

A New Approach to Enhance Bioavailability: Dosage Forms with Extended Residence Time in the Stomach

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A New Approach to Enhance Bioavailability: Dosage Forms with Extended Residence Time in the Stomach

Biyoyarlanımı Artırmada Yeni Bir Yaklaşım: Midede Kalış Süresini Uzatan Dozaj Formları

SUMMARY

In recent years there has been an increase in studies aiming to enhance bioavailability by extending the residence time of active substances absorbed in the stomach and the upper part of the small intestine in the gastrointestinal system (GIS). From the studies conducted, it has been proved that the residence time of dosage forms in GIS can be extended and bioavailability can be enhanced by preparing high density systems, floating dosage systems, swelling and expanding systems, superporous hydrogel systems, mucoadhesive and bioadhesive systems, and magnetic systems. This article includes information on the classification of dosage forms that reside in GIS, which characteristics of active substances need to have for the preparation of these dosage forms, the factors impacting the residence time in GIS, the physiology of the GIS area, the gastric discharge procedure, gastric pH, and studies conducted on these issues.

Key Words: Bioavailability, floating dosage forms, swelling systems, mucoadhesive systems, high density systems.

ÖZET

Son yıllarda midede ve bağırsağın üst kısmından emilen etkin maddelerin midede kalış süresini uzatarak biyoyarlanımının artırılması yönünde yapılan çalışmalar artış göstermiştir. Yapılan çalışmalarda, yüksek dansiteli sistemler, yüzen dozaj sistemleri, şişen ve genişleyen sistemler, süperporöz hidrojel sistemler, mukoadhesif ve biyoadesif sistemler ve magnetik sistemler kullanarak, dozaj formlarının gastrointestinal sistemde (GIS) kalış süresinin ve biyoyarlanımının artırılabilirliği kanıtlanmıştır. Bu makale, GIS'te kalış süresini uzatan dozaj formlarının sınıflandırılması, etkin maddenin hangi özelliklere sahip olması gerektiği, kalış süresini etkileyen faktörler, GIS fiziyojisi, gastrik boşaltım döngüsü, gastrik pH ile bu konuda yapılan çalışmaları içermektedir.

Anahtar kelimeler: Biyoyarlanım, yüzen dozaj formları, şişen sistemler, mukozaya yapışan sistemler, yüksek dansiteli sistemler.

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INTRODUCTION

Oral dosage forms are the most preferred dosage forms owing to the ease of administration, patient compliance in their use and the variety they provide in the preparation of the formulation. However, in the use of oral dosage forms, it is difficult to precisely determine the release of active material from the dosage form and there can be variations among individuals. Some dosage forms can leave the absorption area before the complete active substance in the dosage forms is released. One of the dosage forms developed to prevent these types of problems are those that can reside in the stomach for an extended period of time.

To produce a dosage form that can reside in GIS for an extended period of time, it is essential to initially know the area where the active substance is absorbed and the factors that affect the residence time of the dosage form in GIS. The factors that affect the residence time of the dosage forms in the stomach include the density, size and shape of the dosage form, the individual's condition of being fed or fasted, the individual's frequency of eating, the structure and calorie content of the foods ingested, gender, age, biological factors, and other drugs administered at the same time (Garg & Sharma, 2003; Streubel et al., 2006)

For the following instances, it has been suggested that an active material should be formulated in the forms that can retain in GIS; a) having dissolution and/or stability problems in the fluids of the small intestine, b) being effective locally in the stomach, c) being absorbed only in the stomach and/or upper part of small intestine (Garg & Gupta, 2008; Awasthi & Kulkarni, 2016). With dosage forms that can retain in GIS for an extended period of time, while maximum bioavailability is ensured from active substances whose absorption window in GIS is narrow, the treatment of local disorders in GIS, such as ulcer, is become easier. By preparing the double layer floating tablets of furosemid, which has a site-specific absorption area, Özdemir et al. (2000) enhanced its bioavailability, compared to its classical dosage forms.

The Physiology of the Gastrointestinal Area

The gastrointestinal area is approximately a nine-meter pipe-like structure that extends from the mouth to the anus and includes the pharynx, the esophagus, the stomach, small intestine and large intestine (Daniels & Allum, 2005).

The stomach is the region where the foods are churned and stored. It has three main sections (fundus, corpus and pyloric region) which can be seen in Figure 1.

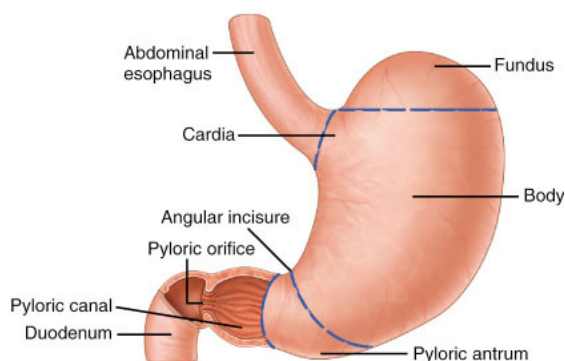


Figure 1. The sections of the stomach

The function of the fundus and corpus (body) sections is to store undigested food. The pyloric antrum is the section where the churning process occurs and which functions as a pump for the excretion of the stomach. Pyloric canal is the area where the stomach and intestine connect. There is a sphincter at both the entrance and the exit of the stomach. The function of this sphincter, called pyloric sphincter, is to prevent the substances in the intestine from returning to the stomach (Noyan, 1988).

The Gastric Excretion Process of the Foods

Gastric excretion occurs as result of gastric contractions based on the structure of the stomach content. When empty, the stomach has a wrinkled appearance with an approximate volume of 50 ml (Rocca-Gutierrez et al., 2003).

Foods are excreted by means of electrical events that are repeated every 2 to 3 hours along the stomach and small intestine and which is called electromechanical activity cycle (interdigestive myoelectric cycle). These cycles are composed of four separate phases and occur as presented in Figure 2 (Fell, 1996; Agnihotri et al., 2004).

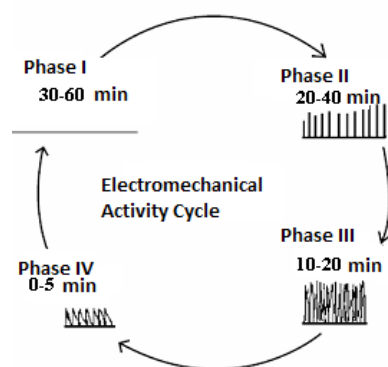


Figure 2. Gastrointestinal motility

Phase I: It is a 30-60-minute period during which sparse contractions are observed.

Phase II: It is a 20-40-minute period during which the frequency and intensity of the contractions increase gradually.

Phase III: It is a 20-40-minute period during which intense and regular contractions are observed. It is the period when the undigested foods are transferred from the stomach to the intestine.

Phase IV: It is a transitional period, which lasts a maximum of 5 minutes, between phase III and phase I of the following cycle.

As a result of stomach contractions after eating, the content in the stomach transforms into small

particles and turns into a form of suspension. In addition, with the contractions, the content in the form of suspension is pushed to the pylor section of the stomach (Takahashi, 2012).

Gastric pH

It has been observed that gastric pH is not a constant value, but varies with the foods ingested, disorders, presence of various gases, lipids acids or other fermentation products, age, pathological conditions, medicines used etc. The pH value of an empty stomach has been found to be 1.1 ± 0.15 and that of a full stomach to be 3.6 ± 0.4 (Fassihi & Talukder, 2004a). The characteristics of the upper part of the gastrointestinal region is presented in Table 1.

Table 1. The characteristics of the upper part of the gastrointestinal region

Region	Length (m)	Transition time (hour)	pH	Number of Microorganisms	The surface area of absorption (m ²)
Stomach	0.2	Variable	1-4	< 10 ³	0.1
Small Intestine	6-10	3 ±1	5-7.5	10 ³ - 10 ¹⁰	120-200

The Classification of Systems that Extend the Residence Time in the Gastrointestinal System

It is classified as follows:

1. High density systems
2. Floating dosage systems
 - a- Single-unit systems
 - b- Multiple-unit systems
3. Swelling and expanding systems
4. Superporous hydrogel systems
5. Mucoadhesive and bioadhesive systems
6. Magnetic systems
7. Systems acting as barriers in the stomach mucosa

1. High Density Systems

They are systems that have a density of approximately 2.5 g/cm³ to ensure long residence time in the stomach. With this purpose, supplementary substances such as barium sulphate, zinc oxide, iron powder, and titanium dioxide are used. As presented in Figure 3, the dosage form residing in the last section of the stomach shows resistance against the stomach's peristaltic powers and in this way prevents the dosage form from passing through the pylor. Even though experiments conducted on ruminants are promising, there are no market products in use for human beings (Hejazi & Amiji, 2002).

Devereux et al. (1990) found that pellets with at least 1.5 g/ml density can reside in an empty or full stomach for an extended period of time.



Figure 3. High density systems

Clarke et al. (1993) maintain that to extend the residence time in the stomach, there should be a critical value varying between 2.4 g/ml and 2.8 g/ml. However, despite all these studies, the values expected in in vivo studies could not be obtained.

2. Floating Dosage Systems

a- Single-unit systems: Because of the residence time in the stomach shows variation, these systems have low reliability and reproducibility (Agrawal et al., 2005).

With the use of hydrophylic polymers (e.g. hydroxypropyl methylcellulose, ethylcellulose, sodium carboxy methylcellulose, alginic acid) that show a swelling feature when they come in contact with gastric liquid in dosage forms, the density can be kept below 1, and the residence time of the dosage form floating in the stomach can be extended. Meanwhile, the release of the active substance through the hydrated layer by diffusion, is presented in Figure 4 (Moës & Timmermans, 1990; Dorozynski et al., 2004).

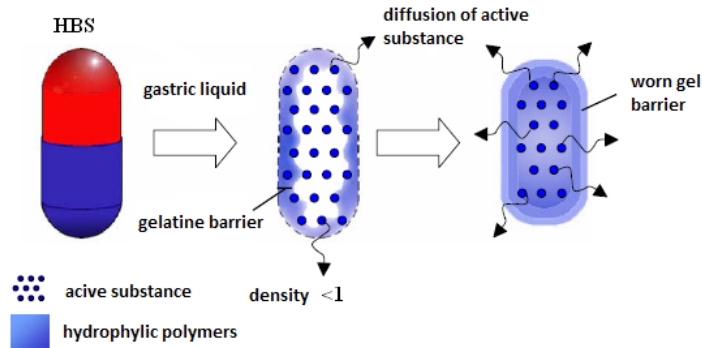


Figure 4. Single-unit systems (Faivre et al., 2006)

Single-unit systems can cause irritation in this region owing to the abundance of active substance release in the GI area (Singh & Kim, 2000).

b- Multiple-unit systems: They are systems that prevent sudden increase of active material and reduce changes in absorption (Efentakis & Koutlis, 2001). In these systems, polymers such as albumin, gelatine, starch, polymethacrylate, and polyacrylamide are used.

Multiple-unit systems can be examined in two sections;

* *Multiple-unit systems with an effervescent structure*

They include effervescent that acquire a floating feature with the release of the carbon dioxide in its structure (microspheres and beads).

They are matrix type systems prepared by mixing effervescent compounds (e.g. sodium bicarbonate, tartaric acid, citric acid) and polymers that swell in gastric liquid (e.g. methylcellulose, chitosan) (Senjoti et al., 2016).

They are systems that obtain a floating feature with the release of CO_2 when confronted with gastric liquid and the entrapment of this gas by floating hydrocolloids (Arora et al., 2005). These systems are presented in Figure 5.

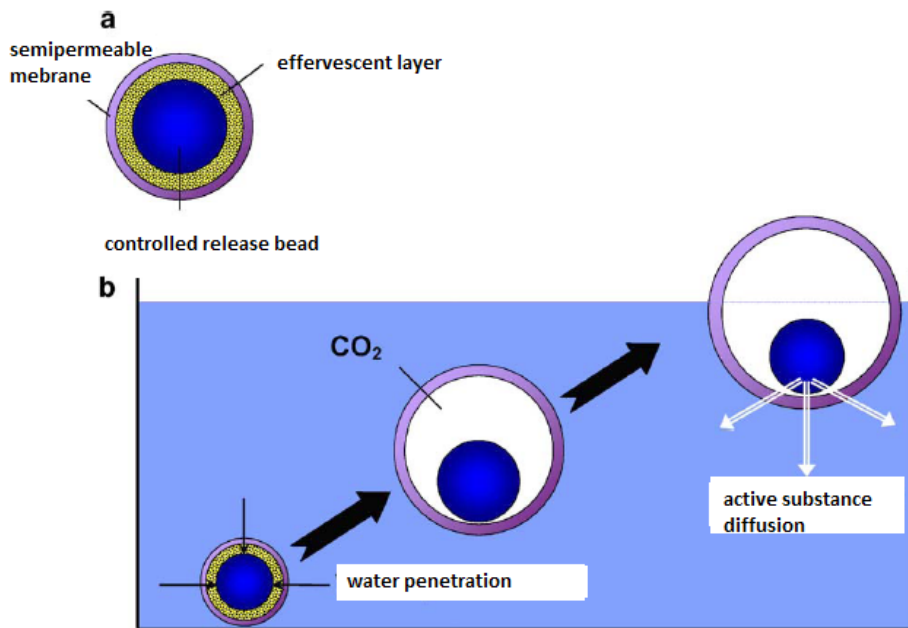


Figure 5. Effervescent floating systems (Faivre et al., 2006)

Park et al. (2002) examined the effects of agent forming CO₂ gases such as CaCO₃ and NaHCO₃ in the preparation of floating alginate beads. CO₂ is released from the microspheres that come in contact with the ambient liquid, and this gas provides a floating feature. It is reported that even though CaCO₃ is a less effective gas-forming agent, beads that have better features with CaCO₃ than NaHCO₃, that produce smaller and smooth-surfaced more effective alginate gel and that are released for a longer period of time are obtained.

Ichikawa et al. (1991) developed a controlled release dosage form that included an active substance in the inner nucleus. There is a floating layer containing tartaric acid and sodium bicarbonate on the nucleus. The outmost layer contains polyvinyl acetate and pure shellac. With the entrance of water from the outmost layer, the CO₂ in the effervescent layer is released, which results in floating.

Atyabi et al. (1996) produced floating beads with an external semi-permeable membrane which prevents the sudden release of the CO₂ gas and that contains ion changing resin and sodium bicarbonate.

*** Multiple-unit systems that do not contain an effervescent structure**

Those that do not include effervescent in their structure that can float owing to the void space they contain (microspheres, microballoons). While floating begins immediately in microballoons, microspheres showing an effervescent feature start floating in the stomach after a certain period of time. This can cause an unwanted rapid transition of the dosage through the pylor (Dube et al., 2014).

In this type of dosage form, polymers such as gel-forming or swelling cellulose type hydrocolloids, polysaccharides and matrix forming polycarbonate, polyacrilate, polymethacrylate and polystyrene are used. The structure of the microballoons can be observed in Figure 6.

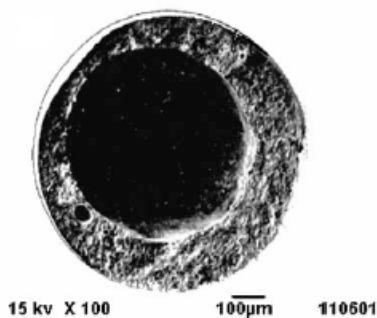


Figure 6. Microballoon

First, the gel forming hydrocolloid is mixed with active substance. When the dosage form comes in contact with gastric liquid, it swells and the air that is entrapped by the swollen matrix produces a floating feature. Active substance is released from the swollen gel (Harshal et al., 2010).

Thanoo et al. (1993) developed polycarbonate microspheres by using the solvent evaporation method. The polycarbonate within dichloromethane enabled the floating of empty beads.

Yuasa et al. (1996) obtained microspheres containing diclofenac sodium adsorbed in calcium silicate. As a result, it was found that by using calcium silicate and by changing the hydroxypropyl cellulose / ethyl cellulose ratio, controlled release floating granules with desired features could be obtained.

Naggar et al. (2001) prepared floating microspheres containing ketoprofen by using the emulsion solvent diffusion method. As polymers, a mixture of Eudragit S 100 (ES) and Eudragit RL (ERL) of varying ratios were used. As a result, by changing the ES:ERL ratio, a floating dosage form with desired features was obtained.

3. Swelling and expanding systems

They are small dosage forms that can be swallowed but can reach the size that prevents it from passing the pyloric sphincter in the stomach. These dosage forms, however, should convert to the size which will enable them to pass through the pylor after active substance release is completed.

Swelling and expanding systems are classified into two: those that can unfold in the stomach as shown in Figure 7 and those that can swell by absorbing the gastric liquid in the stomach as shown in Figure 8 and Figure 9 (Hoffman et al., 2003).

*** Systems that can unfold in the stomach**

These types of systems can in the shape of a lobe, disc, ring and tetrahedron.

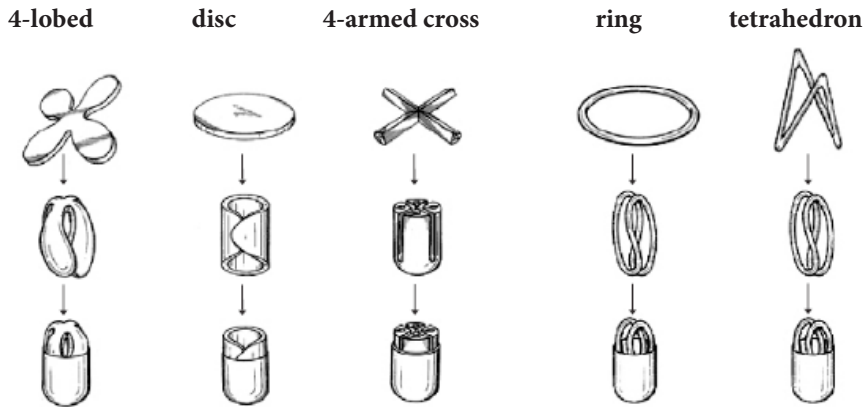


Figure 7. Systems that can unfold in the stomach into different geometrical shapes

Curatolo and Lo (1995) developed a arc-shaped system, the arms of which are fixed with a gelatine

band. With the dissolution of the gelatine, the controlled release of the active substance is achieved.

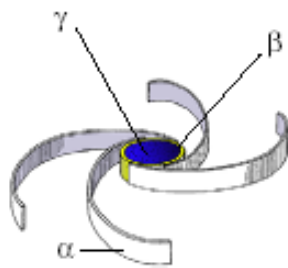


Figure 8. The system that can unfold in the stomach (Curatolo & Lo, 1995)

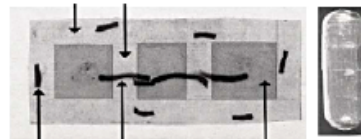
Klausner et al. (2003) developed a dosage form composed of polymeric membrane containing rigid strips in the internal layer and which can unfold in the stomach. With the dosage form placed into a capsule, 67% of the active substance is released in five hours.

*** Systems that can swell by absorbing the gastric liquid in the stomach**

The swelling feature is provided with the absorption of water via the osmotic effect. As a result of its contact with the gastric liquid, the dosage form, which is small at the beginning, swells, enabling it to

before folded **after folded**

**rigid strips
(internal layer)**



opposing strips

external layer

Figure 9. The system that can unfold in the stomach (Klausner et al., 2003)

reside in the stomach for an extended period of time (Hoffman et al., 2003).

Mamajek and Moyer (1980) produced a system covered with an elastic polymeric membrane that enables the permeation of body liquids. This system contains an active substance depot and a swellable agent, such as swellable resin or colloid. In this way swelling occurs with osmotic pressure. As a result of the study, it was found that the system could reside in the stomach more than 12 hours (Figure 10).

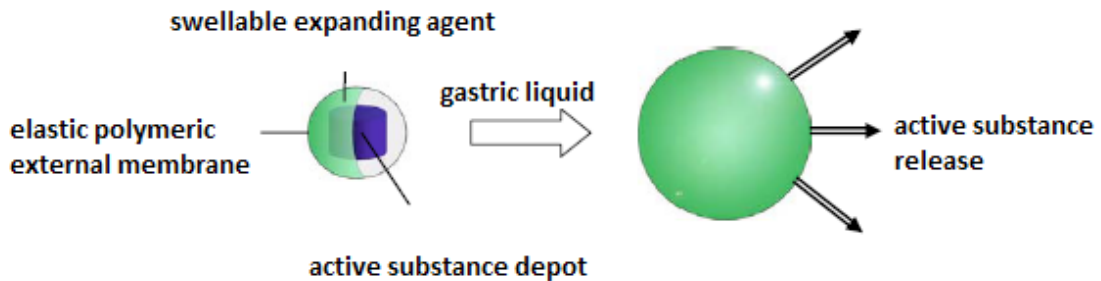


Figure 10. Swellable systems in the stomach (Mamajek and Moyer, 1980)

Developed by Urquhart and Theeuwes (1984), systems prepared by dispersing, within a polymeric hydrogel matrix, small beads that are coated with wax

and have active substance in the internal section can release controlled active substance when in contact with body liquids (Figure 11).

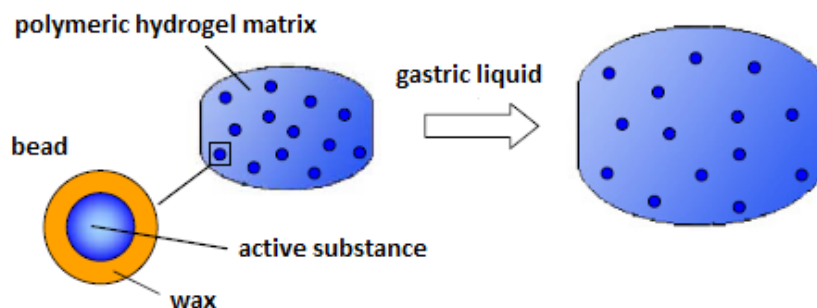


Figure 11. Swellable systems in the stomach (Urquhart and Theeuwes, 1984)

4. Superporous Hydrogel Systems

They are systems that can increase in size by absorbing water in a very short time through the many pores that they contain in their structure (Faivre et al., 2006). These systems are displayed in Figure 12.

Because they contain a high ratio of water, their mechanical resistance is low. To increase their mechanical resistance and to enable rapid swelling, the use of Ac-Di-Sol was found to be effective (Chen et al., 2000).

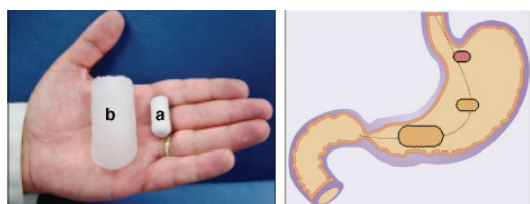


Figure 12. Superporous hydrogels (Faivre et al., 2006)

5. Mucoadhesive and Bioadhesive Systems

In these systems presented in Figure 13, the dosage form is made to reside in the stomach for a long time

by making the dosage form stick to the mucosal surface via various mechanisms. However, because they cause irritation in the stomach mucosa, their use is limited (Davis, 2005).

Smart and Kellaway (1989) developed a mucoadhesive dosage form that can reside in the stomach for a long time by making a carbomer coating.

Preda and Leucata (2003) produced gelatine microspheres containing polyacrylic acid. These microspheres are made to reside in the stomach for a long period owing to their bioadhesive polymer content.

Kockisch et al. (2003) compared microspheres containing different polymers. In the studies conducted with the use of polyacrylic acid, citosan and Gantrez', they found that polyacrylic acid was better than other polymers in terms of mucoadhesive and swelling features.

6. Magnetic Systems

The systems displayed in Figure 14 are systems that can reside in the stomach for a long period of time with their magnetic substance content and the applied magnetic field.



Floating microspheres in the stomach liquid

Microspheres stuck to the mucosal surface

Figure 13. Bioadhesive microspheres residing in the stomach (Davis, 2005)

Ito et al. (1990) experimented bioadhesive granules containing iron oxide (Fe_2O_3) on rabbits. These granules were applied to the esophagus of the rabbit with the presence of an external magnet.

Fujimori et al. (1994) applied magnetic tablets containing hydroxypropyl methyl cellulose, cinnarizin and 50% w/w iron oxide on hound dogs. With the administration of the magnetic field, the tablet was made to reside in the stomach for eight hours.

Groning and Berntgen (1996) prepared the oral magnetic depot tablets of acyclovir. With the long residence of the dosage form in the stomach by using extracorporeal magnet, high bioavailability was obtained.

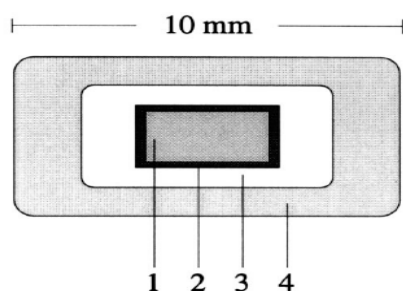


Figure 14. Magnetic tablet

7. Systems Acting as Barriers in the Stomach Mucosa

When sodium alginate solutions containing carbonate or bicarbonate come in contact with gastric liquid, they form a visco gel containing CO_2 . These types of formulations can be prepared with antacids such as aluminium hydroxide or calcium carbonate to decrease the acidity of the stomach. These systems forming a layer on the upper part of the gastric liquid and displayed in Figure 15 are generally recommended in the treatment of reflux (Washington, 1987; Havelund et al., 1997).

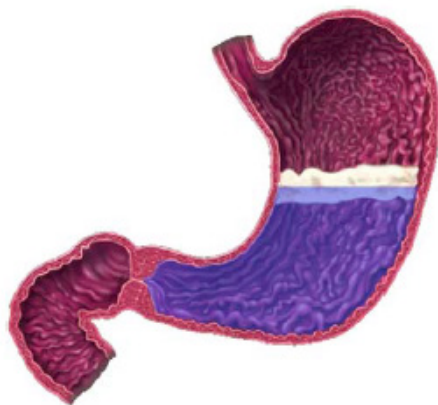


Figure 15. Systems acting as barriers in the stomach mucosa (Havelund et al., 1997)

CONCLUSION

By extending the absorption period of the active substance with systems residing in GIS, maximum bioavailability of the active substance can be obtained. In these systems, the amount of substances absorbed in the upper parts of the small intestine and the absorption of active substances in any region of GIS can be increased. Depending on the polymers, the selected dosage form and the method used in these systems, the controlled release of the active substance for the desired period of time and the enhancement of bioavailability can be obtained. Some of the gastroretentive products available in the market are, Cifran OD[®] (Ciprofloxacin), Madopar[®] (L-DOPA and Benserazide), Valrelease[®] (Diazepam), Topalkan[®] (Aluminum-magnesium antacid), Almagate FlatCoat[®] (Aluminum-magnesium antacid), Liquid Gaviscon[®] (Aluminium hydroxide), Conviron[®] (Ferrous sulfate) and Cytotec[®] (Misoprostal) (Nayak et al., 2010).

All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Studies conducted on this topic are hopeful on the development of new treatment methods. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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