Cristina Mesquita Oliveira

EMERGING TRENDS IN PHARMACEUTICAL DOSAGE FORMS

Dissertation of Pharmaceutical Biotechnology Master Degree under orientation of
Dr. Cláudia Sousa Silva and Prof. Dr. Sérgio Paulo Magalhães Simões, presented to Faculty of Pharmacy of University of Coimbra

July of 2015

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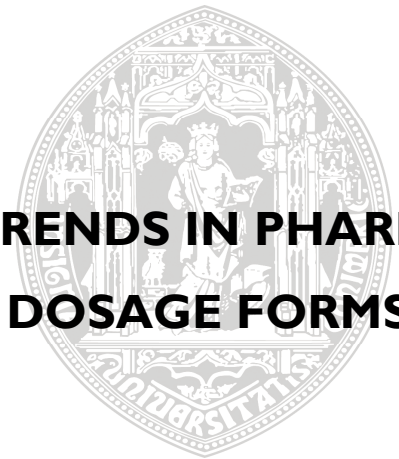

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ACKNOWLEDGMENTS

I would like to show my gratitude to those who gave me the possibility to conclude my dissertation and those who contributed to its success. This section is surely not enough to thank, as it should, to all the ones who contributed, directly or indirectly, for the dissertation as well as my academic path. In this way, I just let a few words, but with a deep feeling and gratitude to those who, over the years, I can call friends.

First, I want to thank to Bluepharma, S.A. for the possibility of contacting with a healthy working environment in Pharmaceutical Industry, for the internship and the opportunity to learn and grow with very competent persons.

To Dr. Cláudia Silva, Chief Scientific Officer of Bluepharma, adviser of this monograph, for all the availability demonstrated, for the scientific knowledge shared and for all the support through counseling and trust.

To Prof. Dr. Sérgio Simões, Professor of Faculty of Pharmacy of University of Coimbra and Vice-President of Bluepharma, intern adviser of this monograph, for being an example of that success comes with dedication and perseverance.

To the team of Galenical Development of Bluepharma, namely João Feteira, Ana Rita, Zé Miguel and Sónia Cipriano, for the good things shared in pharmaceutical development and comradeship. Also to Salomé Gomes for all the initial help, support and orientation in Bluepharma.

To the ones in Bluepharma that shared good moments inside and outside of the company, and who became good friends. As so, to B043 and especially to Joana Matos, Carolina Torres and Inês Martins.

I want to show my gratitude to all my friends, for the support, patience and tolerance. To Tânia Costa for being that great friend always present and available with her kind heart, for the pleasant long years of understanding, laughing and caring. To Inês Cintrão for all the funny theories and explanations of facts, all the company and friendship from the long years of adolescence, and until today. To Joana Vilaça for the spontaneity of her soul, for the good moments shared and for reminding me that distance is not a burden even though the

nostalgia. To Rita Santana for the too much in too little and for being that passionate genuine person and friend. To Rita Leones for being a truly good friend that is continuously present even from several quilometers away. To Gonçalo Ferreira for all the sharing and friendship through the years. To David Gomes for all the distracting moments, conversations and continuous presence. To João Pedro for the continuous worrying and infinite friendship. To Bruno Marques for all the love, kindness and good care, as well as for the endless patient for my ramblings.

To Balololotelli e a Bóia for the friendship and fellowship that comes from our academic path in Chemical Department of University of Coimbra and that was transferred into the everyday life.

To the ones that shared Classegest with me in the most grateful year in Coimbra, especially Alexandra Arede, Tânia Costa, Inês Cintrão and Joana Vilaça. Also to the ones that shared the second year of Classegest with me, namelly Alexandra Teixeira, Carmen Guerreiro, Inês Ferreira an again Rita Santana, it was a pleasant last year in Coimbra.

To Centro Universitário Manuel Nóbrega for being the coziest place to spend the uncountable hours of work.

The most affectionate gratitude goes to my parents and my brother. Besides all the acknowledgements I do here, this is the most special and important. I want to thank for all the support and love, all the confidence in me and in my choices, along with the infinite patient. They have the greatest responsibility in my academic pathway and an important role in my growth as a human being. Thanks for everything.

ABSTRACT

Among the distinct routes of drug administration (e.g. oral, parenteral, transdermal, mucosal), the oral route is the most convenient and promising one, due to its non-invasiveness, ease of administration, versatility of dosage forms and the higher levels of patient compliance. Nonetheless, this route of drug delivery poses some limitations, such as low retention times in the stomach, first pass metabolism in the liver, solubility of the drug in gastrointestinal fluids, drug permeability across biological membranes and poor control over drug release that may hinder oral bioavailability of the drugs.

This monograph focus on emerging trends in pharmaceutical dosage forms that are being developed to address some of these limitations.

The following dosage forms are discussed: Gastroretentive Floating Drug Delivery Systems, Medicated Chewing Gums, Pulsatile Drug Delivery Systems and Self-Microemulsifying Drug Delivery Systems.

For each one it is clarified the state of the art, the advantages and limitations, the parameters for evaluation of performance, the products available on the market and the regulatory considerations.

Keywords: New Drug Delivery Systems, Oral route, Bioavailability Enhancement, Patient Compliance, Gastroretentive Floating Drug Delivery Systems, Medicated Chewing Gums, Pulsatile Drug Delivery Systems, Self-Microemulsifying Drug Delivery Systems.

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LIST OF ABREVIATIONS

BCS	Biopharmaceutical Classification System
CG	Citroglycine
CO_2	Carbon Dioxide
Di-SGC	Di-Sodium Glycine Carbonate
DS	Drug substance
EC	Ethylcellulose
EOP	Elementary osmotic pump
Eur. Ph.	European Pharmacopoeia
FCC	Functionalized Calcium Carbonate
FDDS	Floating Drug Delivery Systems
FTIR	Fourier transform infrared
GET	Gastric emptying time
GIT	Gastrointestinal tract
GMP	Good manufacturing practices
GRAS	Generally Recognized as Safe
GRDDS	Gastroretentive Drug Delivery Systems
GRT	Gastric residence time
HBS	Hydrodynamic Balanced System
HLB	Hidrophilic-Lipophilic Balance
HPMC	Hydroxypropyl Methylcellulose

IVIC	*In vitro-in vivo* Correlation
LCST	Lower Critical Solution Temperature
LCTs	Long chain triglycerides
MCC	Microcrystalline cellulose
MCG	Medicated Chewing Gums
MCTs	Medium chain triglycerides
MMC	Migrating Myoelectric Complex
NDDS	Novel Drugs Delivery Systems
PDDS	Pulsatile Drug Delivery Systems
PEO	Polyethylene oxide
PNIPA	Poly(N-isopropylacrylamide)
PVA	Polyvinyl Alcohol
SEDDS	Self-Emulsifying Drug Delivery Systems
SMEDDS	Self-Microemulsifying Drug Delivery Systems
Smix	Surfactant:co-surfactant mixture
S-SMEDDS	Solid Self-Microemulsifying Drug Delivery Systems
USP	United States Pharmacopoeia

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1. INTRODUCTION

1.1. Pharmaceutical Contextualization

Since ancient times, human civilization is focused on finding medicines that can reach human's needs, concerning every single aspect of life and health (1). For thousands of years, drugs were based on natural resources with lack of scientific reasoning on the molecular structure of the drug substance (DS) that is responsible for the therapeutic effect (1, 2). The use of natural extracts was responsible for soothe or eradicate some diseases or symptoms (2), and medicine was practiced through observation and empiricism (1).

Nevertheless, it was only by the 19th Century that the pharmaceutical industry came up with more systematic and scientific practices (1). The constant growing of knowledge in terms of chemistry and biology came up through the 20th Century along with a technological revolution that provided more precise techniques of screening and evaluation (1 – 3). That allowed a better molecular control of the drugs that were manufactured and a better understanding on what was behind the pharmacological effect of those raw materials found in nature (2). Some of these drug exhibit pharmacological properties that are still recognized in the present times (1). After that, science progressed to a point at which large scale production of synthetic drug candidates proved to be economically feasible (2).

Two matchless achievements of pharmaceutical industry were the launch of Aspirin® by Bayer in late 19th Century and the commercialization of penicillin at the end of the Second World War, leading to a pharmacological explosion (3).

1.2. New Drug Delivery Systems

Over the years, pharmaceutical companies and scientists have been making efforts to find optimal drug delivery systems centered on patients' needs (5), in order to increase patient compliance and acceptability (4). Scientific developments had provided viable dosage alternatives that can be administered via different routes, such as oral, parenteral, transdermal, and mucosal (4). Among all routes of drug administration available, the oral route is the most convenient and promising delivery system (4 – 6), due to its non-invasiveness, ease of administration, versatility of dosage forms, relatively low cost of therapy and the higher levels of patient compliance (4 – 6). Around 50% of the available medicines in the market consist in oral drug delivery systems (6). Although there are many advantages in the oral delivery, there are some limitations that may hinder the oral bioavailability of the

drug substances. Those limitations include low retention times of the drug in the stomach, the hepatic first pass metabolism, solubility of the drug in gastrointestinal fluids, its permeability across biological membranes (5) and the poor control over release of the drug along with its potential side effects (4).

During the last decades efforts have been made to develop novel and more efficient oral drug delivery systems able to overcome the limitations of this route of drug administration, by releasing the drug after a predetermined time, in a predetermined place and at a controlled rate in a single dose (6).

One challenge in oral drug delivery is to increase the retention times in the gastrointestinal tract (GIT) and also to overcome the unpredictable gastric emptying rates (4, 7). Gastroretentive Drug Delivery Systems (GRDDS) are a good approximation to achieve that purpose (4, 7). Many approaches have been exploited for the development of GRDDS, such as floating systems, high-density systems, low-density systems, expandable systems, super porous hydrogel systems and mucoadhesive systems (4, 7). Among those, Floating Drug Delivery Systems (FDDS) will be discussed in this monograph. Those systems show a density lower of that of gastric fluids, thus remaining buoyant over the gastric contents while releasing the drug substance, without affecting the gastric emptying rate for a prolonged period (7). As a consequence, the drug shows higher bioavailability, being FDDS more advantageous for drugs absorbed in the upper parts of the GIT (7).

Medicated Chewing Gums (MCG) are a novel approach of drug delivery that is intended to be chewed but not swallowed, while the drug is slowly released in the oral cavity (8). The drug substance is meant to act locally in mouth diseases or to be directly absorbed into the systemic circulation by the jugular vein, thus allowing to overcome the first pass metabolism in the liver (8). Besides that, these drug delivery systems are advantageous because high plasma peak concentrations are avoided, reducing side effects of drugs (8). A great advantage of MCG, that increases patient compliance, is the possibility of a discrete administration without water (8).

Pulsatile Drug Delivery Systems (PDDS) are another type of dosage form addressed in this monograph. This drug delivery system is developed with an intimate connection to chronotherapeutics views, since some diseases display circadian variations of their symptoms (9, 10). PDDS allow to deliver the right dose of the drug at a specific time and in a specific local, providing spatial and temporal delivery (9, 10). This property results in an optimized

efficacy of the drug and a minimization of the side effects (9, 10). The drug release profiles are characterized by two phases: a lag time of no drug release, followed by a complete release within a short period of time (9, 10).

A high percentage of the new drug candidates are lipid drug substances, thus having poor water solubility and influences their oral bioavailability (5). This had turned attentions to dosage forms capable of delivering lipid drugs at reasonable rate and extent of oral bioavailability (5). In this monograph special attention is given to Self-Microemulsifying Drug Delivery Systems (SMEDDS) and to their solid forms, Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS). These drug delivery systems consist on mixtures of oil, surfactant, co-surfactant and drug substance, which spontaneously form transparent oil-in-water microemulsions upon contact with the aqueous medium of GIT and its motility (11). They have the advantages of presenting the drug substances in dissolved form by forming microemulsions with a droplet size of less than 50 nm, thus providing a large interfacial surface area for drug absorption (11).

1.3. Gastrointestinal Tract Anatomy and Physiology

The gastrointestinal tract consists on a tube of about seven meters long that includes the oral cavity, esophagus, stomach, small intestine and large intestine (12). The anatomical and physiological parameters of the GIT are depicted in Table 1.1. As it is possible to conclude, parameters such as anatomy, absorption characteristics, pH and microbial environment vary significantly along the distinct sections of the GIT (12, 13).

1.3.1. Oral Mucosa

The anatomy and physiology of oral cavity has been extensively reviewed (12). The oral cavity is composed by cheeks, hard and soft palates and tongue (see Fig. 1.1). The oral mucosa is relatively permeable and has a rich blood supply (16, 17), and microscopically can be subdivided in three layers as depicted in Fig. 1.2:

- Oral epithelium
- Lamina propria
- Sub-mucosa

The oral epithelium consists on a stratified squamous epithelium having a thickness of around 40 – 50 cell layers and a turnover time of around 5 – 6 days (16). The epithelium is mainly non-keratinized, but it is keratinized in areas subjected to mechanical stress such as gingivae and hard palate, which are relatively impermeable to water, in contrast with keratinized epithelia (16). Lamina propria and sub-mucosa are connective tissues (12).

The permeability of the oral mucosa is variable along the distinct regions of the oral cavity (16, 17), being measured by the permeability coefficient (17). This coefficient is a measure of how easily the drug can permeate a membrane (17), and is based on the relative thickness and degree of keratinization of the distinct tissues (16, 17), and the physicochemical properties of the drug (17). Thus, non-keratinized tissues show higher permeability, as well as thinner tissues.

Table 1.1. Parameters of the various segments of the gastrointestinal tract.

	Parameters					
Section	Average Length (cm) (13, 14)	Absorbing surface area (m^2) (13, 15)	Villi Present (12, 14)	Transit time of food (h) (14)	pH (14)	Microorganism (counts/g)[2] (15)
Oral Cavity	15 – 20	–	Absent	Short	5.2 – 6.8	–
Esophagus	25	–	Absent	Very short	5 – 6	–
Stomach	20	0.1	Scarcely present	0.25 – 3.00	1.3 – 3.5	10^2
Small Intestine	350 – 700	120 – 200	–	–	–	–
Duodenum	30	0.1	Scarcely present	1.00 – 2.00	4.6 – 6.0	10^2
Jejunum	300	60	Abundantly present	–	6.3 – 7.3	10^5
Ileum	400	60	Abundantly present	1.00 – 10.00	7.6	10^7
Large Intestine	90 – 150	0.35	–	–	–	–
Cecum	10 – 30	0.05	Scarcely present	Short	7.5 – 8.0	10^{11}
Colon	150	0.25	Absent	4 – 20	7.9 – 8.0	10^{11}
Rectum	15 – 19	–	Absent	Variable	7.5 – 8.0	–

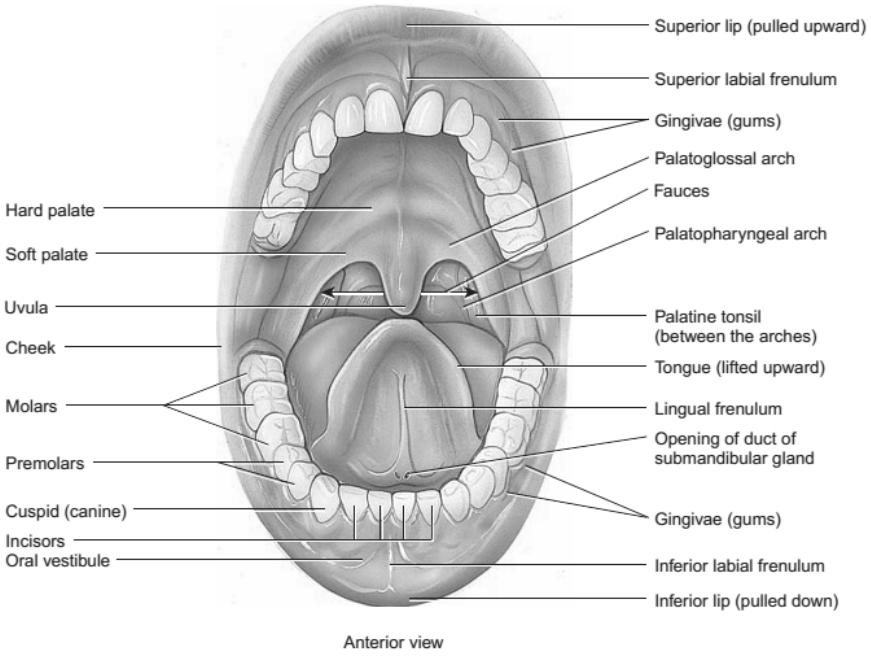


Figure 1.1. Schematic representation of oral cavity anatomy (12).

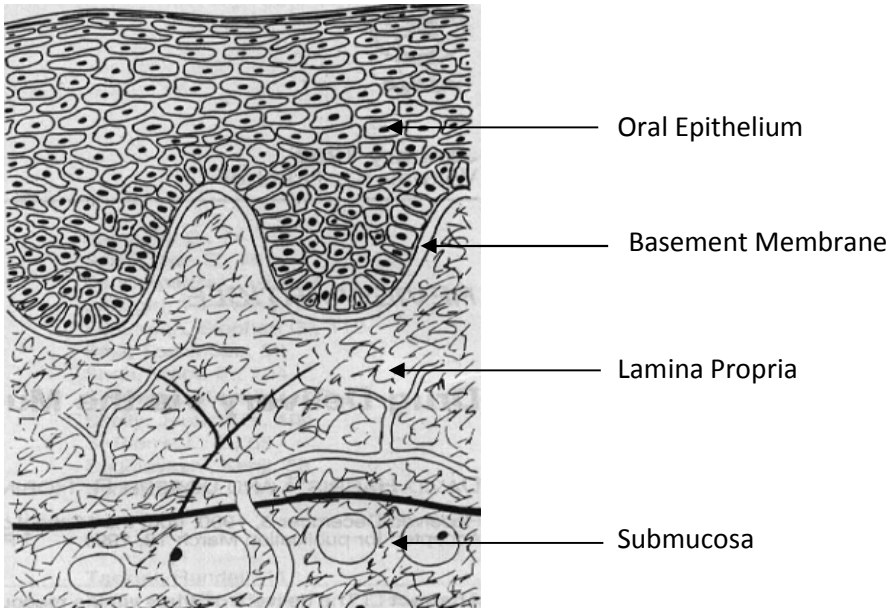


Figure 1.2. Schematic representation of the oral mucosa. Adapted from 16.

1.3.2. Stomach

The stomach is anatomically divided into four regions: cardia, fundus, body and antrum (pylorus) (12), see Fig. 1.3. It is a J-shaped expandable portion of the GIT located between the esophagus and the small intestine (12). It has the main functions of acting as a mixing chamber, as a reservoir of ingested food, and performs digestion of the meal contents to a liquid called chyme (12, 18). The digestion is both mechanical with aid of muscular contractions and chemical with aid of secretions (12). Then the chyme is forced through the pylorus into the duodenum at controlled slow rate in a phenomenon called gastric emptying (12, 18).

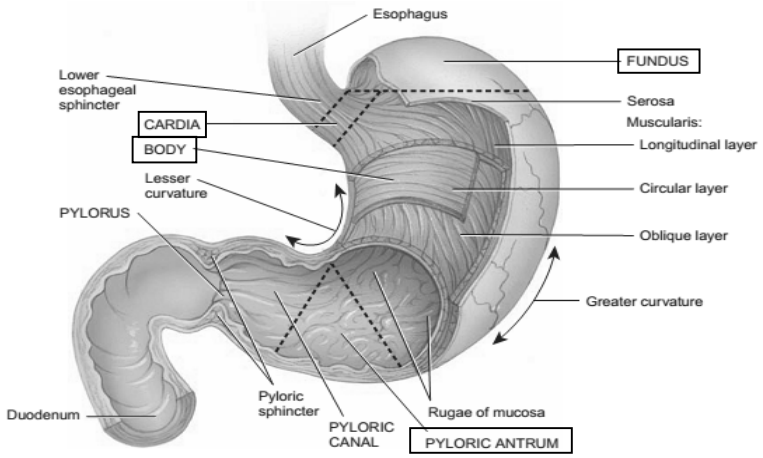


Figure 1.3. Schematic representation of Human stomach. Adapted from 12.

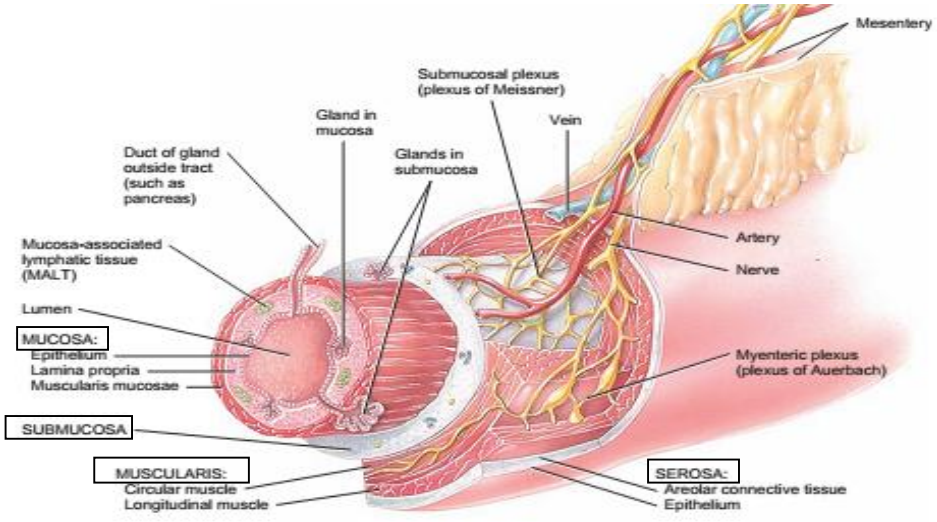


Figure 1.4. Schematic representation of Human gastrointestinal tract histology. Adapted from 12.

Histologically the wall of the stomach is similar to the other parts of the GIT (Fig. 1.4), except for the presence of an additional oblique layer of smooth muscle in the muscularis (12). In the fasted state, the stomach is empty and the mucosa lies in distinct large folds called rugae (Fig. 1.3).

1.3.3. Gastric Emptying

Gastric emptying takes place in both fasted and fed states, with distinct motility patterns in each state (14). During the fasted state a series of electrical events takes place between the stomach and the intestine every 2 – 3 hours, which is commonly called migrating myoelectric complex (MMC). The MMC is divided into the following 4 phases (14), see Fig. 1.5:

- *Phase I* (basal phase) is a quiescent period that lasts for 30 – 60 minutes with rare contractions.
- *Phase II* (pre-burst phase) lasts for 20 – 40 minutes and registers intermittent action potential and contractions, with gradual increase of intensity and frequency.
- *Phase III* (burst phase) lasts for 10 – 20 minutes and includes the housekeeper waves, which are intense and regular contractions for short period. It is responsible for sweep off the undigested materials from the stomach.
- *Phase IV* (transition phase) lasts for 0 – 5 minutes and is the transition period between phases III and I of two consecutive cycles.

After the ingestion of food, the pattern of contractions changes from fasted to that of fed state which is characterized by a continuous pattern of spike potentials and contractions, called postprandial motility (14).

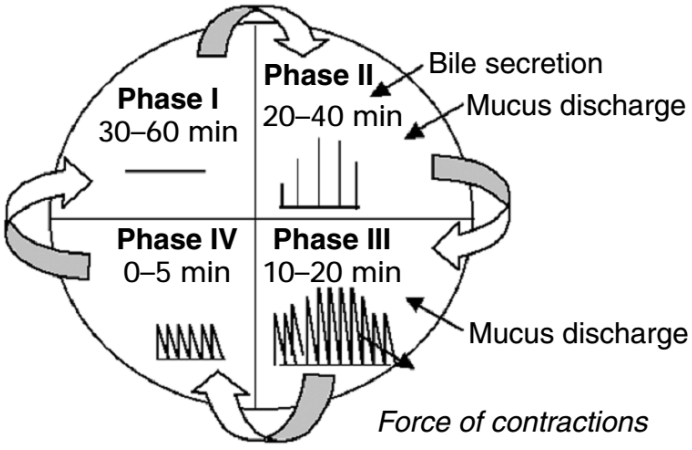


Figure 1.5. MMC and motility patterns of the GIT in the fasted state (14).

1.3.4. Gastric pH

The gastric pH is variable and may be influenced by many factors such as diet and feeding state (19), age (20), drugs and pathological conditions (21), all along with the intra and intersubject variations (19 – 23). It is reported that the mean value of gastric pH in fasted healthy volunteers is around 1.3 (20), due to the strong acidic secretions in the stomach (12), a value that raises approximately three units when a meal is administered (20). The pH in the duodenum rises when compared to the pH in the stomach. This is due to the secretion of bicarbonate by the pancreas (pH 7.1 – 8.2) that buffers the acidic chyme peristalted from the stomach (12). Along the small intestine the pH rises up to a value around 7.4 (23) and maintains a basic range of pH values in the large intestine.

1.4. Aim Of The Monograph

The main objective of this monograph is to discuss the state-of-art of novel pharmaceutical drug delivery systems that were developed in order to overcome some of the limitations of conventional dosage forms.

2. CHAPTER I

Gastroretentive Drug Delivery Systems

2.1. Gastroretentive Drug Delivery Systems

Physiological characteristics concerning short gastric residence time and unpredictable gastric emptying rates are a limiting issue that has to be taken into account when developing a suitable delivery system (24). Having this in mind, several attempts have been made to develop dosage forms capable of increasing the gastric residence time, leading to an increase of the oral bioavailability, to reduced chances of dose dumping and to enhance the solubility of drugs that are less soluble in high pH environments (25). Gastroretentive Drug Delivery Systems are an approach to reach this goal, since they are intended to be retained in the stomach for a prolonged time, for improving the therapeutic outcome of the drug substance (24, 25).

Investigation in academia and industry has been driven in distinct ways in order to achieve the better approach to prolong gastric residence time of drug delivery systems (25). In the present time several are the approaches to gastric retention found in literature, see Fig. 2.1. Besides that there are few Gastroretentive drug delivery systems available in the market (25). In this monograph it will be given special attention to a subtype of these dosage forms, the Floating Drug Delivery Systems (FDDS) which is one of the most frequent approaches studied, due to the absence of any adverse effect on the motility of GIT. Moreover, these novel dosage forms may be manufactured using conventional equipment (24). Those systems are intended to achieve a buoyancy state when in contact with gastric contents, taking advantage of the relative density between the drug delivery system and the gastric

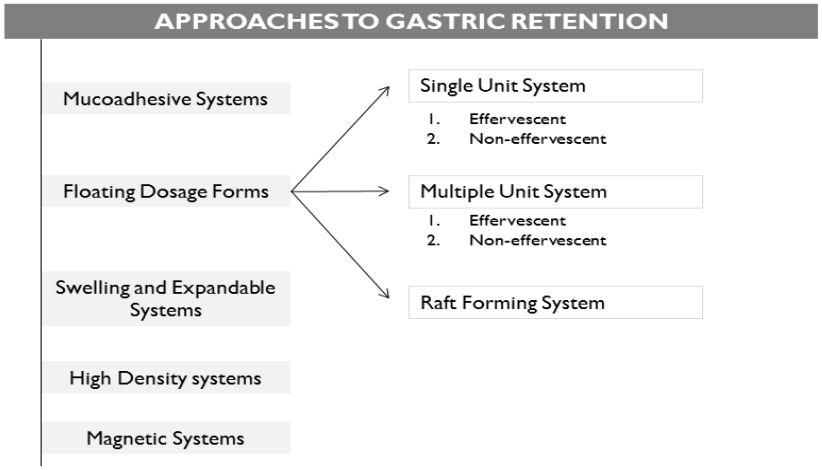


Figure 2.1. Different approaches to develop gastroretentive drug delivery systems (24, 25).

fluids (25). In this way it is possible to prolong the gastric residence time of the drug, thus increasing oral bioavailability without compromising the gastric emptying rate (24, 25).

2.2. Floating Drug Delivery Systems

Floating Drug Delivery Systems captured the attention of researchers and companies since the late 60's, after floating system was first described in 1968 by Davis (26). These are low-density systems designed to be retained in the stomach and to prolong the gastric residence time, delivering the drug slowly and in a desired rate, thus contributing to an enhancement of absorptive capacity of drug substances and consequently greater oral bioavailability (27). This is achieved by enabling a buoyant state, which is the capacity of the dosage form to float above gastric contents without compromising gastric emptying rate (25), of the dosage form in the stomach (27). To reach that state, a system with a density smaller than the density of gastric fluids may be achieved (27). As a matter of fact, those systems must have three main characteristics in the stomach: have a bulk density of less than 1 $g.cm^{-3}$, maintain its structural integrity and finally, the release of the drug should be constant, without affecting the gastric emptying rate (28). They are also eliminated when all the drug substance is released (25, 28). To achieve this buoyancy state different excipients have been investigated and will be referenced forward in this chapter.

When designing floating dosage forms it is of crucial importance to consider the factors affecting their buoyancy state, namely factors concerning the formulation parameters and the patient related variabilities (27, 28). It is also very important to have fundamental knowledge in anatomy and physiology of the GIT and to understand the process of gastric emptying (Introduction sections 1.3.2. – 1.3.4.), because they may affect FDDS efficacy (24). The floating formulation is intended to remain in the upper part of the stomach so that undesired gastric emptying can be more efficiently avoided. This makes the floating lag time, i.e., the time that the dosage form takes to float in the stomach after contact with gastric contents, a crucial variable to control (28, 29). Floating lag time has a relation of inverse proportionality with efficacy (29): the lower the time to achieve buoyancy state, the less the probability for dose dumping, enhancing the safety and the efficiency of the dosage form.

2.2.1. Classification and Manufacturing Processes

Floating Drug Delivery Systems can be classified in three categories, as shown in Fig. 2.1, according to the mechanism of buoyancy (30 – 32) taking into account that single and multiple unit systems can be both formulated:

I. Effervescent Systems
II. Non-effervescent Systems
III. Raft Forming Systems

It is important to retain the idea that single unit systems consist of an individual particle, while multiple unit systems consist on a conjugation of a large number of small sized particles, being developed as hollow microspheres (microballoons), granules, mini-tablets or pellets (28). It is more challenging to develop multiple unit systems and it usually requires more specialized equipment. In spite of that, multiple unit systems have advantages over single unit systems such as reduction of the risk of dose dumping by avoidance of *all-or-none* gastric emptying of the dosage form, uniform release of the drug substance and reduction of intra and intervariability in absorption (32, 33). These advantages allow an enhancement of the absorption efficacy (32).

I. Effervescent Systems

Effervescent systems remain buoyant due to their low density as a result of gas generation and entrapment inside the dosage form (28). These systems include matrices with swellable polymers such as methylcellulose, hydroxypropylmethyl cellulose (HPMC) and chitosan based polymers, effervescent agents, which include gas generating agents such as carbonates and bicarbonates (e.g. sodium bicarbonate) and organic acids such as citric and tartaric acid, or chambers containing a liquid, such as ether or cyclopentane, that gasifies at body temperature (37 °C) (27, 28, 30, 34). This makes effervescent systems able to be classified in two categories, according to the formulation type:

A. Gas Generating Systems

These systems are formulated in a way that when in contact with acidic gastric fluids, carbon dioxide, CO_2, is generated and remains entrapped inside the dosage form (Fig. 2.2A) (28,

34). This *in situ* CO_2 generation is responsible for the buoyancy state of the dosage form, since density decreases below 1 $g.cm^{-3}$, and is a result of the reaction between gas generating agents and the organic acids present in the formulation, empowered by the absorption of water by the dosage form (27, 30).

Intra Gastric Single Layer Floating Tablets or *Hydrodynamically Balanced System (HBS)*. The basic principle behind the formulation of these systems is to develop a matrix consisting of an intimate mix of the drug substance and CO_2 generating agents (Fig. 2.3). When these type of tablet dosage forms (27) contact with gastric fluids, an effervescent reaction occurs. This leads to the generation of a gas that is entrapped in a jellified hydrocolloid layer of the system (Fig. 2.4A). Alternatively, it is also possible to develop capsular dosage forms (28) based on a similar mechanism: the drug is mixed with gel-forming hydrocolloids encapsulated

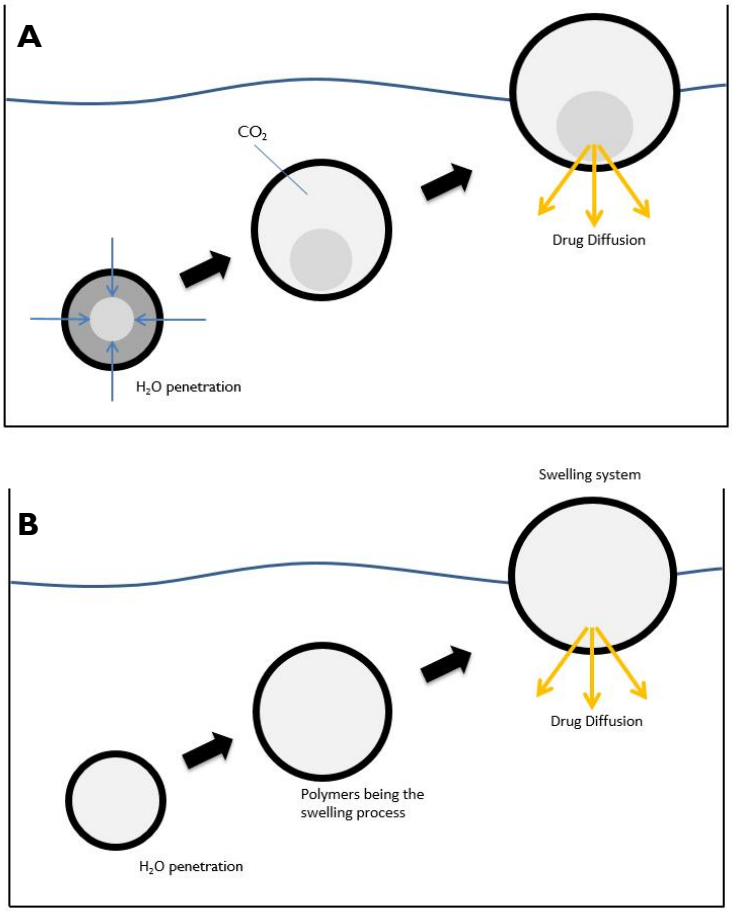
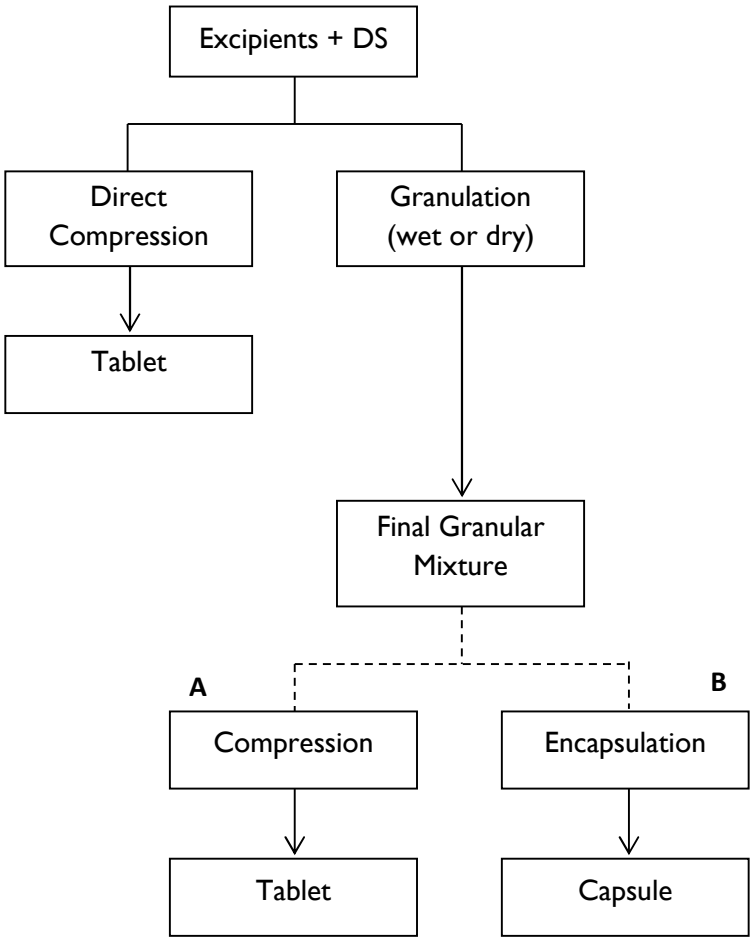


Figure 2.2. Schematic diagram of Intragastric Single Layer Drug Delivery Systems manufacturing process: (A) tablet dosage forms and (B) capsular dosage forms (35).



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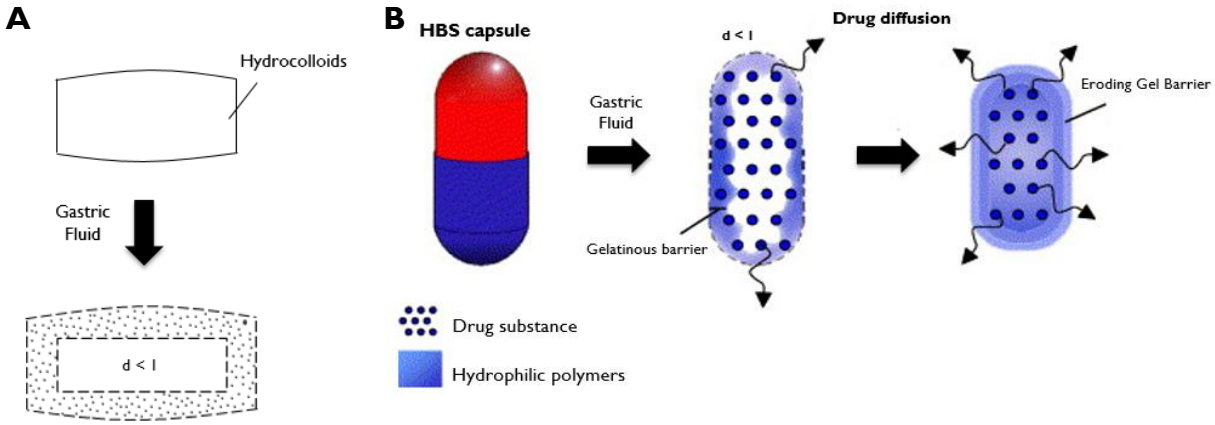

Figure 2.4. Formulation and mechanism of action of Intragastric Single Layer Drug Delivery Systems, (A) in tablet dosage forms (27) and (B) in capsular dosage forms. Adapted from 28.

in a soluble capsule shell. After administration, the capsule shell dissolves and its interior is exposed to the gastric fluids (28). Then the hydrophilic polymers swell to form a gelatinous barrier which is responsible for the buoyancy state (Fig 2.4B). In both cases the drug is released by diffusion and erosion of the gel barrier.

Intra Gastric Bilayer Floating Tablets. These tablets are similar to those previously described but with the particularity of containing two layers (27): a first layer, which immediately releases an initial dose of the drug for the system, and a second layer that absorbs gastric fluids, forming a colloidal gel barrier on its surface that releases the drug in a sustained way (Fig. 2.5). The manufacturing process is identical to that of intra gastric single layered tablets, but includes an additional step: when the single layer floating tablet is developed, a second compression takes place to add the immediate release layer (36, 37). This step makes the process more complex (36, 37). All bibliographic sources consulted refer to the use a single punch compression machine for the second compression.

Multiple Unit Type Floating Pills. The concept sustaining this multiple unit floating dosage form is the development of sustained release pills as *seeds* surrounded by double layers (Fig. 2.6), which float as a consequence of CO_2 generation (29), showing a buoyant behavior as described in Fig. 2.2A. While the inner layer includes the effervescent agents, such as sodium bicarbonate and tartaric acid, being segmented in two sub layers in order to avoid direct

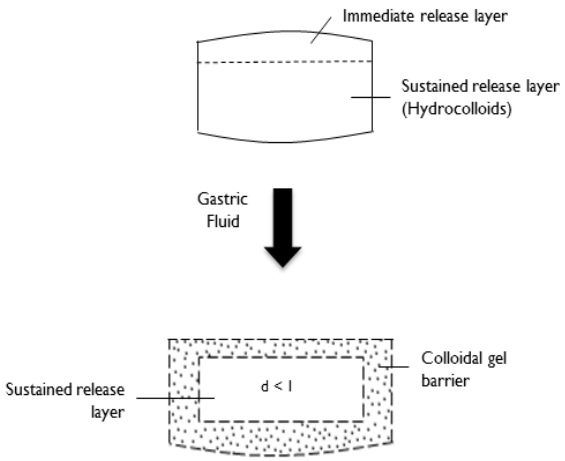

Figure 2.5. Formulation and mechanism of action of Intragastric Bilayer Drug Delivery Systems (27).

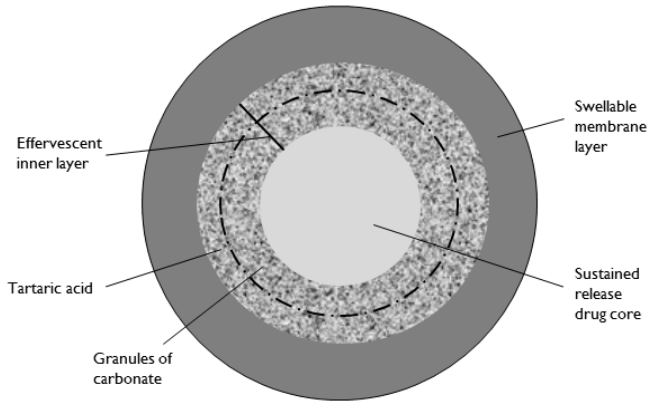

Figure 2.6. Formulation of multiple unit floating pills as *seeds* (29).

contact between distinct effervescent excipients (29), the outer layer includes swellable polymers, such as polyvinyl alcohol (PVA) and shellac (30, 34). Once in contact with the dissolution medium at body temperature, the system sinks in the solution. At that point, the solution permeates into the effervescent layer through the swellable layer (29). Consequently, gas generation by the neutralization reaction between the two effervescent excipients in the dosage form takes place, allowing the buoyant state and forming swollen pills like balloons (27, 29). These delivery systems are able to be designed by multiple coating of non pareil seeds in a fluid bed granulator (38), as described in Fig. 2.7, and may be further inserted into capsules (by capsule filling) or converted to tablets (by powder direct compression) containing a variable number of these pills (39).

B. Volatile Liquid/Vacuum Containing System

This formulation consists of a matrix containing a chamber or a reservoir that inflates in the acidic environment of the stomach, allowing the flotation of the dosage form (34). Distinct approaches are possible to be developed, as referred in literature, and are described below.

Inflatable Gastrointestinal Drug Delivery System. These systems consist on a biodegradable gelatin capsule filled with an inflatable chamber in a drug reservoir that can be a drug impregnated polymeric matrix (Fig. 2.8). The inflatable chamber incorporates liquid ether that gasifies at body temperature. It is the process of forming a gas that is responsible for the

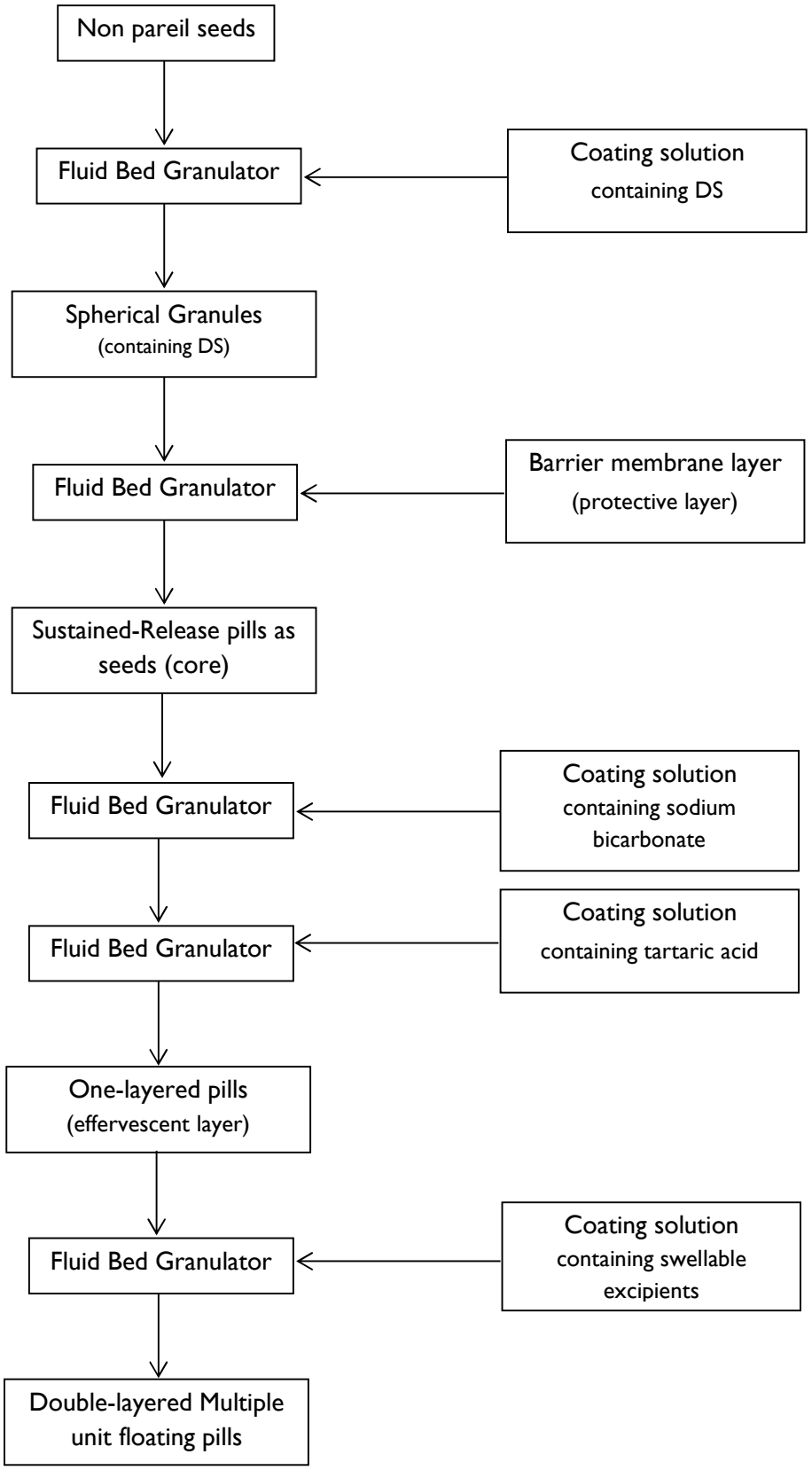

Figure 2.7. Schematic diagram of multiple unit floating pills manufacturing process (38).

fluids the capsule disintegrates to release the drug reservoir together with the inflatable chamber (27). As a consequence, the chamber inflates allowing drug reservoir to be retained in the stomach while releasing the drug continuously into the stomach (27). After the drug release the system leaves the stomach. It was not possible to find any information regarding the manufacturing process of such drug delivery systems.

Intra Gastric Osmotically Controlled Drug Delivery System. This system consists on an intragastric osmotically controlled drug delivery device, comprising an inflatable floating support and an osmotic pressure controlled drug delivery device, loaded in a biodegradable capsule (Fig. 2.9). The inflatable floating support contains a biodegradable plug that erodes after a predetermined time in order to deflate the support (27). The osmotic pressure controlled drug delivery device consists of two components: a) a drug reservoir compartment, which is enclosed by a pressure responsive collapsible bag impermeable to liquid and vapor and has a drug delivery office, and b) an osmotically active compartment, which is enclosed within a semipermeable housing and contains an osmotically active salt (29). After oral administration the dosage form enters the stomach and contact with gastric fluids. At this moment, the capsule disintegrates and releases the intragastric osmotically controlled drug delivery device (27). Then the inflatable chamber forms a hollow polymeric bag that contains a liquid, such as ether or cyclopentane that gasifies at physiological temperature to produce a gas, being responsible for the floating behavior of the dosage form (27). The water in the gastric fluids is then absorbed through the semipermeable membrane into the osmotically active compartment and dissolves the osmotically active salt (27). This process creates an osmotic pressure that acts in the collapsible bag and forces the drug reservoir compartment to reduce its volume (27). Then it releases the drug solution formulation into the gastric environment through the delivery orifice, enhancing its bioavailability (27). After a predetermined time, the vapor escapes from the device and the deflated drug delivery system is emptied from the stomach (27, 29). Again, it was not possible to find any information regarding the manufacturing process of such drug delivery systems.

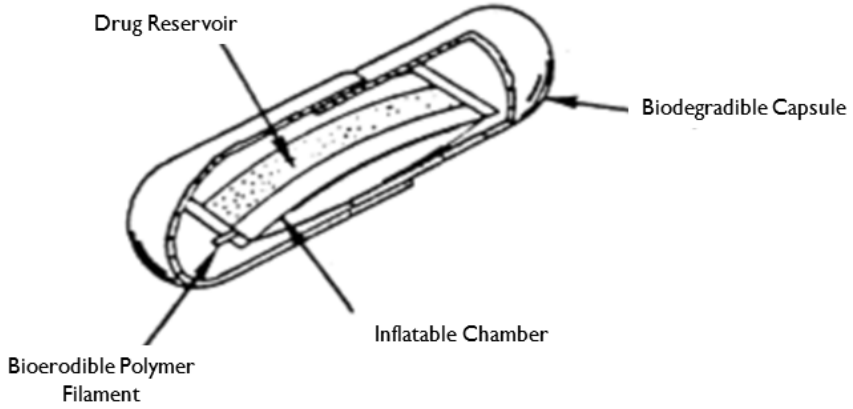

Figure 2.8. Inflatable Gastrointestinal Drug Delivery System. Adapted from 27.

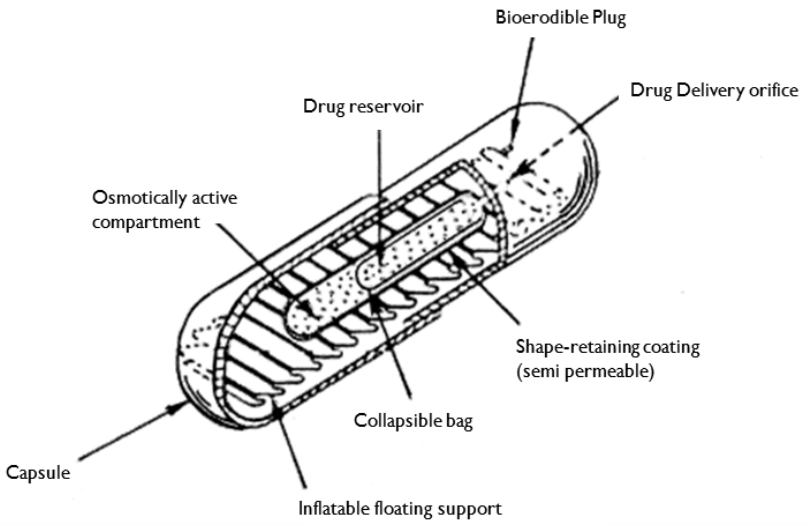

Figure 2.9. Intragastric Osmotically Controlled Drug Delivery System (29).

II. Non-Effervescent Systems

Floating non-effervescent dosage forms are based on a mechanism of swelling of polymers due to their soaking and capacity to absorb water, when in contact with gastric fluids after oral administration (29, 30, 32 – 34). As a consequence they remain buoyant and are retained in the stomach while releasing the drug substance. The most commonly used polymers are gel forming or highly swellable cellulosic type hydrocolloids (e.g. hydroxyl ethyl cellulose (EC), HPMC and sodium carboxymethyl cellulose), polysaccharides and matrix forming polymers (e.g. polycarbonates, polyacrylates and polystyrene) (29, 30, 32 – 34, 36)

as well as bioadhesive polymers such as chitosan and carbopol (34). Those excipients are incorporated in high level, from 20 to 75% w/w, in tablets and capsules (32). The general mechanism of floating of swellable non-effervescent systems is described in Fig 2.2B.
Floating non-effervescent systems are able to be developed as tablets and capsules, and also as multiple unit system approaches, such as alginate beads or hollow microspheres (29).

Single Layer Floating Tablets/Colloidal Gel Barrier Systems. The formulation of this dosage form consists on the intimate mix of the desired drug substance with the gel-forming hydrocolloid (27, 34). The system maintains a bulk density lower than 1 $g.cm^{-3}$ due to the air entrapped in the swollen polymer after contact with gastric fluids, allowing the dosage form to remain buoyant (27, 34). The gel barrier formed after contact with water controls the rate of fluid penetration and consequent release of the drug substance (34). Visually this dosage form is identical to Fig. 2.4A in case of tablets, and Fig. 2.4B in case of capsules, and the manufacturing process is identical to that of HBS (Fig. 2.3) with the excipient differences.

Bilayer Floating Tablets. These systems contain two distinct layers with two distinct functions. The immediate release layer is responsible for the release of an initial dose of the drug from the system (27). On the other hand, the sustained release layer absorbs gastric fluids, consequently forming an impermeable colloidal gel barrier on its surface (27). This allows the system to remain buoyant in the stomach with a density lower than 1 $g.cm^{-3}$. Visually this dosage form is identical to Fig. 2.5 and the manufacturing process is also identical to that of intra gastric bilayer tablets, except for the differences in the excipients used in the formulation.

Microporous Compartment Systems. The formulation of this dosage form consists on the encapsulation of a drug reservoir inside a microporous compartment, as depicted in Fig. 2.10, whose top and bottom walls show apertures that allow water penetration to dissolve the drug and to make it available for absorption (34). Having the peripheral walls completely sealed it is crucial to prevent contact between undissolved drug and gastric mucosa (34). The flotation chamber containing entrapped air is responsible for dosage form floating behavior in stomach. It was not possible to find any information regarding the manufacturing process of such drug delivery systems.

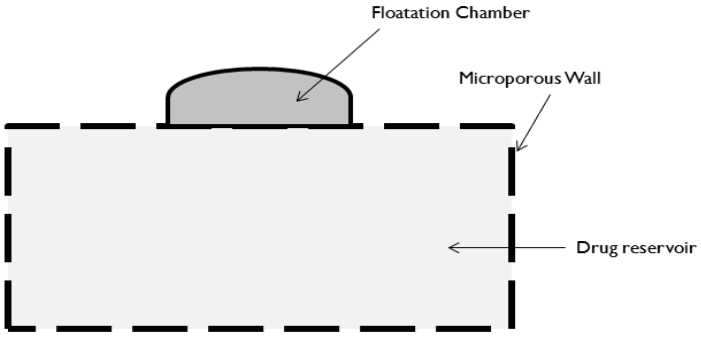

Figure 2.10. Microporous Compartment System (30).

Floating Beads/Alginate Beads. Alginate beads are floating multiple unit systems (27). Most of literature works and reviews describe alginate beads prepared by the freeze drying method (40). Spherical floating beads of 2.5 mm in diameter are obtained by dropping a sodium alginate solution into aqueous calcium chloride, leading to the precipitation of calcium alginate (40). The beads are then separated, snap-freezed with liquid nitrogen before being freeze-dried at -40°C for 24 hours (40). The result is a porous system which remains buoyant in the stomach for over 12 hours and has a prolonged gastric residence time of more than 5.5 hours (40). But the method used for production of alginate beads is not suitable for application in conventional pharmaceutical companies, since it requires sophisticated specific equipment or conditions usually not available.

Hollow Microspheres. Hollow microspheres, also called microballoons, are multiple unit systems of floating dosage forms able to float over gastric contents (41). This type of FDDS consists of low-density spherical porous empty particles without core (Fig. 2.11), having a size less than 200 μm and the drug dissolved or dispersed throughout the particle matrix (41). When in contact with gastric fluids, the polymers (such as chitosan, Eudragit, polycarbonates and others) of the formulation hydrate and form a colloidal gel barrier that controls fluid penetration and consequent drug release (41). Hollow microspheres are commonly prepared by solvent diffusion and evaporation method, as described in Fig. 2.12, to create the hollow inner core (33). In this method the polymer is dissolved in an organic solvent and the drug is dissolved or dispersed in the polymer solution (41). Then, the solution containing the drug is emulsified into an aqueous phase containing PVA to form stable oil in water (o/w) emulsions (41). Then the organic solvent is evaporated by increasing

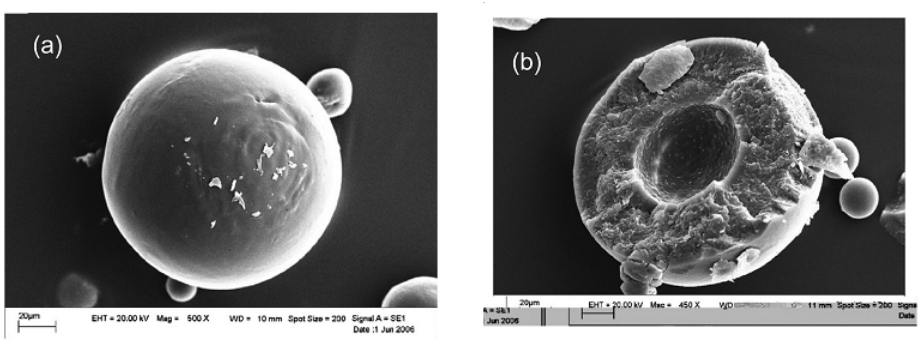

Figure 2.11. SEM photographs of (a) outer surface of a hollow microsphere, (b) inner surface of a broken half of a hollow microsphere. Adapted from 42.

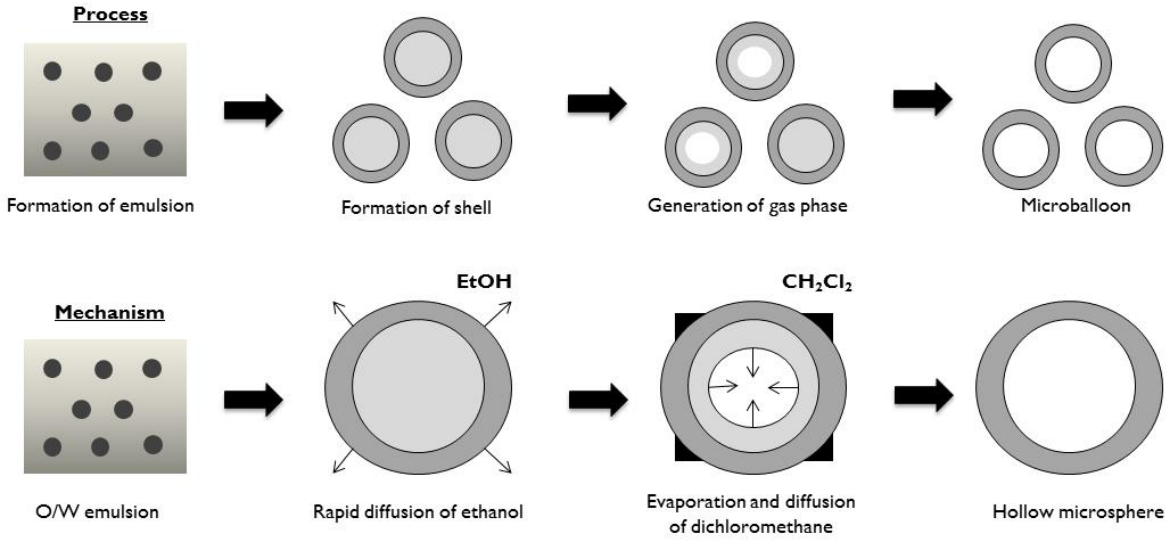

Figure 2.12. Preparation of hollow microspheres by emulsion-solvent dissolution method and mechanism of microballoon formation (33, 42).

the temperature under pressure or by continuous stirring (41). This leads to polymerprecipitation at the o/w interface of droplets, forming a cavity and thus making them hollow to impart the floating properties (41). Alternatively, emulsion solvent diffusion method can be applied to develop hollow microspheres loaded with drug in their outer polymer shell (43). In this case, a solution of drug and polymer, dissolved in an ethanol-dichloromethane mixture, is poured into an agitated aqueous solution of PVA, with stirring to form o/w emulsion droplets (43). The ethanol rapidly partitions into the external aqueous phase while the polymer and the drug are induced to precipitate on the outer surface of the droplets (43). The remaining dichloromethane enclosed in the droplets suffers evaporation

and diffusion, leaving an air cavity inside the spheres (43). At this point we have hollow microspheres developed.

III. Raft Forming System

The floating concept can also be applied in the development of various anti-reflux formulations, called raft forming systems (31, 44). This name is a result of the capacity of these systems to expand and form a foam continuous layer called a raft on the surface of gastric contents (Fig. 2.13), blocking the possibility of gastric reflux into the esophagus (31, 44). When in contact with acidic gastric fluids, the system forms a viscous cohesive gel *in situ*, wherein each portion of the liquid swells forming a continuous layer upon the gastric content, containing entrapped CO_2 (44). The floating properties of the raft formed are result of its low bulk density created by effervescent formation of CO_2. When the entire drug content is released, at specific desired rate, the system is emptied from the stomach. These systems can be formulated as liquid (29) or as tablets (31). The development of raft forming tablets (31) may be similar to that found in Fig. 2.4, taking into account all excipient and active ingredient's needs.

I find it important to mention that Fig. 2.4 represents just a basis of tablet or capsules manufacturing process. There might be a need to add further steps or shorten steps, accordingly to the formulation characteristics and needs (45). The choice of a method requires throughout investigation in many distinct ways.

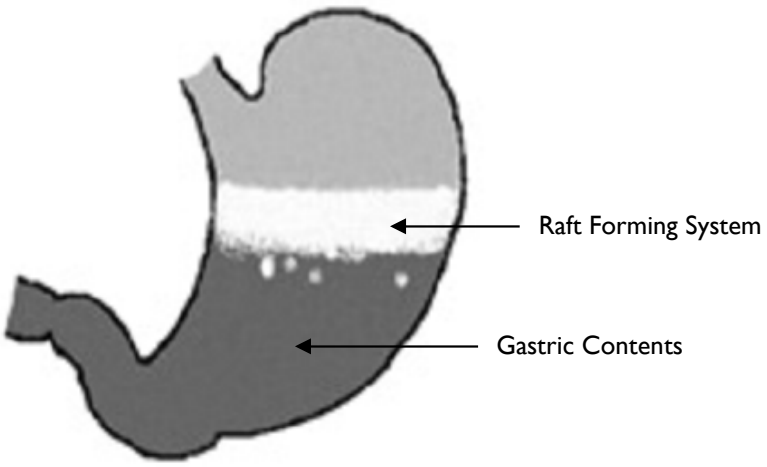

Figure 2.13. Raft forming system mechanism of action. Adapted from 44.

From the distinct types of floating dosage forms described above, only few are possible to develop with pharmaceutical conventional equipment. This group includes all effervescent gas-generating systems, taking into account the need of a single punch compression machine in case of intra gastric bilayer floating tablets, the non-effervescent colloidal gel barrier systems and bilayer floating tablets, also requiring a single punch tableting machine, hollow microspheres (besides the requirement for very specific development conditions (33, 43)) and raft forming systems in the form of tablets. On the other hand, the remaining dosage forms may need non-conventional manufacturing equipment or the processes of development were not found. This group includes all effervescent volatile liquid or vacuum containing systems, and non-effervescent alginate beads because of the need of some specialized equipment, namely needle gauges and the equipment used in snap-freezing and freeze-drying methods (40).

2.2.2. Suitable Drugs and Main Excipients Used In Formulation

As expected not all drug substances are ideal to be included in floating dosage forms. There are some important specific characteristics of drug substances that researchers should consider for the development of such systems. Those characteristics are selection criteria for potential development of FDDS and are enumerated below (27, 32, 33):

1. Drugs having incomplete absorption due to a narrow absorptive window in GIT, such as riboflavin in a vitamin deficiency and levodopa;
2. Drugs with site-specific absorption in the stomach or upper part of the small intestine, such as chlordiazepoxide and cinnarazine;
3. Drugs which have local therapeutic action in the stomach, such as antiacids, misoprostol and antibiotics against *Helicobacter pylori*;
4. Drugs that disturb normal colonic bacteria, such as amoxicillin trihydrate;
5. Drugs having low stability in the lower parts of GIT, such as metronidazole and diazepam.

Table 2.1 summarizes the drug substances tested FDDS research and development. As we can see the majority are developed in the form of tablets and capsules for oral delivery.

Besides choosing the most appropriate dosage form for each drug substance, when developing novel dosage forms it is crucial to include the most adequate excipients in the formulation (46), in order to achieve the best target product profile. This is even more important when we are discussing novel dosage forms with such an impact in the pharmacokinetic profile of the drug substances (46). The combination of the drug substance and the most appropriate and compatible excipients allows the development of dosage forms with the desired properties But the process of achieving an adequate formulation is complex and takes a long time to perform the necessary research studies (46). In a single study several distinct formulations may be evaluated, being studied distinct ratios and concentrations of polymers and other excipients.

Table 2.2 enlists the excipients most widely used in FDDS formulations, according to its principle and main function. Low-density inert fatty materials, used in proportions from 5% to 75% (34), can decrease the hydrophilic property of the formulation and also increase buoyancy (34). Effervescent agents are used in gas generating systems dosage forms, accordingly to the classification of FDDS. Release rate accelerants and retardants, in proportions from 5% to 60% (34), are used to control the release rate of the drug

Table 2.1. Drug substances used in formulation of FDDS according to dosage form (27, 31, 41).

FDDS dosage form	**Drugs included in floating dosage forms**
Tablets	Acetaminophen, Acetiylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Captopril, Ciprofolxacin, Chlorpheniramine maleate, Cinnariziine, Furosemide, 5-Fluorouracil, Isosorbide mononitrate and dinitrate, Diltiazem, Nimodipine, Prednisolone, Quinidine, Riboflavin, Sotalol, Varapamil HCl,
Capsules	Nicardipine, L-Dopa and benserazide, Chlordiazepoxide HCl, Propanolol HCl, Diazepam, Furosemide, Misoprostal, Urodeoxycholic acid
Films	Cinnarizine, Drug Delivery Device
Microspheres	Acetylsalisylic acid, Verapamil, Ibuprofen, Terfenadine, Ketoprofen, Tranilast
Granules	Indomathacin, Diclofenac Sodium, Prednisolone

Table 2.2. Examples of polymers and other excipients used in the formulation of FDDS (25, 27, 28, 32, 34, 41).

Type of Excipient	Examples	Range of concentration (%)	Effect on the formulation
Polymers	HPMC, Eudragit polymers, Calcium alginate, Croscarmellose Sodium, Sodium alginate, Propylene foam, EC, poly methyl methacrylate, Methocel K4M, polyethylene oxide, β-cyclodextrin, CMC, PEG, polycarbonate, PVA, HPC-L, HPC-H, HPC-M, CP 934P, Metolose S.M. 100, PVP, polyox, acrylic polymer, xanthan gum, guar gum, carbopol, polyvinyl acetate, agar	-	-
Inert Fatty Materials	Beeswax, fatty acids, long chain fatty alcohols, Gelicures 39/01 and 43/01	-	Decrease hydrophilic properties and enhance the buoyant capacities
Effervescent Agents	Sodium bicarbonate, citric acid, tartaric acid, Di-Sodium Glycine Carbonate (Di-SGC), citroglycine (CG)	-	Gas generation in effervescent FDDS
Release Rate Accelerants	Lactose, mannitol	5-60	Increase the release rate of drug substance
Release Rate Retardants	Dicalcium Phosphate, talc, magnesium stearate	5-60	Decrease the release rate of drug substance
Buoyancy increasing agents	EC	Up to 80	Enhance the buoyant capacities
Low Density Materials	Accurel MP 1000	7 – 75	Enhance the buoyant capacities

substances, as the name suggests. Buoyancy increasing agents, used up to 80% (34), are used to enhance the buoyant capacities of the dosage form, as much as low density materials (34). It is crucial that companies have conditions to store excipients accordingly to each ones specifications in order to avoid stability problems.

Recently, Eberle *et al* (48) described a pharmaceutical excipient showing great and improved buoyancy characteristics suitable for the preparation of floating tablets and for the development of future innovative FDDS: functionalized calcium carbonate (FCC). This excipient is highly porous and has an inherent low apparent density, approximately 0.6 $g.cm^{-3}$ that enables a mechanism of buoyancy of tablets with no lag time, showing almost instant flotation (48). Additionally, it has a higher specific surface, approximately 70 m^2, which allows sufficient hardness for further processing. FDDS based on FCC appear to be promising (48).

2.2.4. Factors Affecting the Floating Process

Making a reliable and predictable gastroretentive formulation, in particular FDDS, is a very difficult process since its success depends on formulation and idiosyncratic factors that influence the gastric retention time of the oral dosage form (32).

The formulation factors, as the name suggests, are related to composition of the dosage form, such as the polymers and excipients selected, the characteristics of powders and dosage forms obtained, and others (32). Below it is a description of the formulation factors mentioned in literature.

1. **Density**. The buoyant properties of floating dosage forms are dependent on the density of the dosage form. It is required a density lower than gastric contents (<1 $g.cm^{-3}$), to exhibit floating properties in order to increase gastric residence time (28, 44).

2. **Size**. The size of the dosage form is very important to increase gastric retention of floating dosage forms. It is mandatory to have a size small enough to pass through the esophagus and larger enough not to be emptied from the stomach into the intestine (28, 44). Besides that, the size is reported to be more important in non-floating

dosage forms, once floating dosage forms adopt a buoyant behavior when in contact with gastric fluids and this is registered regardless their sizes (32).

3. **Shape**. Studies in beagle dogs reported that tetrahedron ring shaped dosage forms (over 6 distinct shapes) exhibit higher gastric retention. A further study was conducted in human volunteers in order to confirm the results. It was demonstrated an 100% gastric retention of tetrahedron dosage forms at 24 hours in beagles, but only one of the human volunteers showed 12 hours retention of the dosage form in the stomach (48). Further studies should be carried out to determine if effectively tetrahedron shaped dosage forms are the most suitable for larger gastric retention times.

4. **Viscosity grade of polymer**. Viscosity of polymers and interactions (between excipients and water) are determinant for the drug release and floating properties of these formulations (49). Concerning floating properties, it is reported that low viscosity polymers are more beneficial than high viscosity polymers, and that the drug release rate increases when the polymer viscosity decreases (49).

5. **Single or multiple unit of dosage form**. As referred previously in this monograph, a multiple unit dosage form shows several advantages over single unit dosage forms. This is determinant for the efficiency of dosage forms because multiple unit formulations allow the co-administration of units with distinct release profiles or drug substances, they have a more predictable behavior and show a shorter margin of failure when compared to single unit formulations.

Otherwise, idiosyncratic factors are related to what concerns human physiology and factors influencing the performance of drug administration and processing (32). At this point it is crucial to understand that the gastrointestinal movements play an important role in the efficacy of each drug delivery device, as much as pharmacokinetic and pharmacodynamic properties (46). Below it is a description of the most important idiosyncratic factors described in literature:

1. **Gender**. Women have slower values of ambulatory gastric emptying than men when comparing people of both genders with the same age and also the gastric resident

time of dosage forms in higher in females, regardless of weight, height or body surface area (50).

2. **Age**. The aging process is associated with alterations in body functions and metabolism. It is reported that elderly, especially those over 70, have significant prolonged gastric residence time than younger individuals (50). This result was obtained with healthy elderly individuals in a way that the effects of aging are separated from disease state (50).

3. **Posture**. Mojaverian *et al* (50) reported no significant difference in the GRT of individuals in ambulatory upright and supine positions. Otherwise, it is reported that floating dosage forms have more probability to suffer undesired and faster emptying from the stomach in supine position, while in the ambulatory upright position floating dosage forms remain buoyant above gastric contents irrespective of its size and thus showing prolonged gastric residence time (30).

4. **Disease state**. Literature reports some disease conditions that may affect drug action and delivery including floating dosage forms, namely Crohn's disease, an inflammatory bowel disease that can affect any part of the GIT, diabetes, gastric ulcer and others (31, 44).

5. **Concomitant intake of drugs**. Concomitant administration of drugs or pharmaceutical excipients, which modify motility of GIT and gastric emptying rate, may affect the performance of FDDS (32). These type of drugs include prokinetic agents (e.g., metoclopramide and cisapride), anti cholinergics (e.g., atropine or propantheline) and opiates (e.g., codeine) (32).

6. **Meal Composition**. The caloric density of a meal plays an important role in controlling gastric emptying rate in humans and it is reported that this relation is independent of the nature of calories (51). As long as the caloric density is the same, it does not make difference whether the meal has high content of proteins, fat or carbohydrates (51). The nature of meals also has implications in gastric emptying rate. The motility pattern of the stomach can be changed to a fed state by feeding of indigestible polymers or fatty acid salts, thus decreasing the gastric emptying rate and prolonging drug release and enhancing drugs oral bioavailability (31, 34).

7. **Feeding Regimen**. The presence or absence of food (fed and fast state, respectively) in the stomach and the frequency of feed are factors that influence gastric residence time of the dosage forms. As referred on the Introduction (Section 1.3.3. and Fig. 1.5), in fasting conditions the gastric motility is characterized by strong motor activity that occurs every 2 to 3 hours, and it sweeps the undigested material from the stomach. If the time of administration of a dosage form coincides of that of MMC, the gastric retention time of the device is expected to be very short (34). Otherwise, in the presence of food, as MMC is delayed, gastric residence time of dosage forms is considerably longer, and it increases drug absorption (30, 34).

As formulation factors are relatively easy to adapt and control, idiosyncratic factors are the most problematic since they are exposed to intra and intervariability and most of the times are difficult to predict. Finding the better formulation that allows overcoming the difficulties imposed by both factors can be an expensive and long process, as investigation may go by several years. Idiosyncratic and formulation factors may not be studied independently, but interdependently in order to achieve the best and more efficient formulation.

2.2.4. Advantages and Limitations

There is a wide range of advantages sustaining the development of floating delivery systems over conventional dosage forms. Although some of those advantages are exclusive of FDDS, others are shared with other drug delivery systems. The advantages are:

- In case of vigorous intestinal movement and diarrhea, FDDS are advantageous because they remain buoyant at the surface of gastric contents, avoiding undesired emptying (30, 32, 34).

- FDDS are advantageous for drugs acting locally in the stomach, such as antacids, or in the proximal part of the small intestine, and for drugs that act in gastrointestinal diseases such as esophageal reflux, and for drugs absorbed through the stomach, such as ferrous salts (30, 32, 34). In those cases, there is an improvement of drug absorption due to a prolonged gastric retention time and prolonged time of the dosage form in the absorption site (34).

- May increase patient compliance by decreasing dosing frequency (30).
- Prolonged release floating dosage forms, especially tablets and capsules, will allow dissolution of the drug substance in the gastric fluids (32). Consequently they will be available for absorption in the small intestine after emptying of gastric contents. This implies that the drug remains in solution for prolonged time even at alkaline pH of the intestine (30, 32).
- The fluctuations in plasma drug concentrations are minimized as much as it is possible to prevent concentration-dependent adverse effects that are associated with peak plasma concentrations of drugs (32).
- Multiple unit systems have advantages over single unit systems: there is a smaller risk of dose dumping and can ensure an uniform drug release (33).

Nonetheless, FDDS have also some limitations that must be taken into account since they may affect the performance and viability of the system. The limitations are:

- These dosage forms are not appropriate for drugs that irritate the gastric mucosa because of their prolonged gastric residence time (34).
- Gastric emptying of FDDS is influenced by factors such as gastric motility, pH and presence of food, which vary significantly from one person to another and compromises a precise prediction of the buoyant behavior (34).
- Floating formulations require a sufficient amount of fluids in the stomach to achieve a buoyant state and work efficiently (21, 32, 34) and also require the presence of food to delay their gastric emptying, in order to increase bioavailability of the drug substance (34).
- Drug substances showing low stability and solubility in acidic gastric fluids or in the GIT are not appropriate to be incorporated in floating systems (31, 32, 34).

- Drugs that undergo extensive first-pass metabolism are not desirable candidates for the preparation of buoyant dosage forms, because the slow gastric emptying may result in low systemic bioavailability of the drug substances (31, 34).
- It is not feasible to administer a FDDS before going to bed because, as said previously, in supine position there is a higher risk of undesired and faster emptying of the dosage form from the stomach and consequently a higher risk of loss of its efficacy (29, 34).

2.2.5. *In Vitro* and *In Vivo* Evaluation

When developing a floating gastroretentive drug delivery system it is important to evaluate the performance of the dosage forms obtained, being some parameters determined *in vitro* while others are evaluated *in vivo* (28, 31). Although both are relevant, good *in vitro* results do not necessarily imply good *in vivo* performances because it is not possible to have good correlations *in vitro* / *in vivo*. Only *in vivo* studies provide definite proof of enhanced gastric residence times obtained with buoyant formulations (28, 30, 32). Below there is a description of these evaluations techniques.

2.2.5.1. *In Vitro* Studies

FDDS should be characterized *in vitro* for parameters such as specific gravity, porosity, buoyancy, floating lag time and others. For example in tablet formulations pre-compression and post-compression parameters can give an idea of their efficacy (34). In summary, FDDS should be evaluated for the following parameters *in vitro*:

1. **Floating lag time** and **floating time** measurements are usually carried out in simulated gastric fluid containing 900mL of 0.1 M HCl (pH 1.2) as a testing medium maintained at 37 °C in USP dissolution paddle apparatus II (31, 32, 34). The floating time represents the total time that the dosage form remains buoyant in the same medium (31).
2. **Drug release or dissolution studies** are also performed in USP dissolution paddle apparatus II in simulated gastric fluids maintained at 37 °C (30, 32). While doing these

tests, samples are withdrawn periodically from the dissolution medium and replaced. Then the samples are analyzed for their drug content after an appropriate dilution, giving information about the quantity of drug that was released along the test (30, 32). These studies are part of the necessary studies to determine pharmacokinetic process and are important to understand the process of degradation or erosion rate of the formulation in the stomach (52).

3. **Swelling index** is measured by studying weight gain or water uptake after immersion of the dosage form in simulated gastric fluid at 37 °C and analysis in terms its diameter and/or thickness as a function of time (32, 34). The floating tablets are removed from the beaker at regular time intervals of 1 hour for 24 hours, and then reweighed. The water uptake (WU) is measured in terms of percent weight gain, as given by the Equation 2.1., in which W*o* is the initial weight of the dosage form and W*t* its weight at time t.

$$WU = [(Wt - Wo)/Wo] \times 100 \qquad \text{Equation 2.1}$$

But USP dissolution paddle apparatus II does not mimic gastric environment *in vivo* and so, good *in vitro-in vivo* correlation (IVIVC) is dubious. With this apparatus the studies are carried out as a function of time, but it would be advantageous to evaluate those parameters as a function of gastric emptying (52), making it possible to reduce individual variability. Highly acidic environments used as dissolution medium favor gas generation and push the floating process. But in the stomach even neutral pH values may be observed as a result of poor mixing and the impact of food, making a pH-independent (in a pH range 1 – 7.4) floating performance desired (53).

Alternatively Gohel *et al* (54) proposed a more relevant *in vitro* dissolution method to evaluate tablet dosage forms of FDDS, which mimics gastric conditions more efficiently. A 100 mL glass beaker was modified by adding a side arm at the bottom of the beaker so that it can hold 70 mL of dissolution medium similar to the one used in USP paddle apparatus II. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 mL/min to mimic gastric acid secretion rate. This test may show good IVIVC since an attempt is made to mimic the *in vivo* conditions such as gastric volume, gastric emptying and gastric acid secretion rate.

2.2.5.2. *In Vivo* Studies

In vivo studies are performed in animals in a first approach or in patients. The aim is to evaluate the performance of buoyant dosage forms in the stomach. As said previously, this type of studies provide definite proof of prolonged gastric residence time of FDDS. Some techniques for the *in vivo* evaluation are enumerated below:

1. **X-ray** is a very popular technique for the evaluation of floating dosage forms. By inclusion of a radio-opaque material into the dosage form it is possible to have access to the location of the dosage form in the GIT by X-ray analysis. This allows a correlation between gastric emptying time and the passage of the dosage form in the GIT (30). Just before the administration of the dosage form it is made a radiograph in order to ensure the absence of radio-opaque material in the stomach. After that, the dosage form is administered and a radiograph image is taken every 30 minutes with the equipment at a constant distance from the subject so that the movement of the dosage form can be easily noticed (32). This method has some limitations regarding the levels of exposure to x-rays and the requirement of high quantity of radiologic images (29, 32), but it has the advantage of being simpler and cheaper than gamma-scintigraphy.

2. **Gamma-scintigraphy** is also a very popular technique for the *in vivo* evaluation of buoyant dosage forms. By inclusion of a properly short lived γ-emitting radioisotope in the formulation, it becomes possible to perform indirect external observation of the dosage form location in the GIT using a γ-camera or scintiscanner (32). The drawbacks associated with this method are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the expensive preparation of radiopharmaceuticals (31).

3. **Gastroscopy** is an invasive and aggressive method because it comprises a peroral endoscopy with a fibereoptic and video systems (28). This method may be used to inspect visually the effect of prolonged stay in stomach milieu on buoyant dosage forms. This technique also allows the removal of the dosage form from the stomach for more detailed evaluation and information.

4. **Ultrasonography** is not routinely used for the evaluation of FDDS. This method allows imaging of some abdominal organs due to their acoustic impedances across interfaces that are reflected by ultrasonic waves (28). But floating formulations do not commonly have sharp acoustic mismatches across their interface with the physiological milieu. Nonetheless, ultrasonography characterization includes assessment of intragastric location of hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis (28).

The necessity to do, at least, some of those evaluations, may represent a drawback to companies that may want to develop floating dosage forms. They must be aware of the necessity to evaluate formulation parameters and must be able to perform them or to establish agreements with other companies that may do these tests for them.
Anyway, the problem mentioned above regarding the dissolution apparatus used may be further studied, because dissolution methods do not provide accurate *in vitro* conditions for gastroretentive formulations. There is still the need to develop an optimum *in vitro* floating time testing method for a floating dosage form that can efficiently evaluate the effect of fed and fasted states in gastric region on the floating capabilities of the developed product (46).

2.2.6. Market and Regulatory Considerations

Literature describes an extensive number of studies and research papers on FDDS encompassing the different types of floating systems (24, 25, 29, 33, 46), but getting them further into the market is a hard task represented by the conflict between investigation and industrial implementation of all gastroretentive delivery systems (46): only few technologies have been commercialized. The success of a formulation is dependent on preformulation studies, optimization studies, and scale up and process validation of developed manufacturing process. Many investigations are limited to the laboratory instead of reaching the market because it is much easier to manufacture a commercial scale batch in the laboratory than a large-scale batch in industry (46). Also due to high intra and intervariability among individuals, studies of bioequivalence and bioavailability of GRDDS are more demanding and this represents a considerable obstacle to formulations aiming to achieve the market.

Table 2.3. Gastroretentive systems available in the market (27, 28, 31, 41, 44, 46, 55).

Name	Drug Substance	Type of Dosage Form	Company Name
Almagate Flot-Coat ®	Aluminum and Magnesium antacid	Floating dosage form	Laboratorios Almirall SA (Spain)
Baclofen GRS	Baclofen	Coated multi-layer floating and swelling system	Sun Pharma (India)
Cifran OD ®	Ciprofloxacine	Effervescent floating tablet	Ranbaxy (India)
Cipro XR	Ciprofloxacin HCl and betaine	Erodible matrix-based system	Bayer (USA)
Conviron	Ferrous Sulphate	Colloidal gel forming FDDS	Ranbaxy (India)
Coreg CR	Carvedilol	Gastroretention with osmotic system	GlaxoSmithKline (India)
Cytotec	Misoprostol	Bilayer floating capsule	Pharmacia, Ltd (USA)
Inon Ace Tablets	Siméthicone	Foam-based floating system	Sato Pharma (Japan)
Liquid Gaviscon®	Aluminum Hydroxide and Magnesium Carbonate	Effervescent floating liquid alginate preparation	GlaxoSmithKline (India)
Madopar HBS ®	Levodopa and benserazide	Floating controlled release capsule	Roche Products (USA)
Oflin OD ®	Ofloxacin	Effervescent floating tablet	Ranbaxy (India)
Prazopress XL	Prazosin HCl	Effervescent and swelling-based floated system	Sun Pharma (India)
Riomet OD	Metmorfin HCl	Effervescent floating system	Ranbaxy (India)
Topalkan ®	Aluminum and Magnesium Alginate	Floating liquid alginate preparation	Pierre Fabre Drug (France)
Valrelease ®	Diazepam	Floating controlled release capsule	Hoffmann – La Roche (USA)
Xifaxan	Rifaximin	Bioadhesive tablets	Lupin (India)
Zanocin OD	Ofloxacin	Effervescent floating system	Ranbaxy (India)

Table 2.3 gives details about marketed products of gastroretentive dosage forms including various types of floating systems. The market has more floating systems than any other form of GRDDS, and it was not found any reference to the existence of high density systems on the market (46). Among those, solid capsules and tablets are the most common final dosage forms, having more products on the market than liquid preparations for example. But it does not count with many products available. India is the country where these dosage forms are widely disseminated, being Ranbaxy the leader in terms of marketed products. Nonetheless of the number of floating dosage forms is low, it is growing as technological and pharmaceutical knowledge increases.

2.3. Conclusion

Gastroretentive floating drug delivery systems have the capacity to prolong gastric residence time without affecting the motility of GIT. The dosage form is retained in the stomach, allowing the drug to reach its absorption site in solution and hence be ready for absorption, and increasing oral drug bioavailability.

Besides being a promising drug delivery system that allows overcoming some limitations of conventional dosage forms, there is a problem of accuracy in dissolution tests. And this represents difficulties for those companies that want to innovate and develop FDDS, because some FDDS can be manufactured using conventional equipment but conventional equipment normally used for the *in vitro* characterization of the dosage forms does not provide a satisfactory IVIVC. This means that the most commonly used dissolution apparatus is not the most appropriate. For further advancing in the development of these novel dosage forms it is very important to develop alternative dissolution apparatus that may evaluate the floating parameters as a function of gastric emptying instead of time, so that better IVIVC may be achieved. As a consequence, nowadays *in vivo* studies are still very important to establish the optimum dosage form for a specific drug. It is also a challenge to choose either a drug substance or the excipients, in order to achieve the target product profile. Many other factors are important when aiming to get a floating or other gastroretentive formulation commercialized. The market of gastroretentivity is still small, which may represent an opportunity, as the research in this area is already substantial. Besides the growth observed

in investigation and in market of GRDDS, these dosage forms are not yet described in United States Pharmacopoeia (USP) or in European Pharmacopoeia (Eur. Ph.).

3. CHAPTER II

MEDICATED CHEWING GUMS

3.1. Medicated Chewing Gums

Chewing gums are widely consumed by society, but with the development of science and technology it is now considered a promising and convenient drug delivery system (56). It was in 1869 that the first patent for the production of chewing gum was filled (57), and the first medicated chewing gum *Aspergum* with the DS acetylsalicylic acid was launched almost 60 years later, in 1928 (56). Nevertheless, it was only in late 70s that chewing gums gained acceptance as a reliable drug delivery system, when nicotine chewing gum became available (58). Only in 1991 MCG were included as a pharmaceutical dosage form in the Eur. Ph. and the guidelines for this pharmaceutical dosage forms were issued by the Committee for Medicinal Products for Human Use (56, 58). In there, they are described as "solid, single dose preparations with a base consisting mainly of gum that is intended to be chewed but not swallowed, providing a slow, steady release of the active ingredients contained" (59). MCG are meant to act locally, in both prevention and cure of oral diseases, or systemically when there is a direct absorption through the buccal mucosa (56, 58). Due to the high vascularization of buccal mucosa (see Introduction Section 1.3.1.), the drug substance can be directly absorbed into the systemic circulation, avoiding first pass metabolism and enabling a faster onset of action and higher oral bioavailability (60). Besides this route of absorption, a portion of the drug substance may reach the stomach dissolved in saliva and be available for gastrointestinal absorption (60). The active drug substance is released from the dosage form as a result of the mechanical and chemical masticatory act (58), so it is required a continuous chewing process, saliva and a minimum chewing time (56).

This dosage form has been formulated and commercialized for a wide range of active substances (56, 58), taking advantage of its characteristics that are able to enhance patient compliance, including the attraction it represents to children over other formulations (58). Many of them are used for systemic purposes such as pain killers, vitamins, alertness enhancers, motion sickness removal and smoking cessation gums (56), while others are commercialized for local purposes, like plaque acid neutralization, fresh breath and bacterial infections (56). MCG are developed according to superior quality standards and Good Manufacturing Practices (GMP) (58), which are imperative parameters to be taking into account, making it a reliable drug delivery system. This drug delivery system is subject to

quality control parameters evaluation in order to guarantee quality and security of the MCG before reaching the market (58). *In vivo* testing may also be required.

3.1.1. Manufacturing Processes

Medicated chewing gums have the possibility to be manufactured by three distinct methods:

A. Conventional/Traditional Method (Melting)
B. Cooling, Grinding and Tableting Method
C. Direct Compression Method.

The Conventional/Traditional Method (Melting) consists of five process steps, as briefly described in Fig. 3.1 (56, 58, 60, 61):

1. The components of gum base are softened or melted in a Kettle mixer;
2. The drug substance and other excipients are added at a determined time;
3. The gum is sent through a series of rollers that transform it into a thin and wide ribbon. During this step a light coating of finely powdered sugar (or sugar substitutes) is added in order to avoid sticking phenomena and to enhance the flavor;
4. Then it is cooled for up to 48h in controlled conditions;
5. Finally, the gum is cut in the desired size and cooled under controlled temperature and humidity.

There are some limitations associated with this process, namely:

- Requirements for elevated temperature during melting, make the manufacture of thermoliable drugs a challenge;
- Difficulty to control the accuracy and uniformity of drug dose if the gum mass is highly viscous;
- Lack of precise form, shape or weight of dosage form;
- Difficulties to formulate chewing gum as tablets due to high moisture content (2-8%). The composition may adhere to the grinding apparatus and to punches, hampering the compression process.

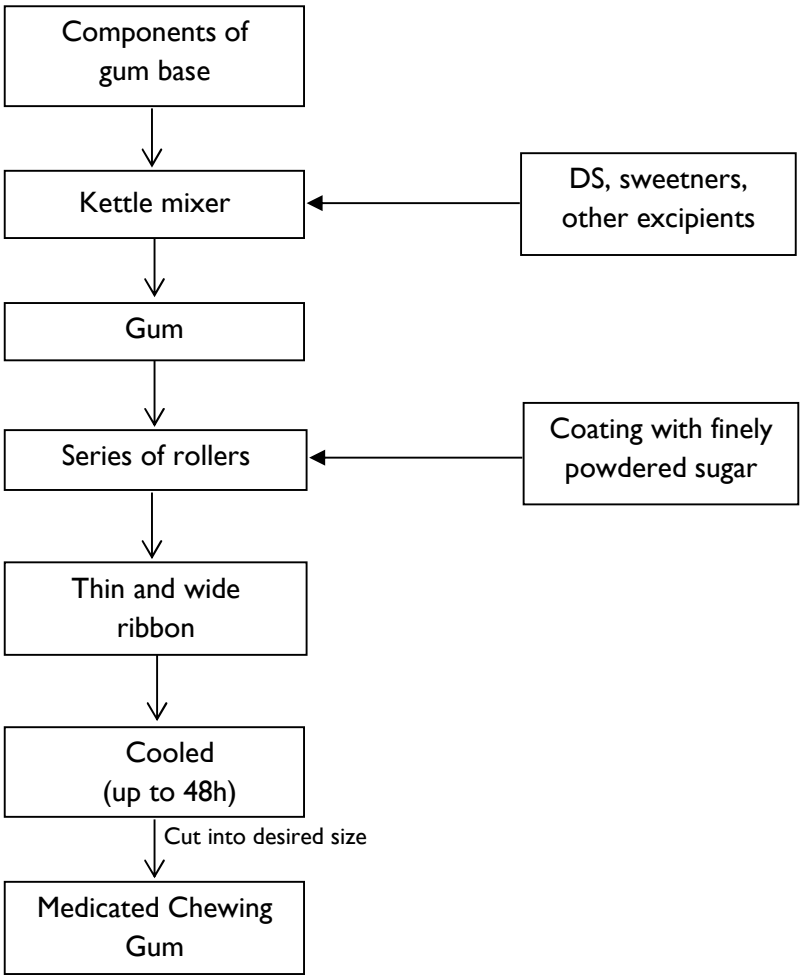

Figure 3.1. Conventional Method for the manufacturing of MCG (56, 58, 60, 61).

Cooling, Grinding and Tableting Method (Thermoliable) arrised as an attempt to overcome the limitations of the Conventional Method by lowering the moisture content (56, 58, 60, 61). This method consists of three process steps, as are briefly described in Fig. 3.2:

1. Cooling. The gum base is cooled to a temperature at which the composition is sufficiently brittle, even for the further step, by addition of a coolant. Such temperature is determined by the gum base composition, and it generally around -15°C. It is desired for the coolant not to be absorbed during the process, not to interact adversely with the processing apparatus and not to leave behind undesirable or potentially hazardous residues. The use of solid silicon dioxide is preferred.
2. Grinding. The refrigerated gum composition is placed in a mill grinder and is ground to obtain minute fragments of finely pieces. Additionally, anti-caking agents such as

precipitated silicon dioxide and grinding agents can be added, in order to prevent agglomeration and to prevent the gum composition from sticking to the grinding apparatus, respectively.

3. Tableting. The coolant is removed from the powder, and the powder is mixed with other excipients (e.g., binders, sweeteners and others) in a suitable blender such as high shear mixing. The granules obtained may be mixed with antiadherents like talc. Finally, the powder is compressed in a conventional compression machine.

This method has also some limitations such as the need of specific equipment (other than conventional tableting equipment) and the challenge of monitoring humidity during the

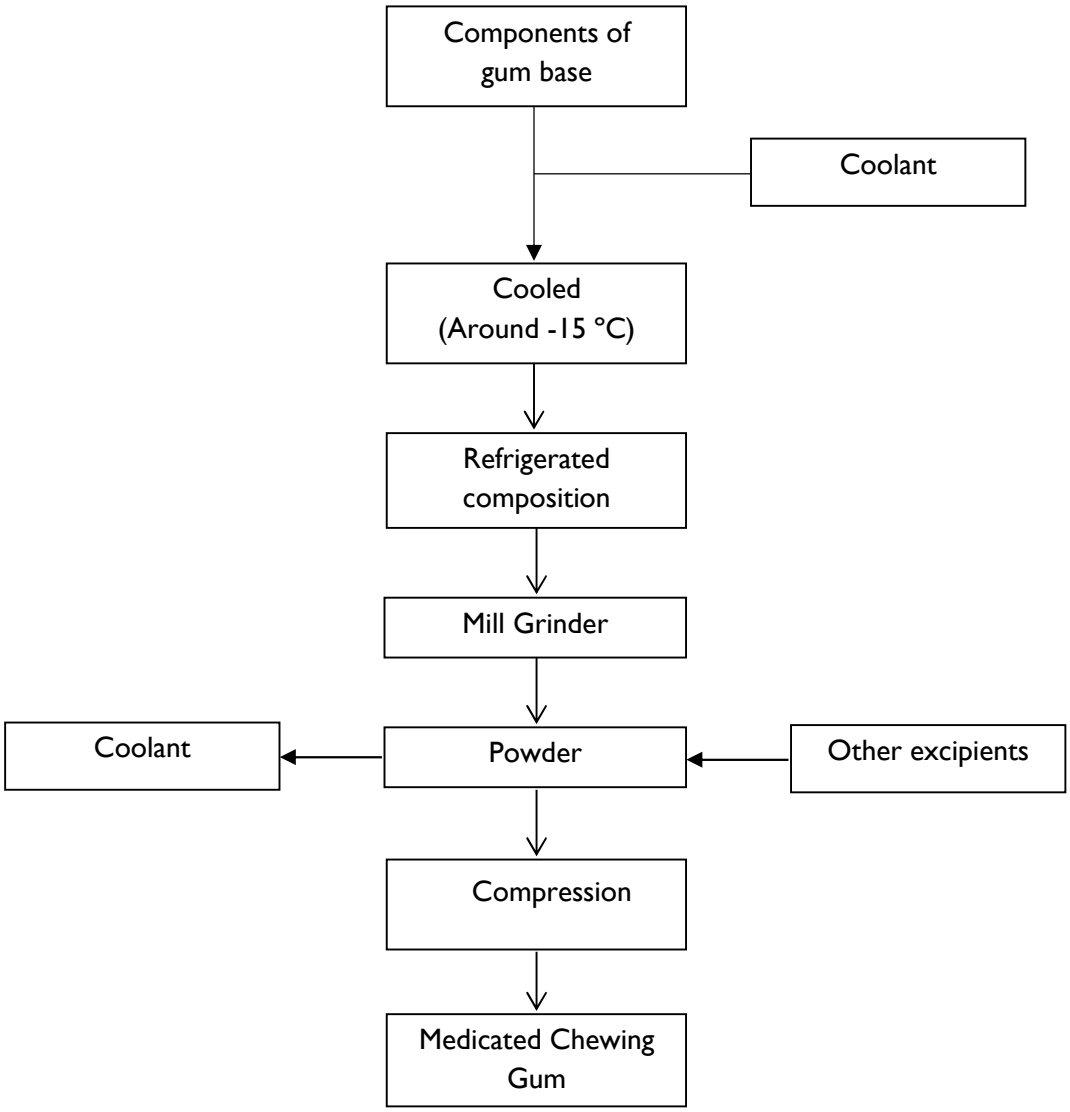

Figure 3.2. Cooling, Grinding and Tableting Method for the manufacturing of MCG (56, 58, 60, 61).

manufacturing process. Besides those limitations, this method is more convenient than the conventional method (56, 58, 60, 61).

The Direct Compression Method allows an easier and faster manufacturing process of the chewing gum if directly compressible gum bases are available, and can overcome the limitations of conventional manufacturing methods (56, 58, 60, 61). Pharmagum, a mixture of polyols and sugars with a chewing gum base, is one such compactable system developed by SPI Pharma that was available as a directly compressible powder, free flowing powder. This mixture could be compacted into a gum tablet using conventional tablet press thus enabling rapid and low cost development of a medicated chewing gum delivery system (56, 58, 60, 61). Pharmagum, which was manufactured under GMP conditions and was considered "Generally recognized as safe" (GRAS), was available in three forms namely S, M and C, that differ on their composition. But for unknown reasons SPI Pharma stopped commercializing this excipient. Other example is *Health in Gum* developed by Cafosa that is a directly compressible powder gum containing a mixture of gum base and polyols, which only requires addition of an active ingredient prior to compression (62). *Health in Gum* has been created to turn the manufacturing process of chewing gums quick and cost-effective (62). It performs

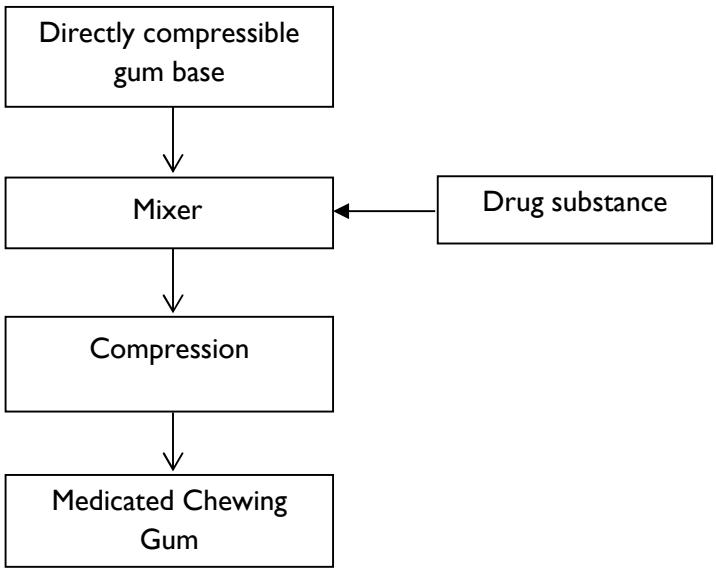

Figure 3.3. Schematic diagram of MCG manufacturing process by Direct Compression Method, based on the use of *Health in Gum* as a directly compressible powder (56, 58, 60, 61).

excellently using standard tableting equipment, with no need for chewing gum specific equipment, and works at room temperature, allowing the use of thermos-sensitive DSs (62). Fig. 3.3 describes the manufacturing steps of Medicated Chewing Gum using *Health in Gum* as a directly compressible powder to which the DS is added (63). With this method a pharmaceutical company that possesses standard direct compression technology is able to develop MCG.

3.1.2. Suitable Drugs and Main Excipients Used In Formulation

Medicated Chewing Gum is a solid, single dose innovative dosage form composed of a masticatory water insoluble gum base with at least one active drug substance (56). The gum base generally comprises a water insoluble chewable gum portion and a water soluble bulk portion (60, 64), although a wide variety of excipients can be used as listed in Table 3.1. The water insoluble gum base generally comprises elastomers, plasticizers and fillers or texturizers (60). Elastomers are used in a percentage of 40 – 70 % by weight of the total gum base (60), in order to provide elasticity, gummy texture and cohesion to the chewing gum (58). Plasticizers are used in a percentage of 3 – 20 % by weight of the gum base (60), in order to regulate the cohesive properties of the gum base (58). Fillers or texturizers, which are used in a percentage of 2 – 60 % of the gum base (60), provide an appropriate texture, improve chewability and provide reasonable size of the gum lump with low dose drugs (58). The water soluble bulk portion of the gum base generally comprises softeners, emulsifiers, sweeteners, flavoring agents and others (60) which are shown in Table 3.1. Resins contribute to achieve a balance between the properties of elasticity and plasticity and have two functions: being a binding agent between elastomers and fillers, and being a mastication substance (58). Emulsifiers and fats are used to soften the mixture and are responsible for giving the required chewing consistency and pleasant mouth feel (58), function that it is common with softeners. Emulsifiers also have the function of promoting the uptake of saliva into the chewing gum during the mastication process. Antioxidants are used to prevent the oxidation of the gum base and flavors (58). Sweeteners, which are used in a proportion of 50 – 65 % of gum base composition (60), are of two types (aqueous and bulk sweeteners) and

Table 3.1. Main excipients used in formulation of gum base for MCG (56, 58, 60, 64).

Type of excipient	**% of usage**	**Examples**	
Elastomers	40 – 70	Natural: latex, jelutong, Leche Caspi, Perillo, Chicle	
		Synthetic: polyisobutylene, butyl rubber	
Plasticizers	3 – 20	Natural: glycerol esters of partially hydrogenated rosin, of polymerized esters, and of partially dimerized rosin, pentaerytthritol esters of resin	
		Synthetic: terpen resins derived from α-pinene and d-limonene	
Fillers or texturizers	2 – 60	Magnesium and calcium carbonate, ground limestone, alumina, talc, titanium oxide & mono/di/tri calcium phosphate	
Resins	-	Natural: glycerol esters from pine resins	
		Synthetic: polyvinyl acetate	
Emulsifiers and fats	-	Monoglycerides, diglycerides, partly hardened vegetable and animal fat	
Softeners	-	Glycerin, lecithin, tallow, hydrogenated tallow, mono/di/tri-glycerides, fatty acids like stearic acid, palmitic acid, oleic acid and linoleic acid	
Antioxidants	-	Ascorbic acid, tocoferol, butylhydroxytoluene	
Sweeteners	50 – 60	Aqueous: sorbitol, hydrogenated starch hydrosylates, corn syrups	
		Bulk	Sugar components: saccharides (sucrose, dextrose, maltose, dextrin, fructose, galactose, corn syrup)
			Sugarless components: sugar alcohols (sorbitol, mannitol, xylitol, hydrogenated starch hydrosolated)
Flavoring Agent	-	Citrus oil, fruit essences, peppermint oil, spearmint oil mint oil, clove oil, oil of wintergreen	
Anti-Caking Agent	-	Precipitated silicon dioxide, solid carbon dioxide	
Grinding Agent	2 – 8	Alkaline metal phosphate, malt dextrin	

can be used as softeners to blend the ingredients and retain moisture. In order to provide longer lasting sweetness and flavor perception, high intensity artificial sweeteners such as sucralose, aspartame, saccharin and others, can be added (58). Flavoring agents are used to improve the flavor in chewing gums and include a variety of essential oils as well as artificial flavoring agents (58). The anti-caking agents may be added to the mixture prior to grinding in order to help preventing agglomeration of the subsequently ground chewing gum particles (58). Grinding agents are used to prevent the gum from sticking to the grinding apparatus, but should be applied rationally due to their tendency to remain in the composition and final chewing gum tablet, which may be problematic from a safety point of view (58). They also have a limited practical use due to the incompatibility of their high alkaline characteristics with acidic ionisable therapeutic agents (58). Bulking agents such as polydextrose, oligofructose and guargum hydrolysate may also be used if low calorie gum is desired (60). It is also important to understand that the formulation has a very low content of water (58, 60) due to the necessity of maintaining the integrity of the dosage form once in contact with saliva in the oral cavity, because it is intended to be chewed and discarded after drug release. The gum base composition is determinant for the basic characteristics of the product, such as texture, elasticity and mouth feel, and also for release profile of active ingredients and of sweeteners and flavors (60). Therefore, the release profile of sweeteners and flavors is usually designed to follow the release profile of the drug substance (64).

The gum core may be coated (60). The coating can be applied as a film of polymers, waxes, sweeteners, flavors and color or as a thick layer of sugar or sugar alcohol.

The active drug substance may be included in gum core, in the coating layer or in both, and the final percentage of drug load may vary between 0.5 – 30 % (60). It is crucial to understand the effects of the nature of DS and its physicochemical characteristics in the formulation, in order to develop an appropriate dosage form. First it is important to understand that the active DS must not have a particle size higher than 100 μm, so that the unpleasant gritty feeling during chewing is avoided and the patient compliance is not affected (56, 58). Chemical characteristics of the drug substance are also important when aiming to develop MCG, namely its lipophilicity and hydrophilicity (58). While hydrophilic active substances are rapidly and completely released from gum core, lipophilic drug substances adhere and are dissolved in the gum base, being slowly and incompletely released (60, 65). Taking this into account, there is a necessity for optimization of the formulation accordingly

to the drug substance's nature. The release rate may be decreased in case of hydrophilic substances, for example, by its encapsulation or by increasing the amount of gum base (65), and may be increased in case of lipophilic drugs, for example, by its coating/encapsulation or by the addition of buffering or solubilizing agents (60, 65).

Any aspect of the formulation may be controlled and considered together and not independently to achieve an optimal formulation with acceptable organoleptic and technological properties (66) and to get it successfully into the pharmaceutical market.

3.1.3. Factors Affecting Drug Release

There is a wide range of factors affecting the drug released from Medicated Chewing Gums (56, 58, 60, 66), and those factors can be divided in three main groups:

1. **Physicochemical properties of drug substance**. As said previously in this monograph, aqueous solubility of the active drug substance plays an important role in the success of the formulation, since saliva is mainly composed of water and the volume of saliva is small (60). So considering the same chewing conditions, hydrophilic drugs will be released quickly and at a higher amount than lipophilic drugs (60). Besides the physicochemical properties of drug substance, also its amount in the formulation is an important factor. As a consequence, the components of the chewing gum may be selected accordingly to the nature and requirements of the drug substance.

2. **Properties of the gum base (formulation factor)**. Composition and amount of gum base affect the release rate of drug substance (56, 60). For example, if lipophilic portion of gum base is increased, it implies a decrease in release rate of hydrophilic drugs (56, 60). Therefore, the formulation may be adjusted to achieve the target product profile for each specific drug substance.

3. **Chew-related factors**. These factors include contact time, chewing frequency and intensity, membrane factors and environmental factors, which may vary from individual to individual.

3.1. **Contact time**. The contact time of the dosage form in the oral cavity influences the local or systemic effect of drug substance (64). Literature reports a chewing time of around 30 minutes to be appropriate (61).

3.2. **Chewing frequency and intensity**. These variables play an important role in the success of drug release from MCG. *In vitro* studies are carried out accordingly to Eur. Ph. specification of 60 chews per minute for proper release of active ingredient (67).

3.3. **Membrane factors**. These factors are related to the characteristics of buccal mucosa and the processes related to the drug absorption (60). Regional differences may affect drug release and absorption to systemic circulation, namely permeability and thickness of buccal mucosa and its keratinization and composition, as referred on the Introduction part 1.3.1. Other factors that also influence drug release and absorption are blood supply, blood/lymph drainage, cell renewal rate and enzyme content of saliva.

3.4. **Environmental factors**. These factors are related to saliva, its properties and flow rate (60). An increase in the flow rate will lead to the secretion of watery saliva. Salivary pH (6.5 – 7.5) depends on the salivary flow rate and location in the oral cavity, and may influence the passive diffusion of the unionized drug (60).

In order to achieve the best and more efficient formulation, each factor should be evaluated having in mind the dependency on the others.

3.1.4. Advantages and Limitations

There is a wide range of advantages sustaining the development of Medicated Chewing Gums over conventional dosage forms. This novel pharmaceutical dosage form provides competitive advantages over conventional drug delivery systems, while other advantages are shared with different delivery systems. These advantages are:

- Chewing gums do not require water to be administered once they are meant to be chewed not swallowed, and so the administration can occur anywhere without

water. So it represents an advantage for patients having difficulty in swallowing and for children (68);

- Not being swallowed, the chewing gum barely reaches the stomach, thus decreasing the risk of side effects due to the excipients and/or active ingredients. The fraction that reaches the stomach is conveyed by saliva, thus there is no direct contact with high concentration of drug and it is presented in a readily bioavailable form (61). Because of this there is a lower risk of intolerance of gastric mucosa to the components of the MCG (60);
- Once the patient starts chewing, the active substance is released from the gum. High plasma peak concentrations of the drug are avoided by promoting a controlled drug release, thus resulting in fewer side effects (58);
- Depending on the active ingredient, some absorption takes place in the buccal mucosa, allowing a systemic delivery of the drug through the jugular veins hence avoiding first pass metabolism and promoting an enhanced bioavailability of the drug (58). In this way, lower doses of the drug substance may be enough to achieve the same therapeutic effect. This also allows a faster onset of action (68);
- The treatment can be terminated at any time, if required by removal of the chewing gum from the mouth (61);
- MCG have some advantageous characteristics that contribute to the increase of patient compliance, such as stress and tension relief, refreshing the breath, cleaning the teeth after meals and reduction of dryness in the mouth by stimulating salivary secretion (60).

Unfortunately there are also some limitations associated with MCGs and its components, which may affect the performance and viability of the drug delivery system. These limitations are enumerated below:

- May induce some allergic reactions due to the use of flavoring agents, colorants and other excipients (60).

- Aspartame, a sweetening agent used in most of chewing gums, can enhance the risk of diabetes, neurological disorder, birth defects and for long users can enhance the risk of cancer and increase the release of mercury vapor from dental amalgam filling (60). Another sweetening agent, sorbitol, can cause diarrhea and flatulence (58)
- Chewing gum may adhere to different degrees to enamel dentures and fillers (61).
- The masticatory act involves a set of muscles, salivary glands and cartilage which when damaged may cause serious problems (60).

The unnecessary damage of the cartilage that acts as a shock absorber in the jaw joints leads to pain and discomfort for a lifetime. The production of steady stream of saliva for chewing gum is a waste of energy and resources that otherwise could be used for essential metabolic activities. Unnecessary damage of facial muscles located to the temples can contribute to chronic intermittent headache, due to the pressure on the nerves. But there is a low probability of this kind of injuries take place or they may be highly avoidable, since the patient chews the MCG up to 30 minutes (58, 60, 61).

3.1.5. *In Vitro* and *In Vivo* Evaluation

As any other drug delivery system, there the need for controlling the variables that can influence the performance of MCG, in order to achieve acceptable organoleptic and technological properties (66). There are some prerequisites that need to be fulfilled in order to achieve patients' compliance such as a pleasant and long-lasting taste, also an optimal chewing volume, anti-adherent properties to the teeth, and acceptable pharmaceutical properties, such as fast and complete drug release from the formulation (66). Two different types of tests are performed to determine the drug product characteristics: quality control tests during manufacture and for market release as well as other performance tests (58, 60, 61).

3.1.4. 1. Quality Control Studies

Medicated Chewing Gums have to comply with the requirements of the Eur. Ph. (60):

1. **Uniformity of Content.** MCG with content of 2 mg or less than 2 % of the total mass of gum must comply with the test A for uniformity of single dose preparations (69), unless otherwise prescribed or justified and authorized (58, 60, 61). If the formulation has more than one active substance, the requirements apply only for those active substances which correspond to the above situation.

2. **Uniformity of Mass**. Uncoated MCG and, unless otherwise justified and authorized, coated MCG must comply with the test for uniformity of mass of single dose preparations (70).

3. **Drug Release from MCG**. Drug release evaluation for MCG is completely different when compared with conventional drug delivery systems (66), having requirements for a specific and particular *in vitro* apparatus which is able to mimic the masticatory movements (67). Below there is the description of two apparatus used for testing *in vitro* drug release from MCG, being both referenced as useful tools for these performance tests (55).

3.1.4.2. *In Vitro* Studies

Apparatus I. Chewing Gum Apparatus, Compendial – Eur. Ph.

The Eur. Ph. adopted this chewing apparatus in 2000 (61) and its representation is shown in Fig. 3.4. The chewing apparatus comprises a chewing chamber where the medicated chewing gum is placed in order to be subject to mechanical forces applied by the two horizontal pistons and the vertical piston (tongue) – which work together at a constant speed – that mimics the human masticatory act. The tongue operates alternatively with the two horizontal pistons and makes sure that the gum is kept in the right place between chews, while the horizontal pistons rotate around their own axes in opposite directions after each chew so that the gum is subject to maximum chewing (67). The procedure is described in Eur. Ph. and the chewing frequency is usually set at 60 cycles/minute (67).

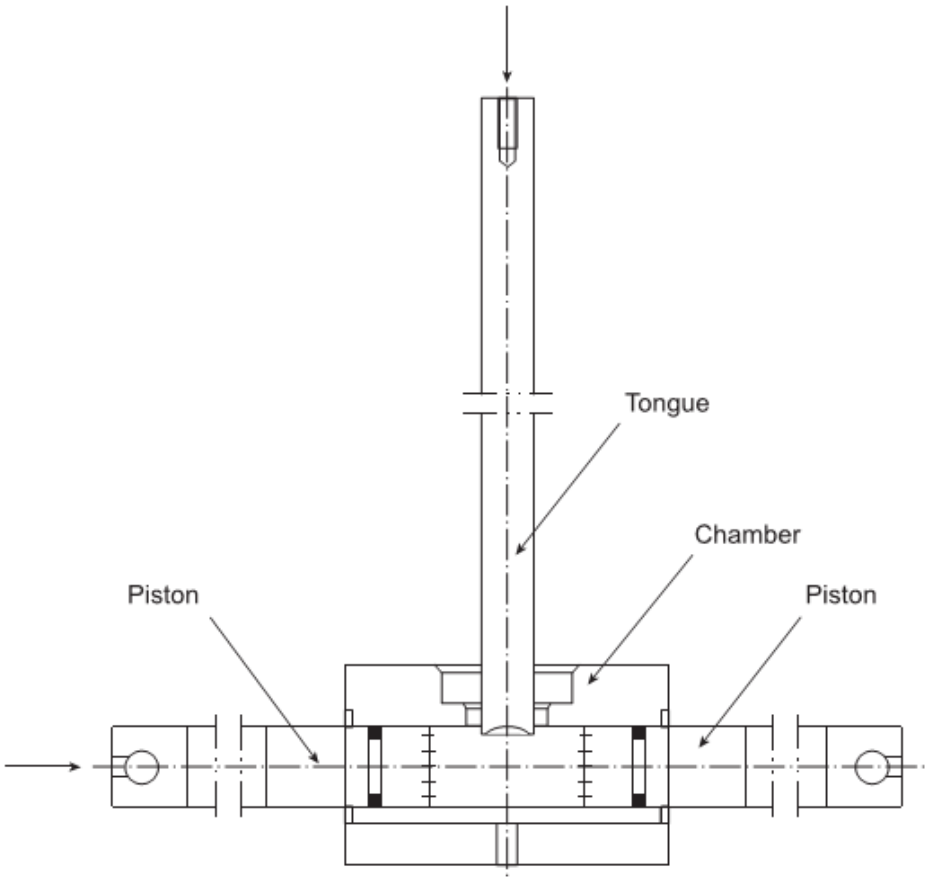

Figure 3.4. Apparatus for the determination of drug release from MCG (67).

Apparatus II. Alternative Chewing Gum Apparatus, Noncompendial – Wennergren

A noncompendial apparatus for *in vitro* drug release test from MCG was developed by Wennergren (71) and its schematic representation is shown in Fig. 3.5A. The apparatus has six chewing modules, being each module a thermostated test cell of glass (71) that contains two vertically oriented pistons holding an upper and a lower chewing surface (Fig. 3.5B), respectively. The medicated chewing gum is placed in the lower chewing surface and the chewing procedure consists of reciprocations of the lower surface in combination with a twisting movement of the upper surface that provides mastication of the chewing gum and at the same time an adequate agitation of the test medium (60, 71). The upper chewing surface is parallel to the central part of the lower one, which has a small brim angled upwards in a 45 degrees angle so that the lower fraction functions as a small bowls with a flat bottom. This helps to prevent the chewing gum from sliding during the mastication process (67). This

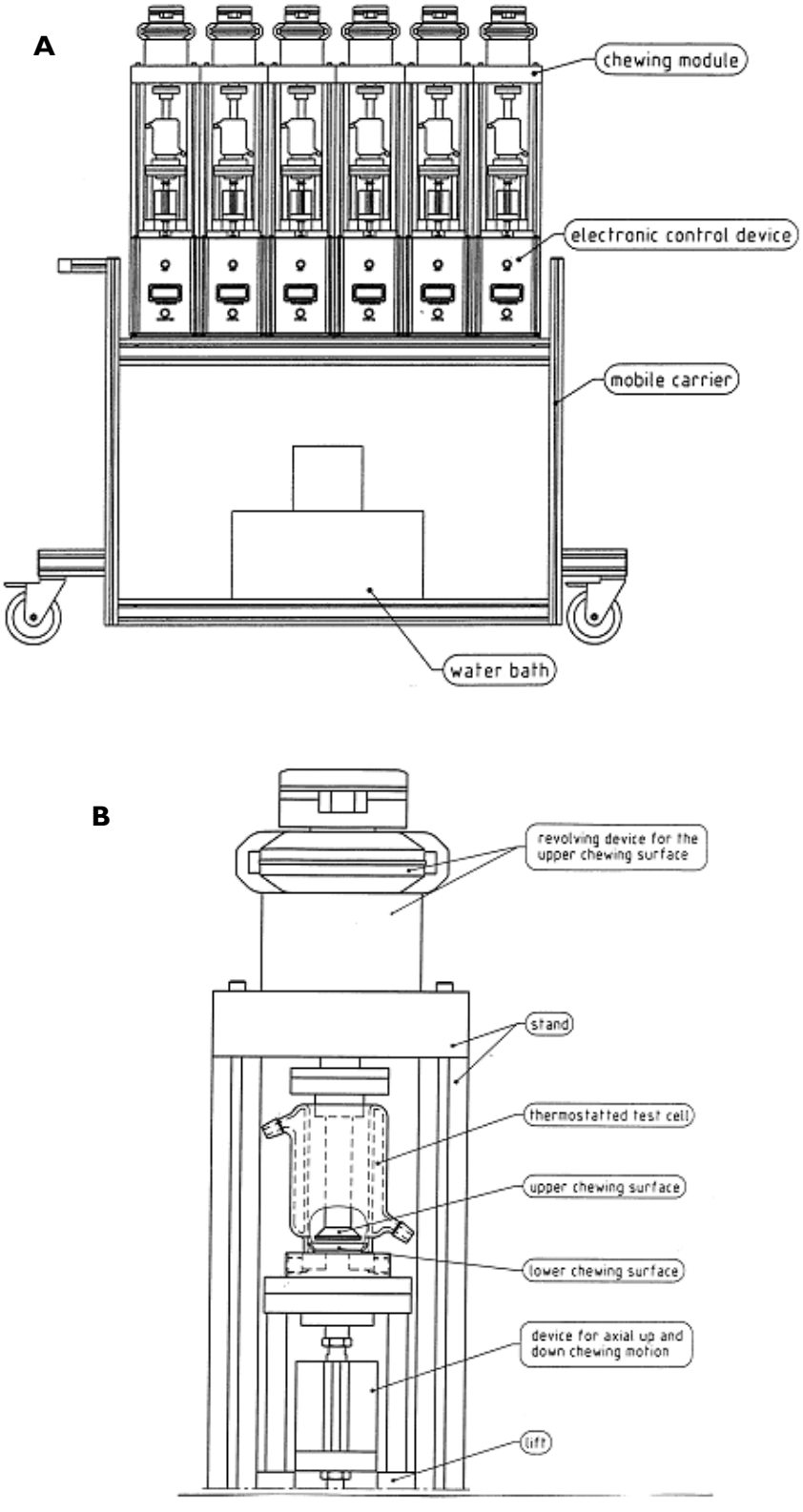

Figure 3.5. (A) Technical drawing of the noncompendial chewing apparatus – the entire setup showed the six chewing modules. (B) Detail of one chewing module (71).

apparatus shows satisfactory results for distinct formulations, since the adjustments of instrumental settings have a large freedom of choice, being adaptable for distinct drug products (71).

Besides being possible to produce MCG with conventional tablet press, the *in vitro* evaluation is a limiting step for pharmaceutical companies, because it requires specific equipment described in the Eur. Ph. (67). It means that if a company aims to develop medicated chewing gums, has necessarily to access an apparatus for evaluation of drug release so that it can be accepted by the regulatory entities.

3.1.4.3. *In Vivo* Studies

In vivo "chew-out" studies are performed in human volunteers in order to evaluate the release of active drug substance from Medicated Chewing Gums. *In vivo* studies are important because the dosage form is subject not only to the mechanical stress of chewing (that is provided by the apparatus for *in vitro* studies), but also to the physiological phenomena during the masticatory process, such as the increase of salivary secretion, variations of salivary pH, swallowing and absorption through the buccal mucosa (64). Those physiological phenomena can highly influence the performance of the dosage form as well as the amount and rate release of the active drug substance (58). The *in vivo* methodologies described in literature are: release of drug in saliva, dissolution test of residual medicated chewing gum, urinary excretion profile of medicated chewing gum and buccal absorption test (58, 61, 72). In each of these tests, volunteers are asked to make use of MCG and thereafter samples of saliva, residual gum or urine are withdrawn and analyzed with proper methods for content of active drug substance (72). Besides the importance of these tests, they are actually alternative methods because there are no guidelines available for *in vivo* performance tests for MCG.

Besides all the available *in vitro* tests and *in vivo* alternatives for determination of drug release from MCGs, it may not be forgotten that pleasant flavor and texture of the gum are crucial to the success of formulation. It means that texture studies are also required, and must be done *in vitro* by instruments and also *in vivo* in human volunteers (61). *In vitro* texture analysis requires an instrument that applies a constant force on the surface of the self-supporting

MCG, on the recommendation of the compression probe to have greater surface are than the MCG. During the process a deformation curve of the response of MCG to the compression is generated, recorded and interpreted. This instrumental analysis test enables a variety of textural properties to be evaluated, namely hardness and adhesiveness (61). In case of *in vivo* texture analysis, the volunteers are simply asked to chew the dosage form for a particular period of time. Then each volunteer describes his chewing experience in terms of the qualities of the MCG, such as product feel, consistency, taste, and total flavor lasting time during the masticatory process (61).

3.1.6. Market and Regulatory Considerations

Table 3.2 gives details about marketed products in the form of medicated chewing gums. The market of MCG is rich in products used for smoking cessation, alertness enhancers and motion sickness removal, as said previously in this monograph. But it does not count with many products available. USA is the country where this dosage form is widely disseminated, with approximately 50% of the world market for MCG (64). Nonetheless the small number of marketed MCG, the market is growing as the technological and pharmaceutical knowledge increases and the population is educated for acceptance of this new patient centric dosage form.

Medicated chewing gums are an attractive dosage form because it allows the reformulation of drug substances already in the market in other dosage forms that will make a differentiation point in pharmaceutical industry and in the upcoming generics competition. This novel drug delivery system is an opportunity for product-line extension (60, 64). A brief research in literature and in patent databases show that there are many patents filled on MCG field (58,61).

3.2. Conclusion

Medicated Chewing Gum is a feasible drug delivery system which shows great patient compliance. That is due not only to clinical benefits, and the possibility to act both locally

Table 3.2. MCG available in the market (56, 58, 60, 61).

Name	Drug Substance	Aim	Commercially Available
Aspergum	Aspirin	Pain relief	North America
Brain	DHA & CCE	Enhanced brain activity	Japan
Chooz	Calciumcarbonate	Stomach acid neutralization	USA
Chroma Slim	Cromium	Diet	USA
Nicorette	Nicotine	Smoking cessation	Worldwide
Nicotinell	Nicotine	Smoking cessation	Western Europe, Australia
Superpep	Dimenhydrinate	Travel illness	Germany, Switzerland
Endekay Vitamin C	Vitamin C	General health	Middle East, United Kingdom
Stamil Vimatin C	Vitamin C	General health	Australia
Source Vitamin C	Vitamin C	General health	Australia
Stay Alert	Caffeine	Alertness	USA
Café Coffe	Caffeine	Alertness	Japan
Buzz Gum	Guarana	Alertness	United Kingdom
Go Gum	Guarana	Alertness	Australia
Fluorette	Fluoride	Cariostatic	USA
Vitaflo CHX	Chlorhexidine	Preventing tooth decay	USA
Travvel	Dimenhydrinate	Motion sickness	USA, Australia
Trawell	Dimenhydrinate	Travel illness	Italy, Switzerland
V6	Xylitol	Prevention of formation of dental caries	United Kingdom

and systemically, but also because MCG are shown to be an attractive, discrete and efficient drug delivery system. In spite of that, the potential of MCG has not yet been fully exploited.

Pleasant taste and flavor are crucial for the market success of the formulation. Medicated Chewing Gums are intended to be chewed but not swallowed, meaning that they are withdrawn from the mouth after the desired effect is achieved or after a predetermined time of chewing. This drags the problem of the sticky nature of chewing gum. It is desired to develop chewing gums composed in a way that they can be removed from surfaces by conventional cleaning methods and technologies (61). It may be promising to incorporate biodegradable excipients so that it disappears by means of nature's own remedies, like water, light and bacteria (61).

Besides MCG being described in a monograph of Eur. Ph., as well as the dissolution apparatus for *in vitro* evaluation of drug release, there is no reference to MCG in USP, nor dissolution apparatus for this drug delivery system. Chewing gums with active pharmaceutical substances are also mentioned in guidelines for pharmaceutical dosage forms by the Committee for Medicinal Products for Human Use. The development of MCG meets high quality standards in pharmaceutical industry but requires specific technologies and facilities different from those normally used in pharmaceutical industry, involving hot-melt processes, which tend to be rare. It makes new gum bases formulations which are compressible, such as *Health in Gum*, available to extend applications of chewing gum and offers a possibility for innovation of conventional pharmaceutical companies. Besides the possibility of developing a promising new drug delivery system with no requirements for specialized manufacturing equipment, regular entities require quality control tests, namely *in vitro* drug release performance tests which require specific apparatus mentioned in Eur. Ph.. In other words, pharmaceutical companies are able to manufacture Medicated chewing gums with standard tablet compression equipment but need to invest in new equipment in order to be able to perform drug release tests.

4. CHAPTER III

PULSATILE DRUG DELIVERY SYSTEMS

4.1. Pulsatile Drug Delivery Systems

Some diseases that are referenced in Table 4.1 show a predictable circadian rhythm (73 – 75). In this way, a controlled timing of medication regimens can improve therapeutic outcomes in these diseases. It means that a strategic time of administration would allow the onset of therapeutic drug concentrations to coincide with the time at which disease symptoms / manifestations are more likely to occur (74), thus having higher therapeutic efficacy and enhancing patient compliance. In this context, Pulsatile Drug Delivery Systems (PDDS) are a type of dosage form that have been developed in close connection with emerging chronotherapeutic views (73 – 75).

PDDS are able to control different crucial variables in drug delivery in such a way that it is possible to deliver the right dose of the drug at a specific time and in a specific local (73, 75),

Table 4.1. Diseases that show a circadian rhythm for pulsatile drug delivery (73 – 75).

Disease	**Chronical Behavior**	**Drugs used**
Asthma	Precipitation of attacks during night and at early morning hours	Antihistamines, β_2 agonists
Arthritis	Pain in the morning. Level of pain increases at night	NSAIDs, Glucocorticoids
Attention Deficit Syndrome	Increase in DOPA levels in afternoon	Methylphenidate
Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinka alkaloids, Taxanes
Cardiovascular Diseases	Blood pressure is at its lowest during sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blockers, ACE inhibitors
Diabetes mellitus	Increase in blood sugar level after a meal	Sulfonylurea, Insulin, Biguanide
Duodenal Ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night	Proton pump inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than daylight	HMG CoA reductase inhibitors
Neurological Disorders	The central pathophysiology of epilepsy and the behavioral classification of convulsive events	MAO-B inhibitors
Peptic Ulcer	Acid secretion is higher in the afternoon and at night	H_2 blockers

thus providing spatial and temporal drug delivery. The drug release profiles of such systems are characterized by two distinct phases (73 – 75), as depicted in Fig. 4.1. The initial phase after the formulation administration is known as lag time and requires a pattern of no drug release at all (73), it is the time between the administration of the dosage form and the beginning of the drug release (75, 76), and it is followed by a second phase characterized by a complete release of the drug within a short period of time (74). Lower lag times are intended to deliver the drug in the upper parts of the GIT, while higher lag times are desirable for the drug release in the lower portion of the small intestine (76). PDDS may be characterized as single pulse systems (Fig. 4.1.A–C) or as multiple pulse systems (Fig. 4.2), depending on the function of the dosage form (76). In single pulse systems the drug is completely released at once and in a specific region of the GIT after the lag time (73 – 76). On the other hand, multiple pulses systems deliver the drug in divided doses in concomitant pulses and may be programmed to deliver fractions of the drug in distinct parts of the GIT (76). Multiple pulses systems are developed as pellets or minitabs (76) with multiple coating layers (77), which may be further converted into tablets or capsules to form a single unit dosage form (76). There is also the possibility of developing multiple pulses release

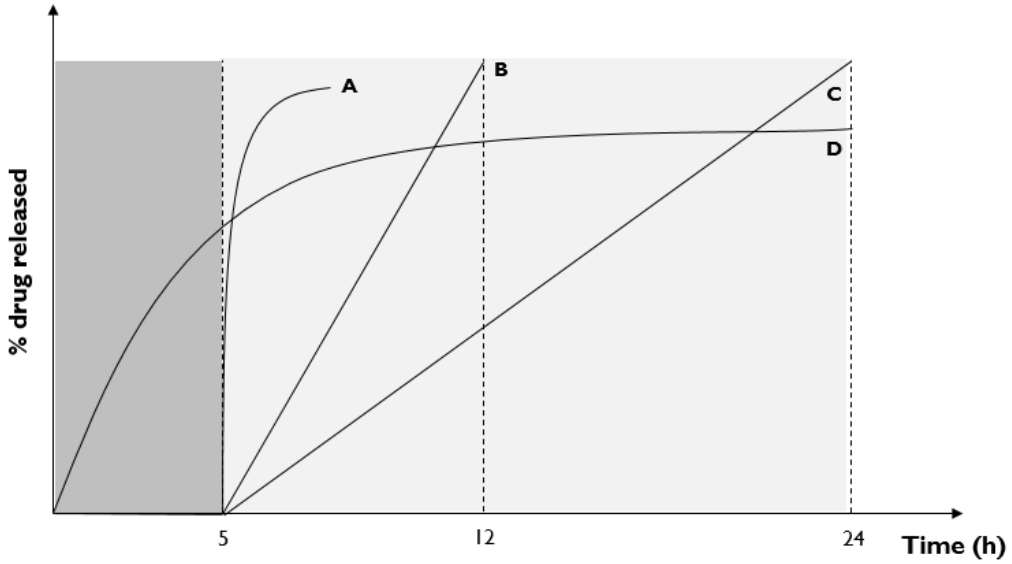

Figure 4.1. Schematic representation of different single pulse drug release profile where (A) is sigmoidal release after lag time, (B) is a delayed release after a lag time, (C) is a sustained release after a lag time and (D) is an extended release with no lag time. For pulsatile drug delivery systems (A, B and C) dark grey represents the initial phase with no release (lag time) and light grey represents the second phase of DS release (73 – 76).

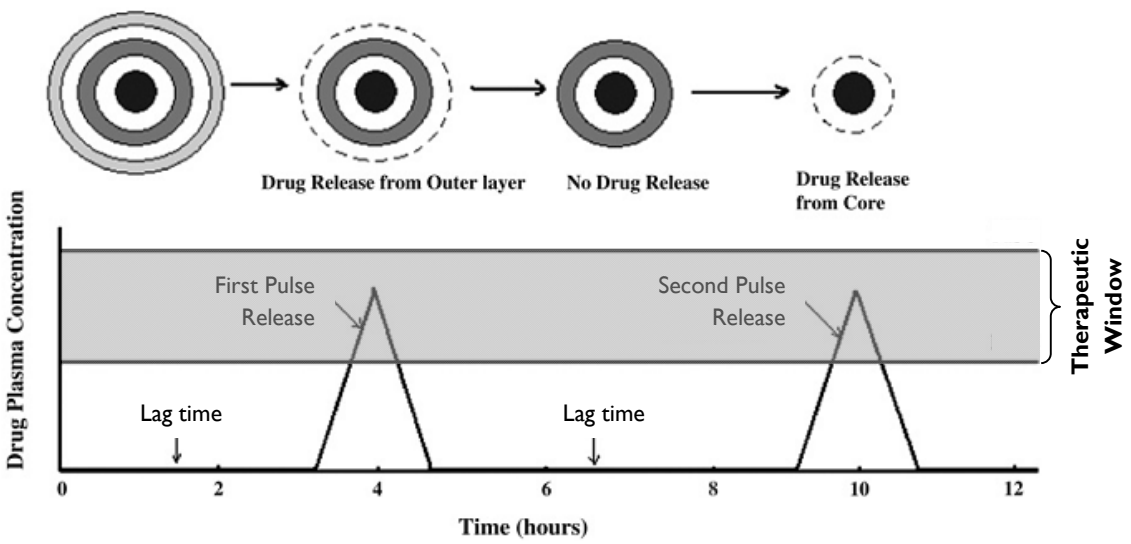

Figure 4.2. Schematic representation of a multiple pulse drug plasma concentration profile from a pellet with multiple containing layers. Adapted from 77.

formulations with different drug substances in each layer, thus with a single dosage form it is possible to act in different diseases with distinct times and/or sites of drug release (77). The off-release lag time may be adjustable by manipulation of the formulation composition, in order to have the best drug release profile for the targeted disease.

Investigation in academia and industry has been driven in distinct ways to develop the most adequate PDDS. In the present time, several are the approaches to pulsatile behavior of dosage forms found in literature (see Fig. 4.3).

4.1.1. Classification and Manufacturing Processes

PDDS can be classified in three categories, as shown in Fig. 4.3: time controlled, stimuli induced and externally regulated.

In those systems the major factor to fine-tune is lag time, and the purpose is to ensure a delivery of the drug in the proper local and proper time to achieve optimal therapeutic effect and minimal side effects.

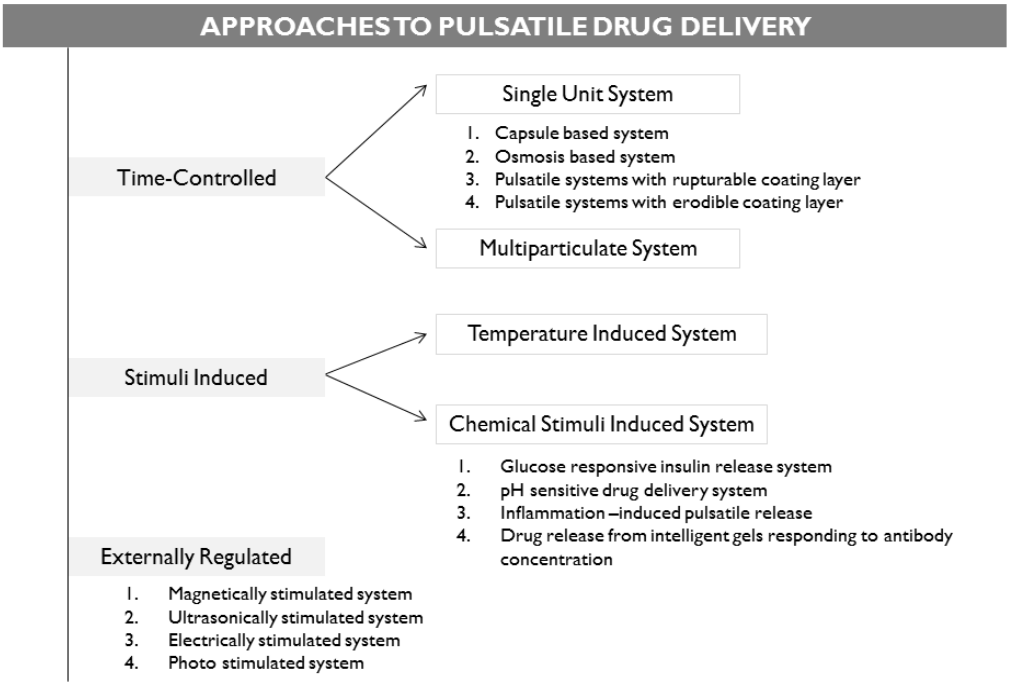

Figure 4.3. Schematic representation of approaches for the development of pulsatile drug delivery formulations. PDDS can be broadly classified in three major categories (time-controlled release systems, stimuli induced release systems and externally regulated systems) (73, 75, 78).

I. Time-Controlled Pulsatile Drug Delivery Systems

In time-controlled pulsatile drug delivery systems, the release of the drug substance is independent from the environmental factors (78). Those systems can be further classified in single unit or multiparticulate systems (73, 74, 78) and are mostly formulated as capsules or tablets for oral administration.

SINGLE UNIT SYSTEMS

Capsule based systems. The general design of capsule based systems consists of a water insoluble capsule body housing a drug formulation entrapped by a plug that pushes itself out of the capsule after contact with the dissolution medium (73) (see Fig. 4.4). The plug is responsible for controlling the lag time prior to drug release and that is achieved by manipulation of its physical and chemical properties and position (73, 75, 78). The plug may be made of different approved excipients and based on its constitution, distinct behaviors are expected: the plug being removed after a predetermined lag time due to swelling, erosion or

dissolution (79). Krögel and Roland (79) reported that an erodible plug is more effective than a swelling one, because it is possible that the swollen plug isn't always ejected as one piece, which may compromise drug release. Additionally a tight fit between the plug and the impermeable capsule body is mandatory to prevent water penetration and premature drug release (79). The drug release rate from the capsular body is then influenced by the inclusion of effervescent or disintegrant agents, which are reported to accelerate the process (79). The manufacturing procedure to develop such systems is similar to that shown in Fig. 4.5. But in this process the capsule was hand filled and the plugs were also placed by hand (79), what may turn this method very difficult to scale-up using standard pharmaceutical equipment.

The first capsule based system for pulsatile drug delivery described in literature was Pulsincap® system, developed by R. P. Scherer International Corporation (80). This system is schematically identical to the one represented on Fig. 4.4: a water-insoluble capsule body containing the drug reservoir that is enclosed by a swellable hydrogel plug. Upon contact with dissolution medium this plug swells until it is ejected from the capsule body allowing a rapid drug release after a lag time (75).

Osmosis based systems take advantage of osmotic pressure in order to achieve a controlled delivery of a certain drug substance (81). The osmotic system consists of a capsular body coated with a semipermeable membrane holding the drug formulation, an insoluble plug and an osmotically active agent (82). When in contact with the dissolution medium, the semipermeable membrane allows water diffusion, what results in an increased inner pressure (78). Consequently the insoluble plug is ejected from the capsular body after a lag time and the active drug substance is released (78, 81). In osmosis based systems, the release rate of drug substances is independent of pH and other physiological parameters, once the semipermeable membrane does not allow solute permeation (81). The lag time of an osmosis based system may be modulated by the semipermeable membrane thickness (82). An example is the Port® system, developed by Therapeutic Research Laboratory Ann Arbor (78, 82). The manufacturing process of this system may be similar to that described in Fig. 4.5, taking into account the differences in the formulation, namely the plug's characteristics and constitution, and the presence of a coating layer. Osmosis based systems are also developed as tablets that have at least one delivery orifice, through which the drug is

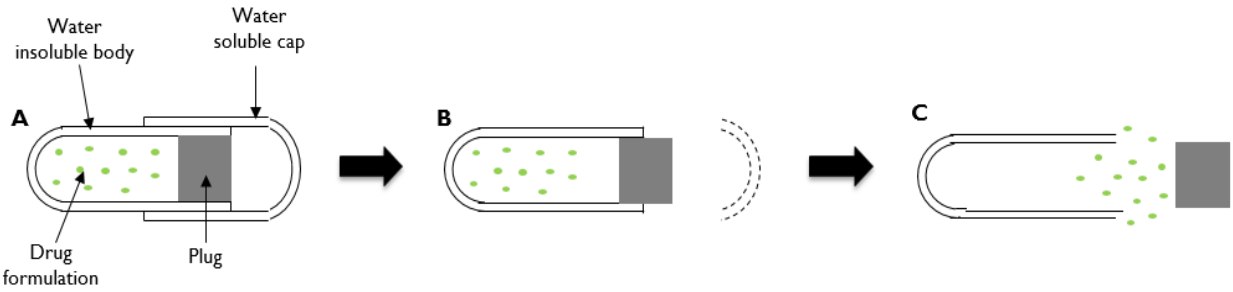

Figure 4.4. Schematic representation of capsule based system (A) and its different stages in drug release. When in contact with dissolution medium (B) the water soluble cap dissolves, the plug pushes itself out of the capsule body and (C) the drug formulation is released (73, 74, 78).

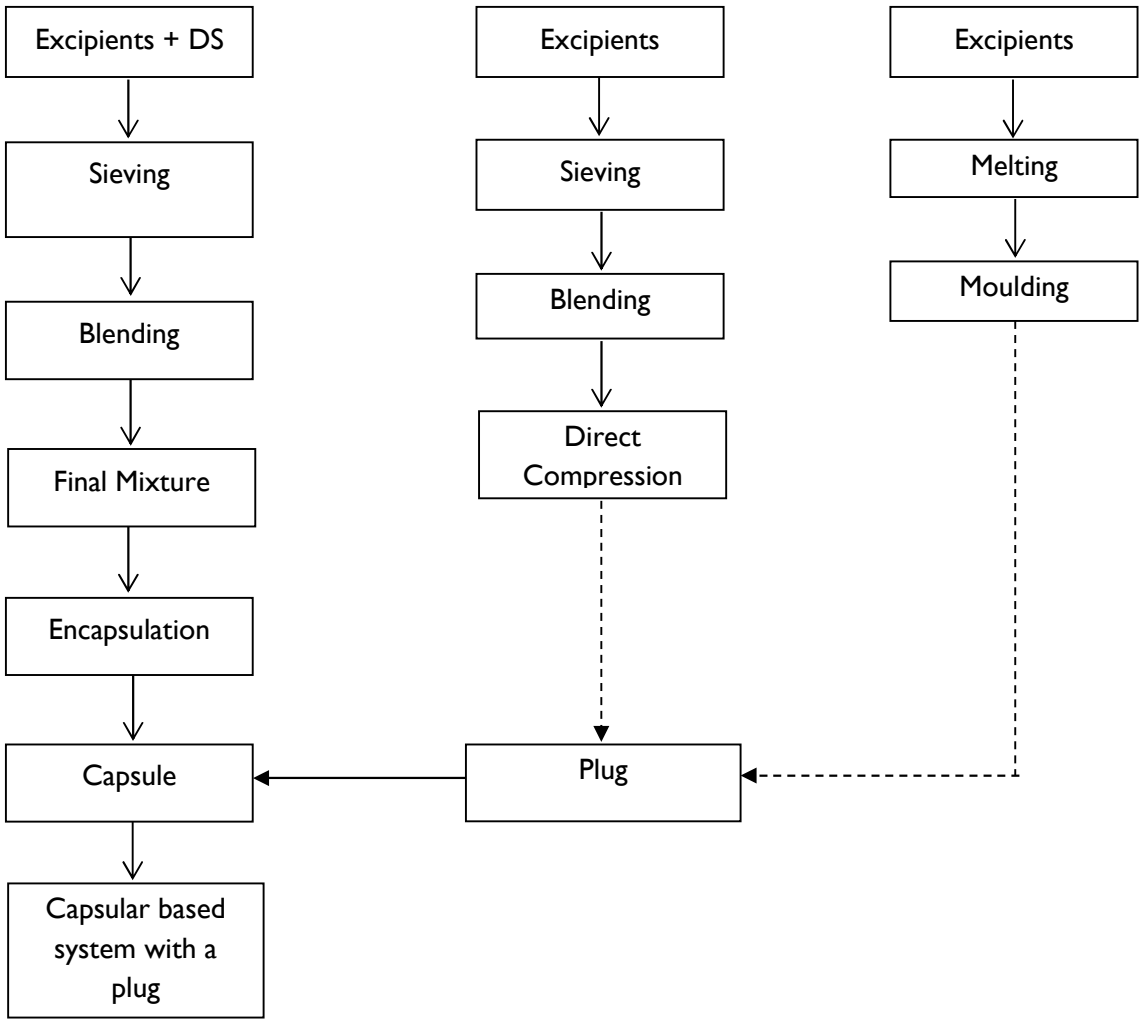

Figure 4.5. Schematic diagram of pulsatile capsule based system design, both with compressed plug or meltable plug (79).

released, an osmotic drug core (optionally containing an osmagent) and a semipermeable membrane that allows water diffusion (81). In its simplest design, the elementary osmotic pump (EOP), the water influx through the semipermeable membrane is responsible for an increased osmotic pressure of core formulation that leads to the drug release (81), see Fig. 4.6. Osmosis based systems with a delivery orifice may also be available in capsular dosage form for the delivery of lipophilic liquid formulations (81). It was not possible to find any information regarding the manufacturing process of such drug delivery systems.

Pulsatile systems with rupturable coating layer (Fig. 4.7A). The release of the drug from these systems is dependent on the disintegration rate of the outer rupturable layer. On the other

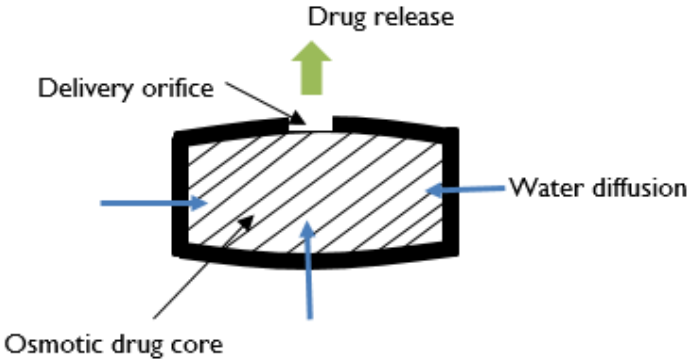

Figure 4.6. Schematic diagram of elementary osmotic pump and its mechanism of drug release (81).

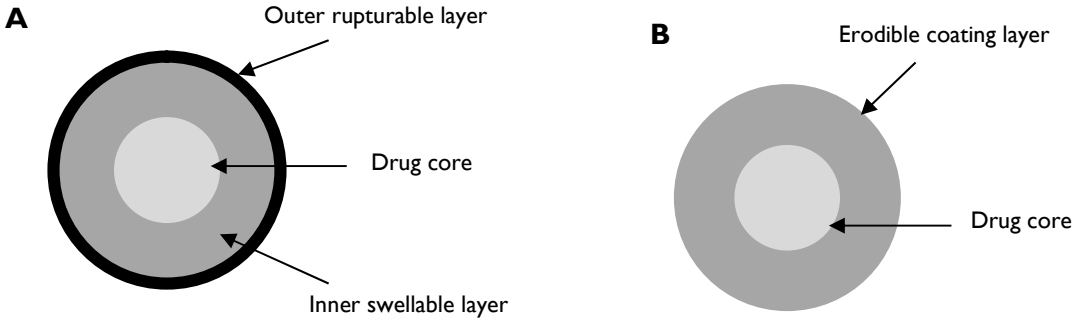

Figure 4.7. Schematic diagram of single unit delivery systems (A) with rupturable layer and (B) with erodible layer (74, 78).

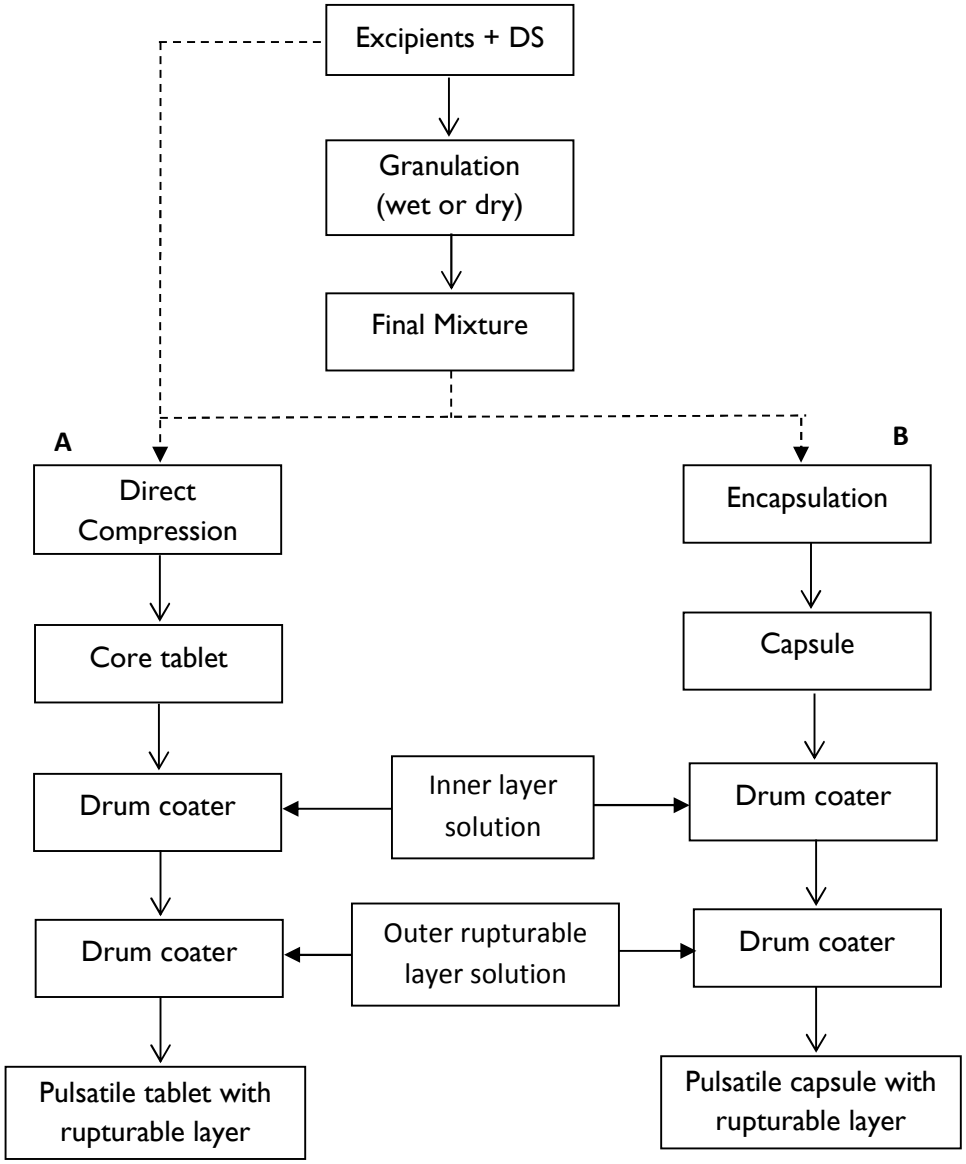

Figure 4.8. Schematic diagram of (A) pulsatile tablet with rupturable and swellable layers design (80) and (B) pulsatile capsules with rupturable and swellable layers (84) manufacturing process.

hand, the formulation, water permeation and mechanical resistance define the lag time prior to drug release (83). The use of effervescent excipients, swelling agents or osmotic agents in the inner layer help to achieve the pressure required to the rupture of the coating triggering drug release (75). Optimization of the system allows drug release to be obtained at a specific time. Sungthongjeen *et al* (80) developed a tablet consisting in a core coated with an inner swelling layer and an outer rupturable layer, following the general manufacturing procedure described in Fig. 4.8A. Capsular systems of this type may be manufactured as described in

Fig. 4.8B (84). In both tablet (80) and capsule (84) the inner layers contain croscarmellose sodium and the outer rupturable layers contain ethylcellulose, which is the widest used polymer since it ruptures efficiently (85).

Pulsatile systems with erodible coating layer (Fig. 4.7B), consist on a reservoir core containing the drug that is coated with a layer that erodes or dissolves after a specific lag time (78). Chronotropic® system and Timeclock® system are both examples of this type of system described in literature. Chronotropic® system consists on a core containing the drug that is coated with the hydrophilic polymer HPMC, being suitable for both tablets and capsules (78). Timeclock® system consists on a solid dosage form, either capsule of tablet, coated with an aqueous dispersion to which is added a water-soluble polymer in order to enhance adhesion to the core (86). When in contact with aqueous media the coating layers of both these systems erode or emulsify after a lag time, releasing the drug. The lag time and the onset of action are controlled by the thickness and the viscosity grades of the polymers used in the coating layers, and are independent of gastrointestinal motility, pH, enzyme and GRT (86). This system can be manufactured using standard pharmaceutical equipment. In case of tablets, conventional compression machines may be used as well as drum coaters (80), following a procedure similar to that shown in Fig. 4.8A taking into account that there is no need for a second coating with the rupturable layer. An alternative way to manufacture this dosage forms is by using the press-coating technique, but this method is less reliable for the industrial scale manufacturing process due to the necessity of a central placement of the core tablet within the press-coated tablet (87). In the case of capsules the manufacturing process adopted may be similar to the one depicted in Fig. 4.8B, also taking into account that there is no need for a second coating with the rupturable layer.

MULTIPARTICULATE SYSTEMS

Multiparticulate systems are developed as capsules or tablets containing a large number of small sized particles – pellets (88). The basic concept is that the drug substance is released by those individual subunits, and the efficiency of the entire dose depends on the quality of each subunit as an individual system and all subunits globally (88). This system allows blending pellets with distinct composition and/or release patterns (77), once each pellet may have its own core drug formulation. Multiparticulate systems share the same basic principles

of single unit systems being the drug release rate from pellets dependent on the type of disintegration mechanism of coating layers: erosion or dissolution, swelling and rupturing (77). Beyond having all the advantages of single unit formulations, multiparticulate systems are being developed in order to overcome some of their limitations (77, 88):

- Improved bioavailability due to a smaller size;
- Less inter- and intra-subject variability;
- Smaller risk of dose dumping (it is less probable that any damage will affect all the subunits at the same time);
- Reduced risk of local irritation.

However there are some drawbacks associated with those systems when compared to single unit systems, namely higher costs of production and multiple formulation steps (77).
Multiparticulate systems may be developed by coating of nonpareil seeds (89), in order to overcome the limitations associated with their production by methods that required high specialized equipment and technology. Among all the available coating techniques, spray-coating in a fluid bed drying is the most commonly used, due to the advantages concerning time, costs and quality in the process development (89). The layering process is applied both for the drug substance load and for the desired coating layers (89). This technique allows the development of pulsatile multiparticulate systems with standard pharmaceutical equipment, such as tableting machines and capsule filling machines.

II. Stimuli induced pulsatile delivery system

In stimuli induced pulsatile delivery systems drug release depends on stimuli from the biological environment like temperature or any chemical stimuli (83). Those systems incorporate polymeric hydrogels that undergo conformational and physical changes by a swelling-deswelling behavior in response to biological stimuli, being those changes reversible if the triggering stimulus is removed (90).

Temperature induced systems are constituted by thermo-responsive hydrogels which undergo volume changes in response to temperature variations and promote drug release in the swollen state (78). Poly(N-isopropylacrylamide) (PNIPA) is the most studied hydrogel for temperature-induced drug release (91, 92), having a lower critical solution temperature

(LCST) around 32 and 34 °C in water, that is possible to be adjusted for drug delivery purposes (90, 92). The critical solution temperature is the temperature at which complete miscibility of two liquids is achieved (90). In case of polymers with LCST, the solubility is inversely proportional to temperature, therefore an increase of the temperature above the LCST results in a shrinking behavior of the system (90). On the other hand, if the temperature decreases below the LCST, the polymer swells and the drug is released (91). It was not possible to find on literature any information regarding the manufacturing process of this type of pulsatile drug delivery system.

Chemical stimuli induced systems release the drug in response to changes due to a chemical stimulus like pH, glucose blood levels and inflammation, when the polymer is in the swollen state (83). Several efforts have been made to develop this type of drug delivery systems. One example is a formulation with pH-sensitive polymers with immobilized glucose oxidase for modulated insulin delivery in response to variations in glucose blood levels (93), as an integrating part of *glucose responsive insulin release systems*. Taking advantage of the variations of pH environments in the GIT, *pH sensitive delivery systems* have been developed. Polymers such as cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose are used to achieve pH dependent drug release. By choosing the suitable pH dependent polymer it is possible to deliver the drug in a specific location, such as drug release in the small intestine by enteric coating (78). It was not possible to find on literature any information regarding the manufacturing process of this type of pulsatile drug delivery system.

III. Externally Regulated Pulsatile Delivery Systems

In externally regulated dosage forms, drug release is achieved by external stimulation such as magnetism, ultrasound, electrical effect and irradiation (93). Besides the existence of different approaches, the externally regulated pulsatile drug delivery systems are still experimental (93). *Magnetically induced delivery system* was one of the first types of these externally regulated pulsatile delivery systems. The incorporation of a magnetic carrier such as iron, nickel, magnetite, cobalt, etc. into capsules or tablets is a way to achieve this objective (73). Those components will respond to the application of an external magnetic field and will slow down the movement of the administered dosage form in the GIT thus changing the timing and/or extent of drug absorption in the stomach or in the intestines (83).

It was not possible to find on literature any information regarding the manufacturing process of this type of pulsatile drug delivery system.

When the aim is to obtain a colonic-specific release of the drug that can be achieved by coating the pulsatile dosage form with an acidic resistant enteric coat layer (75).

In this chapter the focus is only these types of systems developed for oral drug delivery in the form of capsules and/or tablets. But there are more of these types of dosage forms such as inflammation induced drug delivery systems and ultrasound induced pulsatile systems that are being investigated in the form of implantable capsules, injectable dosage forms, and tissues permeation dosage forms (85, 93).

4.1.2. Suitable Drugs and Main Excipients Used in Formulation

According to previous information in this monograph, the suitable drugs to incorporate in PDDS formulations are those which are adequate to treat diseases with a predictable circadian rhythm. Table 4.I summarizes the type of drug substances used in each of that known diseases, in both research and development. Singh *et al* (94) published a review on drugs used in PDDS for cardiovascular diseases, arthritis and asthma, which are summarized in Table 4.2. In the case of cardiovascular diseases, those studies were published for treatment of hypertension, angina pectoris and myocardial infarction (94), and studies on arthritis were published for treatment of arthritis and rheumatoid arthritis (94). But if we analyze in more detail the research studies in PDDS we will see that more active ingredients are being studied, included in the categories referenced in Table 4.1. For example, Krishnaveni *et al* (87) reported the development of a tablet dosage form containing Montelukast Sodium to treat asthma with awakening nightly phenomena, based on a principle of drug administration at bedtime and programmed drug release in early morning hours, when the symptoms increase.

Nevertheless, using the most suitable excipients to formulate pulsatile dosage forms is crucial to its success. Since there are distinct types of pulsatile system, the excipients have to be chosen very carefully to fulfill the formulation requirements and to make the dosage form effective. In this way, the selected excipients must go through strong selection criteria and all

Table 4.2. Drug substances used in studies to formulate PDDS (87, 94).

Diseases	**Type of drugs used**	**Drugs substance (trials)**
Cardiovascular diseases	Nitroglycerins, calcium chanel blockers, ACE inhibitors	Losartan potassium, metoprolol tartarate, pronanolol hydrochloride, lisinopril, atenolol, captopril
Arthritis	NSAIDs, glucocorticoids	Aceclofenac, flurbiprofen, indomethacin, lornoxicam, methotrexate, meloxicam, diclofenac sodium,
Asthma	Antihistamines, β_2 agonists	Montelukast sodium, salbutamol sulphate, terbutaline sulphate, theophylline

Table 4.3. Examples of excipients used in formulation of PDDS.

<table>
<tr><th colspan="4">Type of system</th><th colspan="3">Excipients widely used</th><th>Refe-rences</th></tr>
<tr><td rowspan="6">Time Controlled</td><td rowspan="4">Single Unit</td><td rowspan="2">Capsule based system</td><td rowspan="3"></td><td rowspan="3">Plug</td><td>Swelling</td><td>Polymethacrilates</td><td rowspan="3">78, 79</td></tr>
<tr><td>Erosion</td><td>HPMC, PVA, polyethylene oxide (PEO)</td></tr>
<tr><td>Dissolution</td><td>GMO</td></tr>
<tr><td colspan="2">Osmosis based system</td><td colspan="3">Cellulose acetate coating</td><td>73, 78</td></tr>
<tr><td rowspan="2">Pulsatile systems</td><td>Rupturable coating</td><td colspan="3">EC</td><td>84</td></tr>
<tr><td>Erodible coating</td><td colspan="3">HPMC</td><td>78</td></tr>
<tr><td colspan="3">Multiparticulate</td><td colspan="3">The excipients used are dependent on the type of multiparticulate system.</td><td>77, 88</td></tr>
<tr><td colspan="2" rowspan="2">Stimuli Induced</td><td>Temperature induced</td><td colspan="4">PNIPA, poly(N,N-diethylacrylamide), Poly(2-carboxyisopropylacrylamide), Poly(N-(l)-1-hydroxymethyl-propylmethacrylamide)</td><td>90, 92</td></tr>
<tr><td>Chemical induced</td><td colspan="4">Cellulose acetate phthalate, polyacrilates, sodium carboxymethylcellulose</td><td>73, 90</td></tr>
<tr><td colspan="2">Externally Regulated</td><td>Magnetically induced</td><td colspan="4">Incorporation of magnetic carrier: iron, nickel, magnetite, cobalt</td><td>91</td></tr>
</table>

relevant properties must be evaluated, as well as interactions between excipients or between excipients and drug substances (87). The combination of the drug substance and the most appropriate excipients allows the development of the most adequate formulation. Table 4.3 enlists some of the excipients used in the distinct types PDDS formulations, commercialized or experimental delivery systems.

4.1.3. Factors Affecting The Pulsatile Behavior

The factor with the major impact in pulsatile behavior of dosage forms is the formulation variables, which are dependent on the type of pulsatile system considered. Those formulation parameters depend on the type of excipients selected, its amount and characteristics (90, 87), the hydrogels used, the constitution and thickness of the polymer coating layer, the characteristics of the plug, and so on. Once there are distinct types of PDDS, for each type, the formulation variables to consider are measured independently from the others, being aware of the fact that distinct parameters may interfere with the pulsatile behavior of the same dosage form.

In time-controlled PDDS it is crucial to control the lag time prior to drug release. In this way, factors such as thickness and constitution of the coating layer (80, 81, 95), constitution and resistance of the capsular plug (79) and permeability of osmotic plug are determinants of the pulsatile behavior. In some cases, the quality of the enteric coating is determinant to have a delivery of the drug at the target place, and in case of capsular systems, a thin fit between the capsular body and the plug is crucial so that water penetration and premature drug release are avoided (79).

The physicochemical properties of the drug substances are also factors that may affect the pulsatile behavior of the dosage form. Coughland *et al* (92) studied the effect of drug physicochemical properties on the behavior of PNIPA hydrogels, and the experiments show a great influence of drug solubility, size and chemical nature in the physical behavior of the hydrogel as well as in the pulsatile drug release pattern.

4.1.4. Advantages and Limitations

There is a wide range of advantages sustaining the development of pulsatile drug delivery systems over conventional dosage forms. The advantages are:

- PDDS are used in chronotherapy for diseases that show circadian rhythms in their pathophysiology, allowing the delivery of the right dose at the right time in the right place (75, 78, 94).
- Increased patient compliance. PDDS allow reduction in dose frequency, strength and cost thus reducing side effects without changing the therapeutic effect (75, 78, 85, 94).
- Prevents the continuous presence on plasma of drugs that produce biological tolerance, thus increasing their therapeutic effect (76).
- Allows site specific drug release at target site of absorption, like the colon, enhancing bioavailability and absorption capacity (75, 85, 94).
- Site targeting enables delivery of poorly bioavailable drugs in an efficient way, and protects gastric mucosa from irritating drugs (75, 78, 85).
- Provide constant drug levels at the site of action and prevent the peak-valley fluctuations in blood stream, maintaining plasma drug concentration within the therapeutic window (75, 94).
- Prevention of drug loss by extensive first pass metabolism, because PDDS provide a fast drug input that saturates the metabolizing enzymes, thus minimizing the pre-systemic metabolism (75, 76)
- Facility to produce combination of dosage forms and ease of combining pellets with different compositions or drug release patterns (multiparticulate systems) (88)

Besides all the advantages mentioned, it is essential to elucidate some limitations of pulsatile drug delivery systems, in order to understand the restrictions of those systems and the pathway that researchers have to draw in order to achieve an optimal dosage form for pulsatile delivery of drugs. Those limitations are:

- Multiple manufacturing steps in case of multiparticulate systems (88)
- Rupture time cannot be always fine-tuned as it depends on the physicochemical properties of the polymer.

- *In vivo* variability in single unit formulations may be observed (94). This means the possibility of an unpredictable IVIVC (78).

4.1.5. *In Vitro* and *In Vivo* Evaluation

4.1.5.1. *In Vitro* Studies

To the best of our knowledge there are no *in vitro* performance tests described in any pharmacopoeia for characterization of pulsatile drug delivery systems. Besides that there are some reports in literature which describe alternative ways of evaluating *in vitro* the performance of pulsatile dosage forms, but there is no uniformity in the apparatus used. For example, in literature it is possible to find descriptions of *in vitro* evaluations of pulsatile tablets with USP apparatus I (95), USP apparatus II (86, 87) and USP apparatus XXIV (80) and *in vitro* evaluation of pulsatile capsules with USP apparatus I (95) and USP apparatus XXIII (79). This lack of uniformity between methodologies makes the comparison of the results difficult and unreliable. Besides that, tablets are normally evaluated for their physicochemical characteristics, such as thickness, friability, hardness and drug content uniformity (87), as well as for interactions between components of the dosage form by Fourier transform infrared (FTIR) spectroscopy (87) and gamma-scintigraphic studies (86, 87).

4.1.5.2. *In Vivo* Studies

To the best of our knowledge there are no guidelines for *in vivo* performance tests. Besides that literature reports one *in vivo* study by gamma-scintigraphy in three distinct groups of human volunteers that was clinically approved (86).

Besides the importance of these tests they are actually alternative methods because there are no guidelines available for both *in vitro* and *in vivo* performance tests for PDDS.

4.1.6. Market and Regulatory Considerations

Some pulsatile technologies and products are already on the market and some examples can be found on Table 4.4. Elan Corporation is the leader in terms of number of marketed technologies and the multiparticulate systems are the most widely available (85). In spite of

that, the market of PDDS in general does not count with many products. Literature reports an extensive number of studies and research papers on PDDS are available (74, 76), but many investigations are limited to the laboratory scale instead of reaching the marketbecause it is much easier to manufacture a small-scale batch in the laboratory than a large-scale batch in industry. Nonetheless, as technological and pharmaceutical knowledge increases, the number of marketed PDDS is growing.

4.2. Conclusion

A chronodelivery system, based on biological rhythms, is a state-of-art technology for drug delivery. The greatest advantage of this delivery system is the possibility to release the drug according to the symptom demands of each disease, thus reducing the risk of drug resistance.

Table 4.4. Pulsatile technologies available in the market.

Technology	Mechanism	Marketed Products	Company	References
CODAS™	Multiparticular system	Verelan® PM	Elan Corp.	75, 77
DIFFUCAPS®	Multiparticular system	Innopran® XL, Zofran, AMRIX®	Eurand's Corp	75, 77
GEOCLOCK™	Single unit tablets	Lodotra®	Skyepharma	75
GEOMATRIX™	Multi-layered tablet	Madopar™ DR, Paxil CR™, Zyflo CR™, Xatral™, Sular™, Coruno™, Diclofenac-ratiopharm™ uno, Requip™ Once-a-day	Skyepharma	96
IPDAS®	High density multiparticulate tablet	Naprelan®	Elan Corp.	75, 85
OROS	Osmotic mechanism	Procardia XL®, Ditropan XL®, Concerta®, Covera-HS®, Invega™	ALZA Corp.	75, 85
PULSYS™	Timme-Controlled system	Moxatag®	MiddleBrook Pharmaceuticals	75, 77
SODAS®	Multiparticular system	Avinza®, Ritalin® LA, Focalin® XR, Luvox® CR	Elan Corp.	73, 97

Besides being a promising drug delivery system, it is not described in any pharmacopoeia and there are no guidelines regarding suitable performance tests for these formulations. For this reason, there is the need to define standard methods for the characterization of the dosage form. It is also important that researchers understand the limitations of those systems and find ways to overcome them. For example, the efficiency of the dosage form is dependent on formulation factors such as the core characteristics, the polymers used in coating layers and their thickness in case of tablets, and on the plug characteristics and capsular body constitution used in case of capsules. All these parameters may be adjusted in order to achieve the desired lag time, which is the major factor encompassing the success of the dosage form. The major challenge is the understanding of the influence of the biological environment on the release performance of pulsatile drug delivery systems in order to develop simple systems based on approved excipients with a good IVIVC.

Literature describes several attempts made by different researchers to achieve the goal of developing the best formulation of this delivery system, and there are inclusively some patents registered on this field. Nonetheless, pulsatile drug delivery systems are still largely experimental (particularly stimuli induced and externally regulated). Although there is many research in this field, there are few products in the market.

5. CHAPTER IV

Self-Microemulsifying Drug Delivery Systems

5.1. Self-Microemulsifying Drug Delivery Systems

A pronounced parcel of new drug candidates are poorly water soluble substances and their oral delivery tend to be challenging due to their low bioavailability, high inter and intra subject variability and lack of dose linearity (98). For this reason, the development of lipid based formulations for the oral delivery of lipophilic drug candidates in order to enhance their bioavailability have gained importance in pharmaceutical industry (98). Great attention has been given in particular to microemulsion based formulations (99, 100) due to the capacity of microemulsions to behave as a reservoir for drug substances (99). Microemulsions are thermodynamically stable and optically isotropic solutions, but are not able to be encapsulated due to their water content (98 – 100), hence, Self-Microemulsifying Drug Delivery Systems (SMEDDS) are being developed (98, 100, 101). These consist essentially on isotropic mixtures of oil, surfactant, co-surfactant and drug substance which, when in contact with an aqueous medium such as GIT, tend to spontaneously form microemulsions (98). These dosage forms bring about some advantages namely enhanced drug solubilization, faster release rates and improved absorption due not only to the already dissolved form of the drugs substance in the formulation but also to the resulting small droplets size of less than 50 nm that provide a large interfacial surface area for drug absorption (98, 102, 103). But SMEDDS have also some disadvantages regarding the manufacturing processes and high production costs, possibility of interaction between the formulation and the capsule shell, the possibility of irreversible precipitation of drugs and excipients, special storage requirements (100, 101), and few choices of final dosage forms since they are presented only as soft or hard gelatin capsules (98). These disadvantages may be overcomed by the development of Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) (100, 101). Generally these dosage forms are prepared by incorporation of the liquid self-microemulsifying excipients into powders by different solidification techniques, and may then be encapsulated or compressed to make capsules or tablets, respectively (100, 101). S-SMEDDS combine the advantages of liquid self-emulsifying formulations and the advantages of solid dosage forms (100, 101) and are promising dosage forms for the delivery of lipophilic drug substances.

5.1.1. Manufacturing Processes

In the process of developing S-SMEDDS, the first step is to achieve the desired liquid SMEDDS formulation and the next step is to apply to that formulation a solidification technique that allows a liquid-to-solid transformation (99, 100).
The schematic diagram of SMEDDS manufacturing process is represented in Fig. 5.1. The different components of the formulation are placed in the same recipient and are mixed by gentle stirring and by harsh mixing (such as vortex mixing (104) or sonication (105)) and are heated on a magnetic stirrer until all drug substance is completely dissolved. The final mixture is a SMEDDS that is stored at room temperature until further use. That further use in this case may be, as represented in Fig. 5.1, encapsulation to form a capsular dosage form of SMEDDS (101, 106) or solidification to form S-SMEDDS.

Literature reports a variety of different reliable solidification techniques to transform SMEDDS in S-SMEDDS (100, 101):

1. *Spray Drying*

The fluxogram of S-SMEDDS manufacturing process by spray drying is represented in Fig. 5.2. Essentially SMEDDS are mixed with a solid carrier (such as dextran 40 (107) and maltodextrin (108)) under continuous stirring. The mixture is heated during the necessary time until an homogeneous dispersion is obtained, that is further placed in a spray dryer (107, 108) to obtain a dry powder able to be encapsulated or compressed into a tablet (100, 101). As the drying process takes place, the load (liquid SMEDDS) adsorbs onto the surface of the carrier and forms granular particles with entrapped drug substance (108). There are some parameters that influence the spray-drying process performance, namely the airflow pattern and the temperature (109) that must be optimized accordingly to the drying characteristics of the product and powder specification (100, 101).
Spray drying is one of the most widely used techniques for microencapsulation with standard pharmaceutical equipment and enables efficient scale-up (108), and solid SMEDDS prepared by this technique are described to preserve the emulsifying properties of liquid SMEDDS (107, 108).

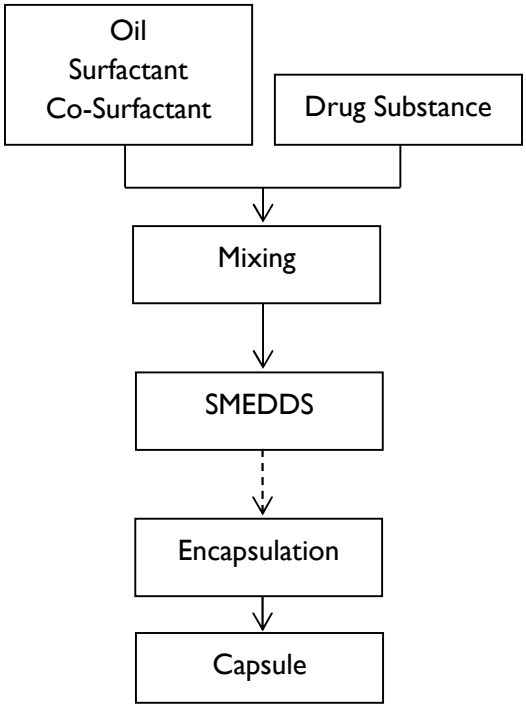

Figure 5.1. Schematic diagram of SMEDDS manufacturing process (98, 104, 105).

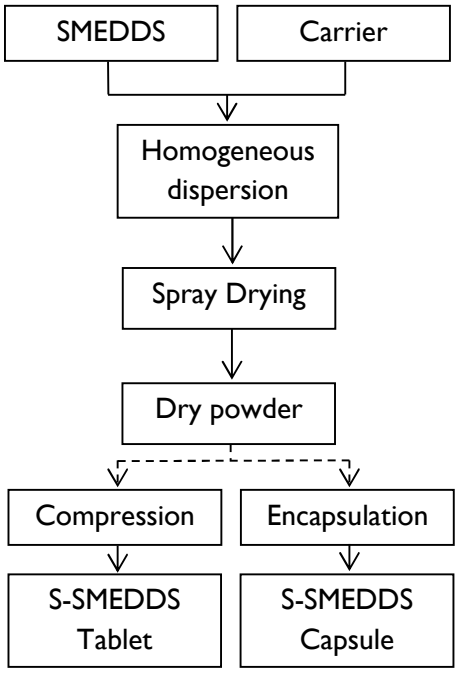

Figure 5.2. Schematic diagram of S--SMEDDS manufacturing process by spray drying technique (107, 108).

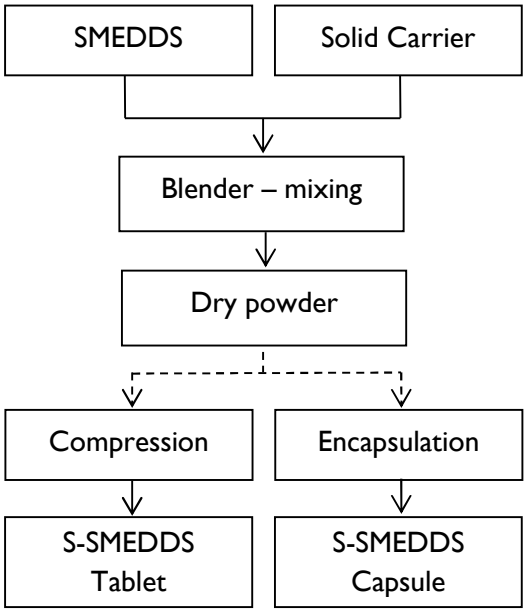

Figure 5.3. Schematic diagram of S-SMEDDS manufacturing process by adsorption to a solid carrier technique (110, 111).

2. *Adsorption to Solid Carrier*

The manufacturing process of S-SMEDDS by adsorption to a solid carrier is represented in Fig. 5.3. Essentially SMEDDS and one or more solid carriers (such as microcrystalline cellulose (MCC) (110) and colloidal silicon dioxide (110, 111)) are mixed in a blender and then dried to a free flowing powder (110, 111) able to be encapsulated or blended with suitable excipients prior to compression into tablets (100, 101, 110). The solid carriers may be materials that provide high surface area with good disintegration characteristics (110) and the liquid SMEDDS adsorb to them, forming free flowing granular particles (111). S-SMEDDS prepared by this technique are described to preserve the emulsifying properties of liquid SMEDDS (110, 111). This solidification technique seems to be easy and effective, but there are some constraints that may affect its success, namely problems related to the compression technique and the final tablet, such as the possibility of exudation, sticking and hardness issues, and the need of a large quantity of solid carrier to adsorb the liquid formulation that leads to a final dosage form with a large volume (102).

3. *Melt Granulation*

Melt granulation is a technique in which powder agglomeration is achieved through the addition of either a molten binder or a solid binder which melts at relatively low temperatures during the process (100, 101, 112), acting like a liquid binder between particles (112). This solidification technique consists on the combination of three phases (112, 113):

I. *Wetting and Nucleation Step.* In this step the binder is blended with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates, upon heating. There are two main mechanisms proposed for the nucleation step, taking into account the relative particle size of different components: a) immersion and b) distribution. Nucleation by immersion takes place when the molten binder droplets are bigger than the fine solid particles, and the mechanism consists on deposition of fine solid particles onto the surface of molten binder droplets, as seen in Fig. 5.4A. On the other hand, nucleation by distribution leads to the distribution of the molten binding liquid onto the surfaces of fine solid particles, as seen in Fig. 5.4B, provided by the collision between wetted particles.

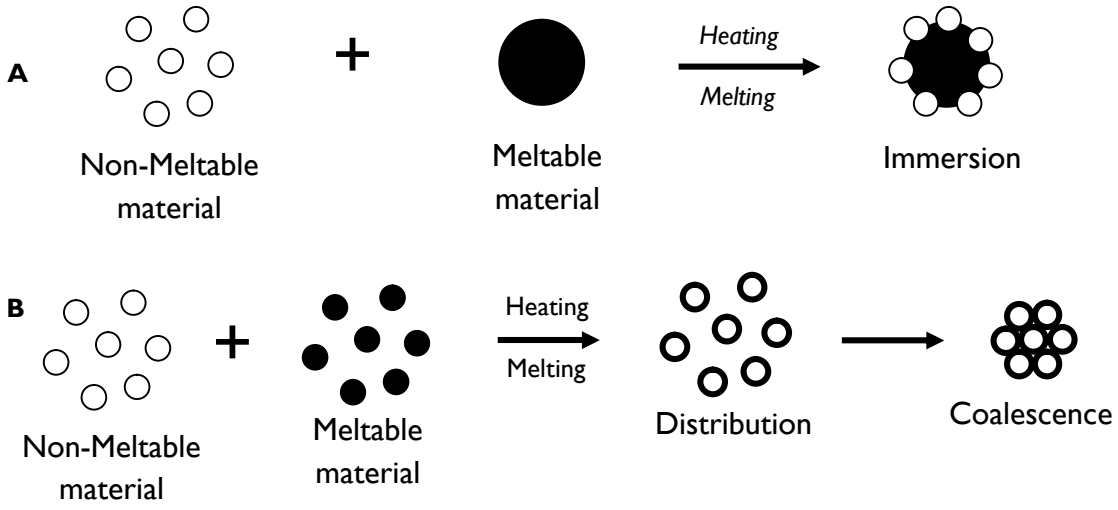

Figure 5.4. Nucleation step in melt granulation solidification technique. A) Nucleation by immersion process and B) nucleation by distribution process (112, 113).

II. *Coalescence step*. In this step a successful fusion of nuclei is observed, which is promoted by surface liquid of nuclei. That surface liquid is essential for enabling the deformation of nuclei surface for coalescent, as well as for promoting the rounding of granulation, since it imparts plasticity to the nuclei.

III. *Attrition-breakage step*. This step refers to the phenomenon of granulation fragmentation. The solidification occurs by train cooling to ambient temperature, excluding the need for drying in a tumbling process.

Some requirements must be fulfilled concerning melt granulation technique. Namely, the meltable binder must be added in a proportion of 10 – 30 % w/w of fine solid particles and must be solid at room temperature and must have a melting point within the range 40 – 100 °C, while the melting point of fine solid particles must be at least 20°C higher than that of the maximum processing temperature (112, 113). There are hydrophobic meltable binders, which are used for prolonged-release formulation (112), such as stearic acid, cetyl and stearyl alcohol and various waxes, and hydrophilic meltable binders, which are used for immediate-release formulations (112), such as polyoxyl stearates and PEG (112, 113). In this technique, there is no requirement for solvent use and the drying process is not necessary, thus fewer process steps are required, making melt granulation advantageous over other conventional granulation methods (112, 113).

Gupta *et al* (114) used melt granulation process to absorb lipids, surfactants and drugs onto solid neutral carriers. Pellets produced by this technique are able to be compressed into tablets (114).

4. *Melt Extrusion/ Extrusion Spheronization*

The manufacturing steps of S-SMEDDS by melt extrusion/extrusion spheronization technique is represented in Fig. 5.5. Essentially SMEDDS are mixed with water to obtain an o/w emulsion that is added to a dry powder of other excipients, and mixed until a wet mass is obtained (115 – 117). Then takes place the extrusion process, in which the wet mass is forced through the extruder under controlled conditions, forming spaghetti-like extrudates

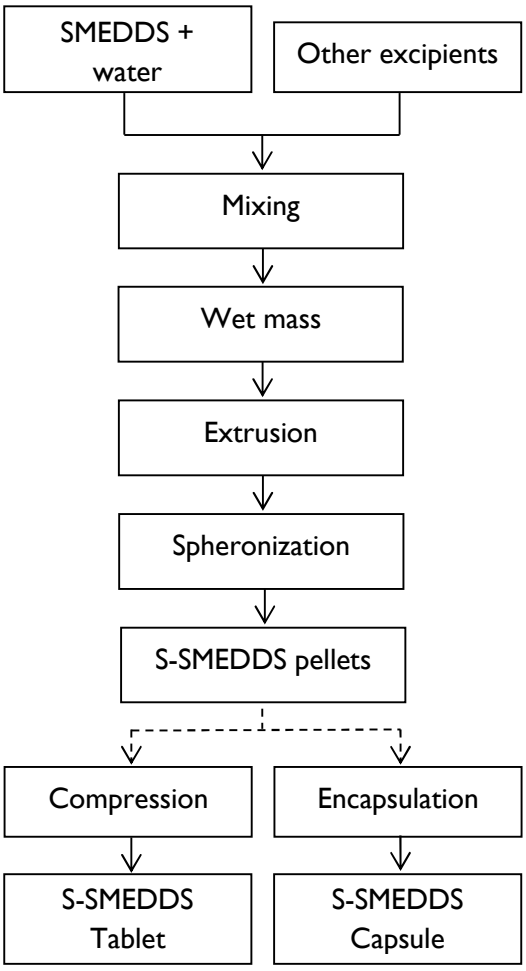

Figure 5.5. Schematic diagram of S-SMEDDS manufacturing process by melt extrusion/extrusion spheronization technique (115 – 117).

(101, 115, 117). Those are then subject to a spheronization process and broken until uniformly sized spheroids are formed (pellets) (116 – 118), which are able to be encapsulated or blended with suitable excipients prior to compression into tablets (117).
This solidification technique is the most reliable for pellet production, due to its capacity to incorporate high amounts of drug substance as well as content uniformity, without producing excessively large particles (100, 101, 117). The water content is determinant for establishment of disintegration time of pellets (100, 101). Since MCC has the capacity to absorb water during the process and also to increase the rheological properties of the wet masses, it is considered as an essential excipient for successful extrusion/spheronization technique (115). But this manufacturing process is not suitable for application in conventional pharmaceutical companies, since it requires sophisticated specific equipment usually not available.

5.1.2. Suitable Drugs and Main Excipients Used in Formulation

The main formulation components of SMEDDS and S-SMEDDS are the drug substance, oil, surfactant and co-surfactant (92, 100). Lipids may affect the bioavailability of the drug substance, by changing its biopharmaceutical properties (101), and the solubility of the lipophilic DS in lipid excipients may promote the entire dose of the drug to be administered in a single dosage unit (98, 100). Thus the selection of oil, surfactant and co-surfactant may be based on the solubility of drug substance and the preparation of pseudo ternary phase diagrams (100). Some parameters may be considered when developing lipid formulations, namely Log P value (values higher than 4 are desired, so that good solvent capacities of drug are achieved (101)), and physicochemical characteristics such as melting point and dose (low melting point and low dose are desired) (98, 100). The melting point is an indicator of the lipid characteristics, as it increases with fatty acid chain length and decreases with its unsaturation level (118). Table 5.1 enlists the main excipients used in solid SMEDDS.
As said previously, SMEDDS are ideally used to increase oral bioavailability of low solubility drugs. Thus drugs from Biopharmaceutical Classification System (BCS) class II and class IV, which have poor water solubility, are preferably used (98, 100, 120), see Fig. 5.6. The

Table 5.1. Example of some excipients used in SMEDDS formulation (98, 100, 121).

Excipient	**Examples**	
Oil	LCTs	Olive oil, Corn oil, Soybean oil, Castor oil
	MCTs	Miglyol 80, Miglyol 812, Captex 255, Captex 200, Tricaprylin
	Fatty Acids	Oleic acid, Palmitic acid
	Mono- and Di-Glycerides	Capmul MCM, Capmul GMO
Surfactant	Tweens, Spans, Cremophore RH40, Labrafil 1944 CS, Labrafil M 2125, Labrafac lipophilel 349 WL, Labrasol, Lauroglycol 90, Capryol 90, Peceol	
Co-Surfactant	Alcohols & polyols	Ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, propylene glycol, HPMC
	Esters	Ethyl propionate tributyl, citrate, acetyl triethyl citrate, acetyl tributyl citrate, ethylene oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol mono- and di-acetate, ε-caprolactone, δ-valerolactone, β-butyrolactone
	Esters of Propylene glycol	Tetra hydrofuryl alcohol, PEG ether (glycofural)
	Amides	Pyrrolidone, 2-piperidone, caprolactam, N-alkypyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, polyvinil
Co-Solvent	Etanol, propylene glycol, PEG	
Consistency Builders	Tragacanth, Cetyl alcohol, Stearic acid, Beeswax	
Polymers	HPMC, EC	

difference is that BCS class II drugs are highly permeable, while class IV drugs are poorly permeable (120). Drugs like ontazolast, simvastatin, danazol, vitamin E, tocotrienols and itraconazole which belong to BCS class II are strong candidates for SMEDDS formulation (121). Taking into account previous information, drug substances with high melting point

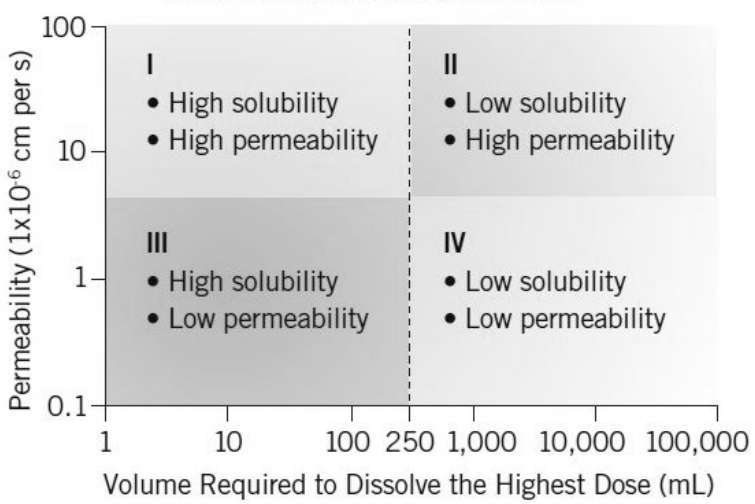

Figure 5.6. Biopharmaceutical Classification System. Adapted from 119.

having low Log P values are not suitable for SMEDDS formulation.

The oil represents one of the major components in the SMEDDS formulation. This is due to the ability to solubilize the necessary dose of the lipophilic drug substance, to assist self-emulsification process and to improve absorption of drug from the GIT depending on the molecular nature of the triglyceride (98). Long chain triglycerides (LCTs) and medium chain triglycerides (MTCs) with distinct grades of saturation have been used in SMEDDS formulation (98, 121).

A surfactant is an agent with amphiphilic nature which comprises two parts with distinct affinities for the solvents: one shows affinity to polar solvents and the other to non-polar solvents (98). Surfactants are used in a range of 30 – 60% of formulation in order to increase stability of the formulation and may have high Hydrophilic-Lipophilic Balance (HLB), so that it can assist immediate formation of microemulsion in the aqueous media (121). HLB is an indicator of the behavior that a surfactant is expected to have, and it measures the proportion between the weight percentages of the lipophilic and hydrophilic parts of the surfactant molecule (122). To form o/w emulsions the surfactant may have an HLB ranged 8–18, once hydrophilic molecules are indicated to have high values of HLB (122). The co-surfactant is used to reduce the oil and water interfacial tension and to allow the spontaneous microemulsification process (98, 121). Generally, hydrophobic co-surfactants with high values of HLB, in range 10 – 14, are used (98, 121).

The co-solvent has the purpose to assist the dispersion process and to aid solubilization of the drug (98, 123) and it also allows to decrease the amount of surfactant in the formulation (123). The consistency builders are incorporated in formulation to modify the stability of the microemulsion (98, 121). Inert polymers are also used due to their ability to form a matrix and are used in a range 5 – 40% of composition relative to the weight (98, 121).

As already mentioned, it is crucial to develop a pseudo ternary phase diagram in order to determine the concentration range of all main excipients that will yield microemulsions (98, 100). Each coordinate of the diagram represents different phases of the mixture, namely aqueous phase, oil phase and surfactant:co-surfactant mixture (Smix) at fixed weight ratios (98). Pseudo ternary phase diagrams are developed using the water titration method (100). It consists on the dilution of mixtures containing Smix and oil with water phase added dropwise, while the mixture is homogenized under constant stirring (124). The microemulsion state is registered when the mixture is transparent (99, 100, 124). Then the distinct ratios of formulation components are chosen based on the boundary conditions of the pseudo ternary phase diagram and the amount of drug is added to those boundary formulations, optimizing the self-microemulsifying formulation (100). Figure 5.7 represents an example of a Pseudoternary Phase Diagram, and the grey area represents the microemulsion region.

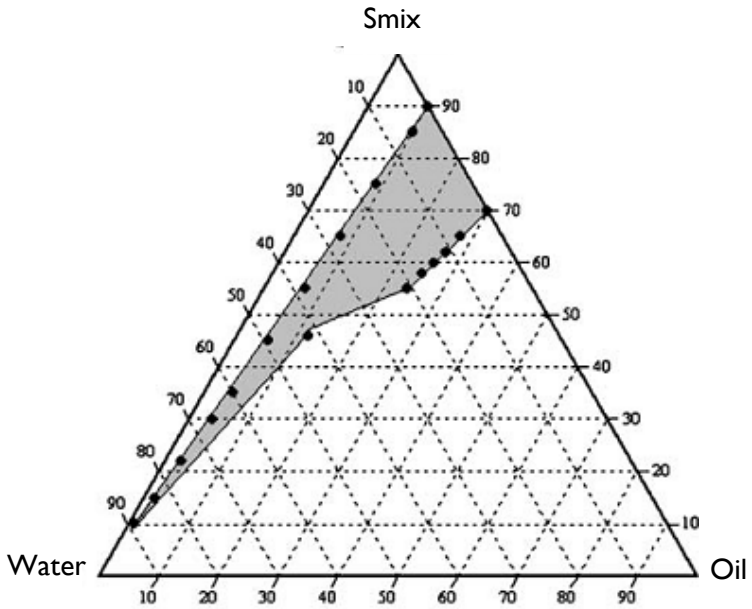

Figure 5.7. Example of a Pseudoternary Phase Diagram. The grey area represents the microemulsion region. Adapted from 110.

5.1.3. Factors Affecting SMEDDS Efficiency

The major factors affecting the efficiency of S-SMEDDS and SMEDDS are mainly the same:

1. **Nature and dose of drug substance**. As already mentioned, the characteristics of drug substance play an important role in efficiency of SMEDDS. Drug substances administered at high doses are not suitable to be incorporated into SMEDDS, except if they have great solubility in any of the components of the formulation, especially in lipid phase (98, 125). Also drug substances which show limited solubility both in water and oil, typically having log P values around 2, are not suitable to incorporate in SMEDDS (98, 125). On the contrary, drug substances with a log P around 4 are feasible candidates for self-microemulsifying formulations (101).

2. **Solubility of drug substance in the oily phase**. It is crucial that SMEDDS maintain the drug substance in their solubilized form which in turn is greatly dependent on its solubility in the selected oily phase (98, 125). There may exist a risk of precipitation when surfactant or co-surfactant greatly contribute to the solubilization of drug substance, once dilution of SMEDDS leads to a decrease of solvent capacity of such excipients (98, 125). This make equilibrium solubility studies important for the assessment of the possibility of precipitation of the DS in the GIT (98, 125).

3. **Polarity of the lipid phase**. Polarity of the lipid phase influences at a high level the release of drug substance from the microemulsion (98, 125). The polarity is an indicator of the affinity of drug towards solvent, oil or water and the type of forces involved (98). The main factors affecting the polarity of lipid droplets are the HLB, the chain length, the degree of unsaturation of the fatty acid, and the molecular weight of the lipophilic portion (98). A high polarity of the lipid phase will promote a rapid release of the drug into the aqueous phase (98), while it is desirable that the drug substance shows low crystallization rates in order to have high concentrations of drug substance in solution (125).

4. **Charge of the emulsion droplets**. Absorptive cells are negatively charged when compared to the mucosal solution in the lumen (98). As so, positively charged microemulsions will improve absorption of the DS in the GIT, because they undergo

electrostatic interactions with the mucosal surface, enhancing the bioavailability of drug substance (98).

When applying a solidification technique in order to achieve S-SMEDDS, it is also important to consider the factors that may affect the efficiency of that conversion to the final solid formulation. For example the choice of solid carrier in case of adsorption to solid carrier or spray-drying technique is crucial to achieve an appropriate S-SMEDDS. It means that the success of the solidification technique will influence the performance of the final solid lipophilic dosage form.
In order to achieve the best and more efficient formulation, each factor should be evaluated having in mind the dependency on the others.

5.1.4. Advantages and Limitations

There are some advantages encompassing the development of S-SMEDDS, since they combine the advantages of liquid dosage forms with the advantages of solid dosage forms.

The advantages of liquid SMEDDS are as follows:

- Enhancement of bioavailability of lipophilic drugs by providing an increased solubility in GIT (98, 100). In this way, these dosage forms may improve their rate and extent of absorption (100).
- Food does not negatively affect drug absorption from SMEDDS, otherwise the lipophilic fatty content from diet aids absorption (126).

Additionally, the advantages of solid SMEDDS over liquid SMEDDS are as follows:

- Can be filled into hard gelatin capsules and may even be incorporated into other solid dosage forms such as tablets (100). This is translated into lower production costs, convenience of process control and higher stability and reproducibility, when compared to soft gelatin capsules dosage forms (100).
- Spontaneously form microemulsions once in contact with dissolution environment (100).

There are also some limitations. S-SMEDDS share all the limitations registered for liquid-SMEDDS:

- It may register chemical instability of drug substances (98) in what concerns solubility and precipitation of drug in GIT (126).
- Surfactants are used at high quantities, and these large amounts may irritate the GIT (98).
- Volatile co-solvents may migrate into the shells of soft and hard gelatin capsules, what leads to the precipitation of the drug substance (98).
- Lack of good predicative *in vitro* models for lipid formulations (126).
- Possibility of lipid degradation by oxidation processes (126).

5.1.5. *In Vitro* and *In Vivo* Evaluation

5.1.5.1. *In Vitro* Studies

To the best of our knowledge there are no performance tests described in any pharmacopoeia for the evaluation of SMEDDS or S-SMEDDS. Besides that there are some reports in literature which describe alternative ways of evaluating *in vitro* the performance of S-SMEDDS dosage forms, but there is no uniformity in the apparatus used. For example, in literature it is possible to find descriptions of *in vitro* evaluations of S-SMEDDS with USP apparatus II (108, 110, 111) and with the paddle method (107, 109). This lack of uniformity between methodologies makes the comparison of the results difficult and unreliable. Besides that, S-SMEDDS powders are normally evaluated for their morphological characteristics by Scanning Electron Microscopy (107–111) and for the physical state of active drug substance by Differential Scanning Calorimetry (107, 108, 110) and X-Ray powder diffraction (107, 108, 110, 111). The interaction and compatibility between components of the dosage form may be evaluated by FTIR spectroscopy (116).

5.1.5.2. *In Vivo* Studies

To the best of our knowledge there are no guidelines for *in vivo* performance tests. Besides that literature reports i*n vivo* studies with animals that were approved by Ethical Committees (107, 111, 116).

Besides the importance of these tests they are actually alternative methods because there are no guidelines available for both *in vitro* and *in vivo* performance tests for SMEDDS nor S-SMEDDS.

5.1.5. Market and Regulatory Considerations

To the best of our knowledge, there are no S-SMEDDS already available in the market. But several studies are being conducted regarding the preparation and characterization of these solid dosage forms, and a few are related to the development and preparation techniques of dosage forms (101). There are many patents concerning SMEDDS and other lipid formulations (98). But besides all the advantages mentioned for those dosage forms and the many studies that are carried out, there are very few SMEDDS products available on the pharmaceutical market, being most of the lipid marketed products Self-Emulsifying Drug Delivery Systems (SEDDS), and these examples can be found in Table 5.2. Abbott and Roche are the leaders in terms of lipid marketed products. Nonetheless the number of SMEDDS dosage forms is low, it may be growing as technological and pharmaceutical knowledge increases.

SEDDS differ from SMEDDS by producing turbid emulsions with higher droplet size (ranged 100 – 300 nm), by having higher concentration of oil (40 – 80 %) and by using surfactants with HLB>12 (98).

5.2. Conclusion

SMEDDS are promising dosage forms which are developed to deliver lipophilic drug candidates by the oral route. SMEDDS deliver the drug dissolved in microemulsions, thus increasing their bioavailability, since they are already available for absorption when in their site of action. These drug delivery systems are presented either as soft or hard gelatin capsules, showing a reduced spectrum of dosage forms available. As an alternative to liquid SMEDDS, S-SMEDDS combine all the advantages of liquid formulations with the advantages of solid dosage forms. For this reason, S-SMEDDS are highly promising candidates to deliver

Table 5.2. Some examples of marketed SEEDS/SMEDDS products (98, 127).

Trade Name	Drug Substance	Formula-tion type	BCS Class of DS	Dosage Form	Company Name
Accutane	Isotretinoin	SEDDS	II (128)	Soft gelatin capsule	Roche
Agenerase	Amprenavir	SEDDS	II (129)	Soft gelatin capsule	GlaxoSmithKline
Aptivus	Tipranavir	SEDDS	-	Soft gelatin capsule	Boehringer Ingelheim
Fortovase	Saquinavir	SEDDS	IV (130)	Soft gelatin capsule	Roche
Gengraf	Cyclosporine A	SEDDS	IV (130)	Soft gelatin capsule	Abbott
Kaletra	Lopinavir and Ritonavir	SEDDS	IV (131) and IV (130)	Soft gelatin capsule	Abbott
Lipirex	Fenofibrate	SEDDS	II (104)	Hard gelatin capsule	Genus
Norvir	Ritonavir	SEDDS	IV	Soft gelatin capsule	Abbott
Panimum bioral	Cyclosporine	SEDDS	II (132)	Hard gelatin capsule	Panacea Biotech
Rocaltrol	Calcitriol	SEDDS	-	Soft gelatin capsule	Roche
Sandimmune	Cyclosporine A	SEDDS	IV (130)	Soft gelatin capsule	Novartis
Neoral		SMEDDS			
Vesanoid	Tretinoin	SEDDS	-	Soft gelatin capsule	Roche

poorly water soluble drugs. Solid formulations incorporate the liquid components of SMEDDS in solid powders that are filled into capsules or compressed into tablets, carrying the advantages of more flexibility on dosage forms, reduced production costs, improved stability and enhanced patient compliance.

Besides being a promising drug delivery system, there are no guidelines regarding the suitable performance tests for these formulations, making results difficult to be compared. For this reason, there are no defined standard methods for the characterization of the dosage form. It is also important to understand the factors that may influence the efficiency of SMEDDS and S-SMEDDS, in order to achieve the most proficient lipid formulation.

Although there is many research in this field, there are few products in the market regarding SMEDDS and none regarding S-SMEDDS.

6. FINAL REMARKS

All over the years significant progress has been made in pharmaceutical area, since patient centered drug design has been widely exploited. New Drug Delivery Systems are becoming available to overcome the limitations of conventional drug delivery systems, and patients have benefited from that progress through the accessibility to several and important medicines that improve therapeutic outcomes.

Even though the oral route is the most commonly used for drug administration it is still possible and important to innovate in oral dosage forms.

It is important to retain the idea that the drug substance must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, and maintain sufficient gastrointestinal residence time. The presented NDDS in this monograph are being exploited and developed aiming to provide more efficient drug absorption as well as enhanced oral bioavailability of drug substances, parameters which increase patient compliance.

In order to improve therapeutic outcomes some important conclusions can be drawn from this monograph:

1) In order to improve the efficacy and safety profile of each drug substance it is very important the choice of the route of drug administration and the type of dosage form.
2) The success of the development of a formulation depends on the careful selection of the excipients, pre-formulation studies and the choice of the *in vitro* characterization tests that should allow the best possible correlation with the *in vivo* behavior.
3) In order to develop novel dosage forms with high probability to reach the market for the benefit of patients it is very important to: select excipients approved for the route of drug administration, to know the regulatory requirements for each pharmaceutical dosage forms, to develop scalable manufacturing processes (cost-effective, with small number of steps and processes that can be conducted in equipment available in the pharma industry) and to develop medicines that address unmet medical needs.

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