomach, requiring frequent drinking of water (Hwang et al., 1998). In conclusion, development of an efficient gastroretentive dosage form is a real challenge. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology.

1.4 MODIFIED RELEASE DRUG DELIVERY SYSTEMS

The modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience (Wilding et al., 1991).

The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period (Abdul and Poddar, 2004). Hydrophilic polymers are becoming more popular in formulating oral controlled release tablets. It is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile (Narasimhan and Langer, 1997, Conte and

Maggi, 2000). The release of a dissolved drug inherently follows near first-order diffusion with an initially high release rate, due to the dissolution of the drug present at the surface of the matrix, followed by a rapidly declining drug release rate. The enhanced release rate observed at the beginning for a short time of the release process is known as burst effect and in many a times undesirable since it may have negative therapeutic consequences (e.g. toxicity due to increase of the concentration of the delivered substance beyond the acceptable higher limits especially on repeated administration). After this burst effect, hydration and consequent swelling and/or erosion of retard polymer occurs. These phenomena control the release process but, with time, the diffusion path-length increases and a saturation effect are attained, resulting in a progressively slow release rate during the end of dissolution span (Narasimhan and Langer, 1997, Conte and Maggi, 2000). There are a number of variables that can affect the constant drug release patterns in polymeric matrix devices. These variables include physico-chemical properties, content of drugs and polymers, drug/polymer weight ratio, administration form and dosage and manufacturing process (Abdul and Poddar, 2004).

Over the years, considerable efforts have been expanded in the development of new drug delivery concepts to achieve zero-order or near zero-order release, since constant rate delivery is the primary goal of controlled release systems, especially for drugs with a narrow therapeutic index. Examples of altering the kinetics of drug release from the more commonly inherent non-linear to linear behaviour included the use of geometry factors (solid units having spherical, cylindrical, conical, biconcave, biconvex, donut shapes, hemisphere with cavity, core-in-cup, circular sectioned cylinder, rings, oval bi-dose divisible tablets), films, erosion/dissolution controlled

and swelling controlled mechanisms, non-uniform drug loading and matrix-membrane combination (Shah and Britten, 1990, Benkorah and McMullen, 1994, Danckwerts, 1994, Hildgen and McMullen, 1995). Various matrix geometries have been recommended over the last two decades to achieve an almost constant release rate of the drug with time and one of these techniques relies on the use of multi-layered matrix tablets as drug delivery devices (Abdul and Poddar, 2004).

1.4.1 Multi layered matrix tablets

Layered tablets, such as bi-layered tablets (Maggi et al., 1999, Choi et al., 2000, Park and Munday, 2002) and even triple-layered tablets (Conte et al., 1993a, Yang et al., 1997, Abdul and Poddar, 2004), have been developed to achieve controlled drug delivery with pre-defined release profiles for different active ingredients (Wu and Seville, 2009). Multi-layered matrix tablet is a drug delivery device, which comprises a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during the tabletting process. The modulating layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate (Conte and Maggi, 1998). The coat layers prevent the water penetration, through the protected core for some duration, which results in reduced hydration rate and controlled area for solute release at the core. Thus, burst effect can be smoothened and the release can be maintained at a relatively constant level during the barrier layers' swelling and erosion process (Figure 1.9). After this phase, during the subsequent portion of the dissolution process, these swollen barriers are erosion dominated and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase of diffusion path-length (saturation

effect) is counterbalanced by the simultaneous increase of the area available for drug release (Conte et al., 1993a). By this way, combining a time-dependent control of the hydration rate of the device with the reduction of tablet surface exposed to the dissolution medium, it is feasible to achieve a linear release profile. It is also possible to obtain various dissolution patterns such as multi modal, pulsatile or delayed delivery, extended release (characterized by reasonably constant rate) for different drugs by varying the formulations of layers. In all the applications, the multi-layered system should swell, gel and finally erode completely, leaving negligible residue in the gastro-intestinal tract (Conte and Maggi, 1998). The system is a unique drug delivery device, which overcomes the major disadvantage of non-linear release associated with most diffusion controlled matrix devices. This system also has the advantage of being compatible with conventional manufacturing methods.

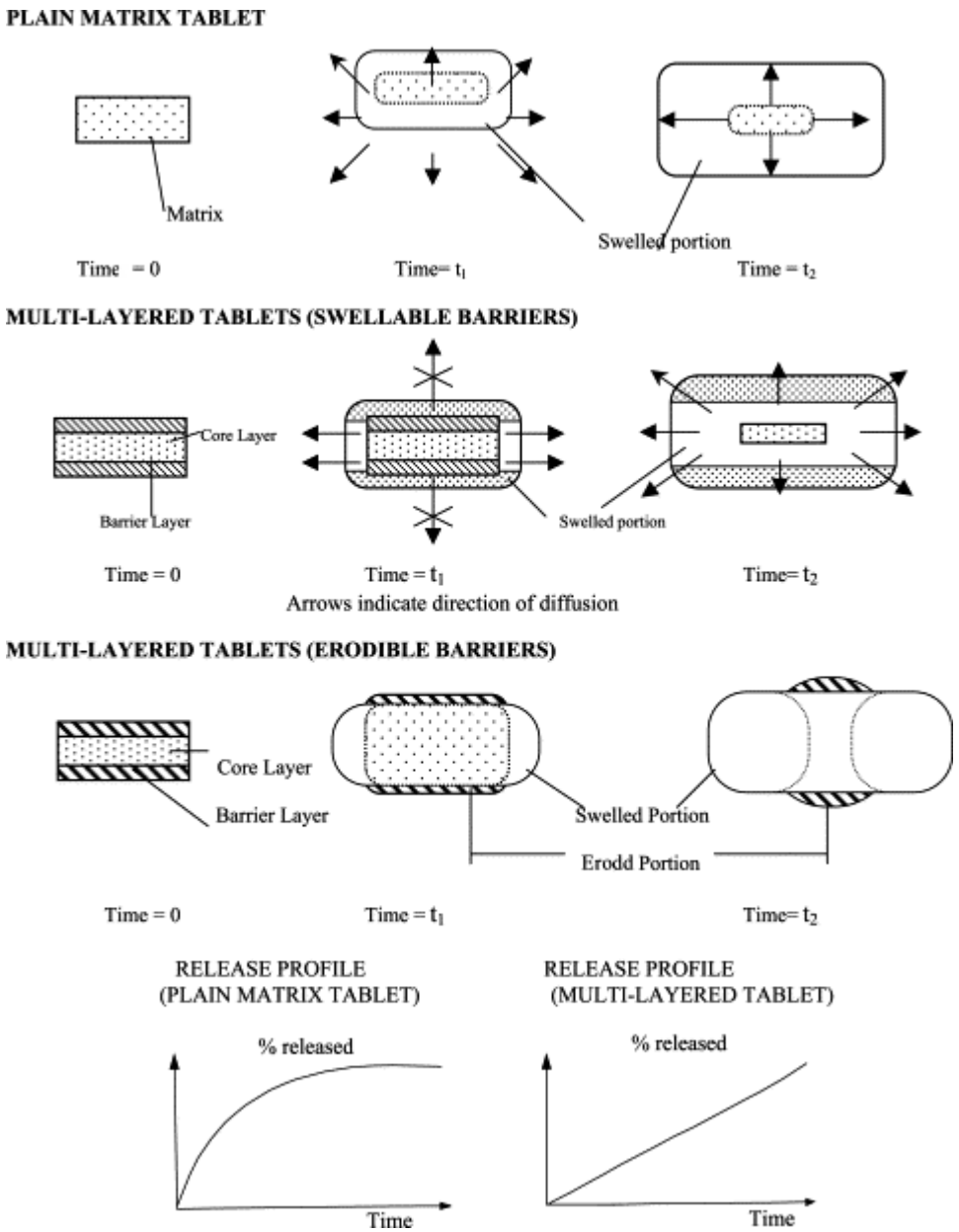

Figure 1.9: Effect of the application of polymeric layers (barriers) on the release of drug from a matrix core (Abdul and Poddar, 2004).

1.4.2 System design

Generally, the drug release mechanism from hydrophilic, swellable matrices is a coupling of polymer macromolecular relaxation and drug diffusion (Lee, 1985, Ritger and Peppas, 1987). Both phenomena depend initially on the rate at which water may enter the device. Multi-layered design is based on the following aspects: (1) matrix hydration rate and consequent swelling and/or lowering of diffusion rate;

(2) modulation of the surface of matrix through which the drug can be delivered. These principles are more effective in the initial phase of the dissolution process and less pronounced as swelling proceeds, leading to linearization of the release profile. To achieve similar objective, coating of the matrix tablets with an inert impermeable film have been attempted (Colombo et al., 1987). The coating was applied extemporaneously on the tablet faces and/or on the sidewall to obtain different coating combinations as schematically represented in Figure 1.10. From their in vitro release performance, it may become clear that as the extent of coating is increased, the release is slowed and the release kinetics approached zero order. The release rate was mainly driven by the surface geometry of the system (coated–uncoated surface ratio). From these observations, it is confirmed that during dissolution, although the matrix swells, the coating considerably reduces the drug-releasing surface compared with the uncoated matrix and also hinted towards the ability of coating design to modulate both release extent and kinetics (Abdul and Poddar, 2004). The casting of impermeable membrane on a portion of the matrix tablet is a manual process (Colombo et al., 1987). To overcome this drawback, which does not allow for the automatic production of the system, different approaches were tried. In particular, the application of polymeric swellable and erodible barrier layers, instead of impermeable film, was evaluated taking into account that the former should exhibit properties of drug impermeability similar to those offered by the latter. The development of the barrier formulation was carried out through two different approaches (Conte et al., 1993). The first was based on the use of inert insoluble polymer (ethyl cellulose) and the second was based on the use of hydrophilic swellable polymer (HPMC). The in vitro release performance of such layered tablets and their morphological behavior were examined and compared to that of partial film

coated system (Conte et al., 1993). The partial film coating does not swell and maintains its original size and shape and offer consistent release retardation for the whole duration of dissolution process. On the contrary, the barrier made of an inert polymer tends to crack and detach itself from the core within hours after water immersion. This effect is due to core volume expansion upon water immersion, by polymer swelling. This stresses the outer barrier layer, which does not expand to accommodate the swelling of the core. The swellable barriers show a more homogenous system in which both the barrier and the core may swell simultaneously without any internal stress during the dissolution process (Conte et al., 1993a). The barriers can be applied using a multi-layer compression process. The easiest example was represented by either double layer (Figure 1.10b) or three layer tablets (Figure 1.10c) in which only one layer contains the active ingredient (active core), while one or two other layers are barrier layers. A considerable time has been devoted to the optimization of suitable barrier formulations that could be applied on the core directly during the tabletting process. The performance of the final barrier formulation was evaluated using many active cores, compositions (Conte et al., 1994) proving the efficiency and flexibility of the multi-layered concept, particularly in controlling the release of drugs of high solubility (Wilding et al., 1995, Conte and Maggi, 1996). Based on this new development, a product was launched in 1992 in US. It is Dilacor® XR (Rhone Poulene-Rorer), a device for the 24-h extended release of diltiazem hydrochloride a drug of high solubility.

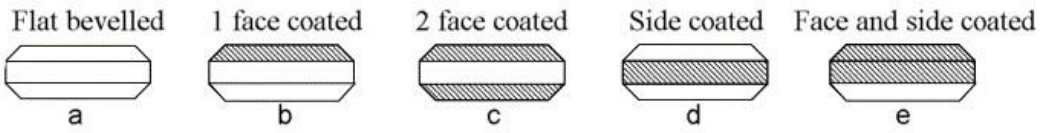

Figure 1.10: Schematic representation of the (a) matrix tablet, (b) 1-face coated, (c) 2-face coated, (d) side coated, and (e) face and side coated designs.

The multi-layer design allows for the production of different tablet designs by varying the geometry of the device or modulating layers characterized by specific release properties to achieve various dissolution patterns (not limited to a constant release) such as delayed, pulsatile or multi modal delivery profiles. The section below deals with various tablet possibilities based on this proposed design.

1.4.3 Different designs

1.4.3 (a) Zero order sustained release

This system is comprises either a hydrophilic or hydrophobic intermediate layer containing the active drug(s) or one or two barrier layers which are press coated to the faces of the tablet core, leaving the sides of the core exposed. Many researchers have evaluated this design, to approach zero-order sustained release (Chidambaram et al., 1998, Qiu et al., 1998). The widely used barrier polymers for sustaining the drug delivery are either hydrophilic and/or hydrophobic materials. In general, linear release profiles can be obtained by applying hydrophilic barrier layers on either of th faces of a hydrophobic matrix tablet or by applying a hydrophilic barrier layer on one face and hydrophobic barrier layer on the other face of the matrix tablet. However, formulation and variables within the matrix and barrier layers need to be controlled rather carefully to achieve zero-order drug release from hydrophobic matrix tablet coated with hydrophobic barrier layers on both faces (Chidambaram et al., 1998, Qiu et al., 1998, Krishnaiah et al., 2002a, Krishnaiah et al., 2002b).

1.4.3 (b) Time-programmed delivery system (press coated tablet)

The concept of the chronopharmacokinetics and chronotherapy of drugs has been utilized in clinical therapy for improving the drug efficacy and preventing the side

effects and drug tolerance (Reinberg, 1992, Smolensky and D'Alonzo, 1993, Lemmer, 1996). The maintenance of a constant drug blood level in the body is not always desirable for optimal therapy. For ideal therapeutic efficacy, a drug with optimum concentration should be delivered only when and where it is needed. Hence, the drug release behaviour should be controlled by time in addition to rate. To avoid developing tolerance, a reasonable and generally accepted rationale is to have a delivery system capable of releasing drugs, in a pulsatile fashion rather than continuous, at predetermined time points and/or sites following administration (Yoshida et al., 1993, D'Emanuele, 1996, Lin et al., 1996). For this purpose, different systems including the time clock system, have been developed using various techniques and functional polymers or additives (Narisawa et al., 1994, Pozzi et al., 1994, Matsuo et al., 1995). Press coating technique is one candidate for such a novel system that not only acts as a rate controlling system but also delivers the drug in the gut when it is required, which is in a time-controlled fashion. This technique has many advantages because no special coating solvents or equipments are needed for coating of tablets and manufacturing speed is also faster. The system consists of a core (either conventional or a modified release formulation), which is coated by compression with different polymeric barriers (press-coated systems) (Conte et al., 1993b) (Figure 1.11). This system delivers the drug from the core tablet after swelling/eroding the hydrophilic or hydrophobic barrier of the coating shell and may exhibit a pulsatile release of the drug (Fukui et al., 2000, Takeuchi et al., 2000). This outer shell may delay the penetration of fluid, thereby inducing a long lag time prior to the start of drug release. Once the solvent penetrates into the interior core tablet, the core tablet will dissolve and/or swell to break the outer shell resulting in rapid drug release (Fukui et al., 2000, Fukui et al., 2001, Lin et al., 2001). This delay in the

start of release is not influenced by the core composition and only depends on the shell formulation. Moreover, except for time lag, the release kinetics of the core is not significantly influenced by the presence of erodible barrier. However, the kinetics is strongly influenced by the presence of gellable or expandable polymeric shell. This type of coating hydrates and gels completely but does not get removed from the surface of the core. The device can be considered as a reservoir system (Abdul and Poddar, 2004). The net release pattern depends on the release kinetics of the core and penetration behavior of the swelled/gelled coat.

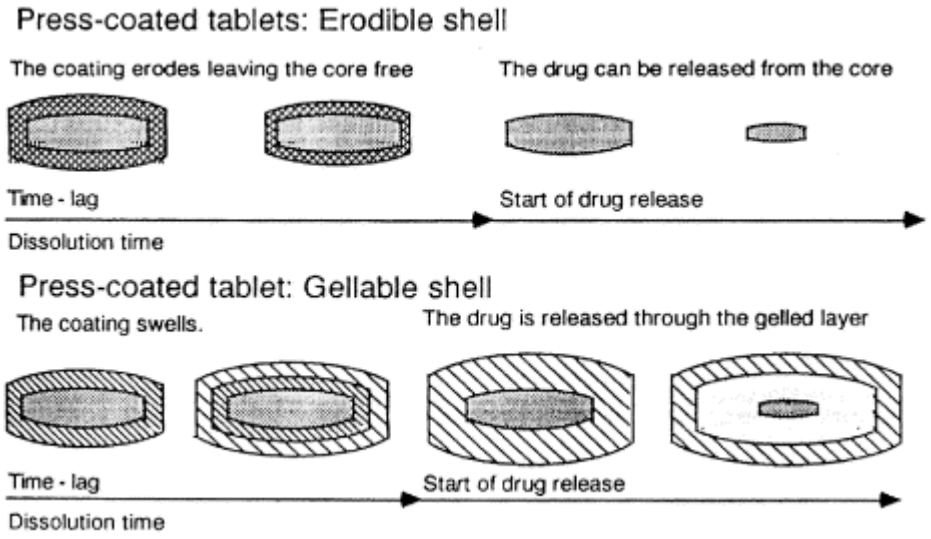

Figure 1.11: Geometric press coated tablets for the delayed release of drugs (Abdul and Poddar, 2004).

1.4.3 (c) Bimodal release profile

An oral controlled release system which releases drug at zero-order rate is often considered an ideal system for maintaining constant drug levels in plasma. This is based on the assumption that drug absorption occurs rapidly and uniformly through the entire GI tract, so that the rate of elimination dictates the rate at which the drug must release from the dosage form. However, for many drugs, absorption is moderately slow in the stomach, rapid in the proximal intestine, and declining sharply in the distal segment of the intestine. This means that to maintain constant

drug absorption, the delivery system should release drug in such a way that it is able to compensate for the changing drug absorption pattern in the GI tract by increasing or reducing drug release rate to adjust the regional flux. Thus, a release system with variable rate of release may indeed be more desirable than a constant zero-order release system. The bimodal release system provides such a variable rate release. Bimodal release is characterized by an initial rapid release, followed by a period of slow and constant release, and again a second phase of rapid drug release (i.e. sigmoidal release profile). Such bimodal release system can offer two major advantages over other systems: (1) it produces rapid drug release during the initial and later phase to compensate for the relatively slow absorption in the stomach and large intestine; (2) it can be used to design programmed pulse release oral drug delivery systems for the therapeutic agents that perform more effectively when drug levels at the site of action undergo periodic changes. Figure 1.12 shows that in bimodal delivery system an additional layer, i.e. fourth layer, containing initial dose rapidly disintegrates to produce quick onset of dissolution, promoting greater concentration gradient in stomach. The release from the SR portion-containing drug is controlled by barrier layers to achieve constant rate release. The appearance of the pH 7.4 in the GIT is the initiator for the second rapid drug release towards promoting the absorption in large intestine (Streubel et al., 2000).

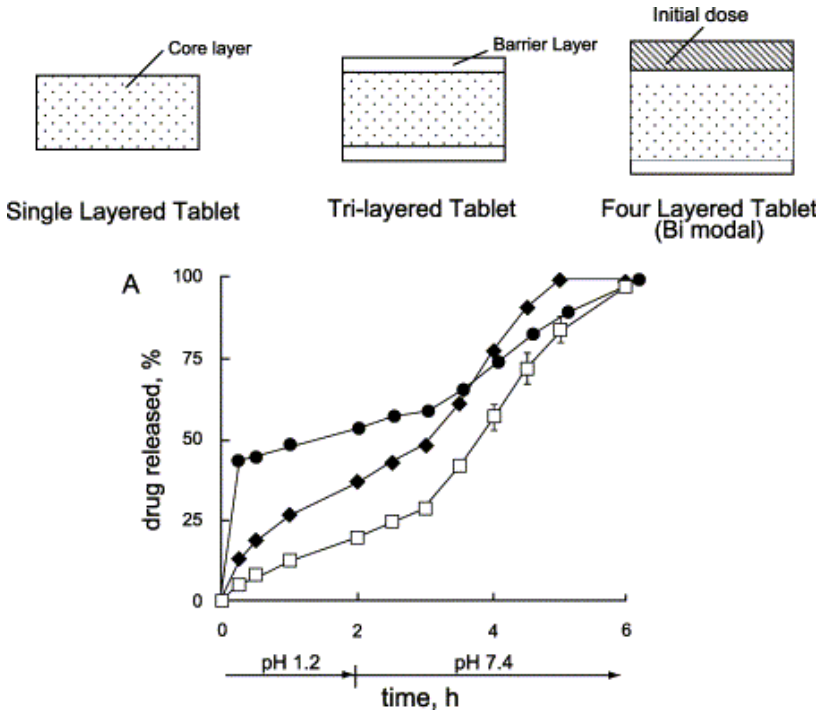

Figure 1.12: Release profiles of theophylline from investigated tablets (●) Bimodal; (♦) Single layered tablet; (□) Tri-layered tablet (Abdul and Poddar, 2004).

1.5 Influence of process and formulation parameters

Since the incorporation of initial dose layer (as in the case of bimodal delivery system and quick/slow delivery system) affected neither the intermediate slow nor the second rapid phase or constant phase, this layer is not necessary to be considered in the formulation process. Therefore, multi-layered tablet consisting of a core and one or more barrier layers and/or a core and outer shell (in the case of press-coated tablet) should be taken into account while determining the parameters involved in the processing. The following factors should be considered for the process and formulation (Kannan et al., 2003a, Kannan et al., 2003b).

1.5.1 Granulation-layer containing therapeutics

The following factors are to be considered while making granulation of active substances: granulation liquid percentage, outlet air target temperature during the