International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(2): March-April 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 22-03-2016; Revised: 18-04-2016; Accepted: 19-04-2016

MICROBALLOONS: AN INNOVATIVE ACCEPTABLE APPROACH IN GASTRORETENTIVE DRUG DELIVERY

B.A. Bhairav[1]*, V. S. Aher[1], R. B. Saudagar[2]

[1]*Department of Quality Assurance Techniques, R. G. Sapkal college of Pharmacy Anjaneri, Nashik, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, R. G. Sapkal college of Pharmacy Anjaneri, Nashik, Maharashtra, India.

Keywords:

Microballoons, Gastric retentive drug delivery

For Correspondence:

B.A. Bhairav

Department of Quality Assurance Techniques, R. G. Sapkal college of Pharmacy Anjaneri, Nashik, Maharashtra, India

E-mail:

bbhairav@gmail.com

ABSTRACT

Gastric emptying is a complex process and makes ***in-vivo*** performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. The Microballoons delivery systems are useful in such application. Microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles without core and ideally having a size less than 200 micrometer. Microballoons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Microballoons improve patient compliance by decreasing dosing frequency; better therapeutic effect of short half-life drugs can be achieved. These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs because of buoyancy.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. Microballoons is an approach to prolong the gastric retention which have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. One of the most interesting fields of research in pharmaceutics is the development of new delivery systems for the controlled release of drugs [1].Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time [2].Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug availability that are less soluble in a high pH environment [3].

Physiology of stomach

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (fig.1).

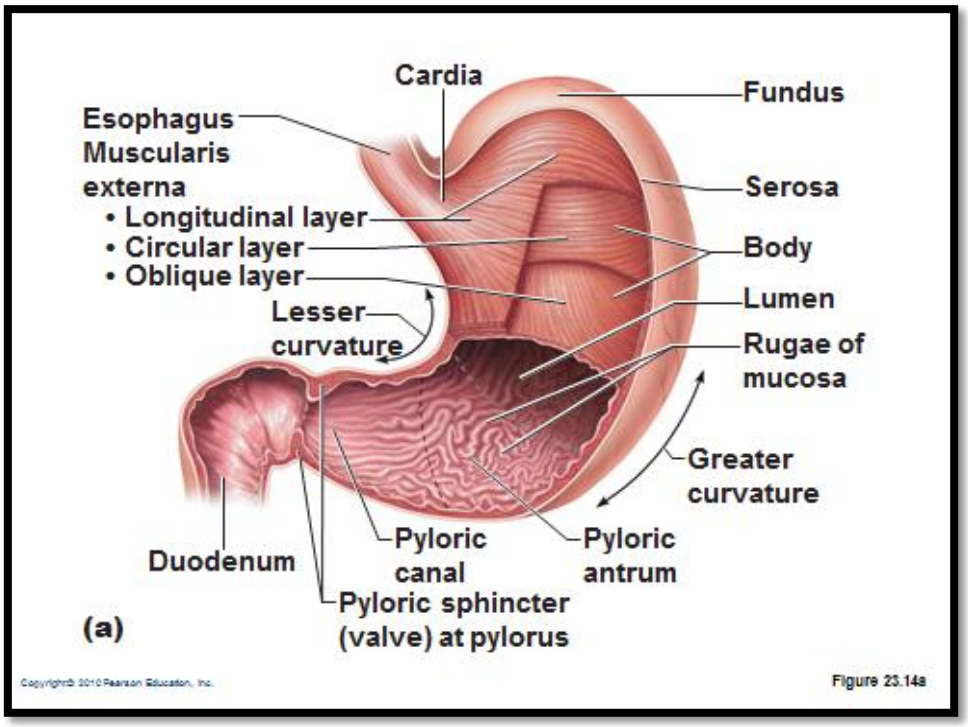

Fig.1. Anatomy of stomach

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 h. This is called the interdigestivemyloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases- (fig. 2)

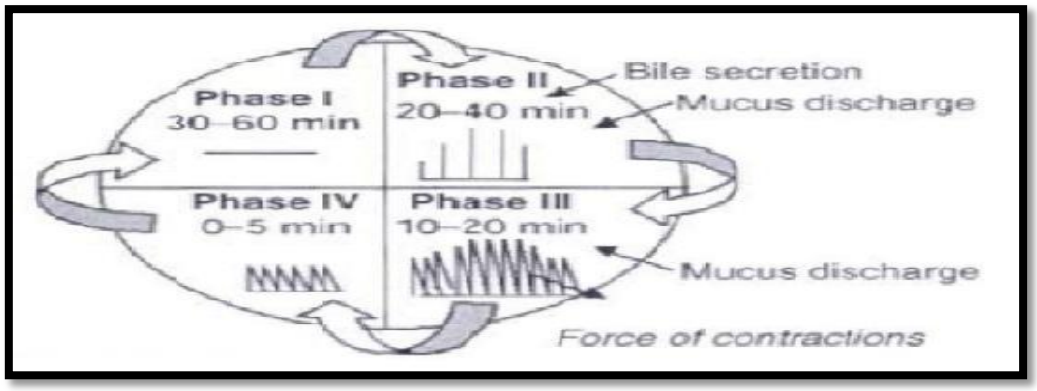

Fig.2: Figure showing interdigestive motility

- Phase I (Basal phase) lasts from 30 to 60 min with rare contractions.
- Phase II (Preburst phase) lasts for 20 to 40 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 10 to 20 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles [4].

Advantages of microballoons:

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilizes only in stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

Mechanism of floating microballoons:

When microballoons come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy.

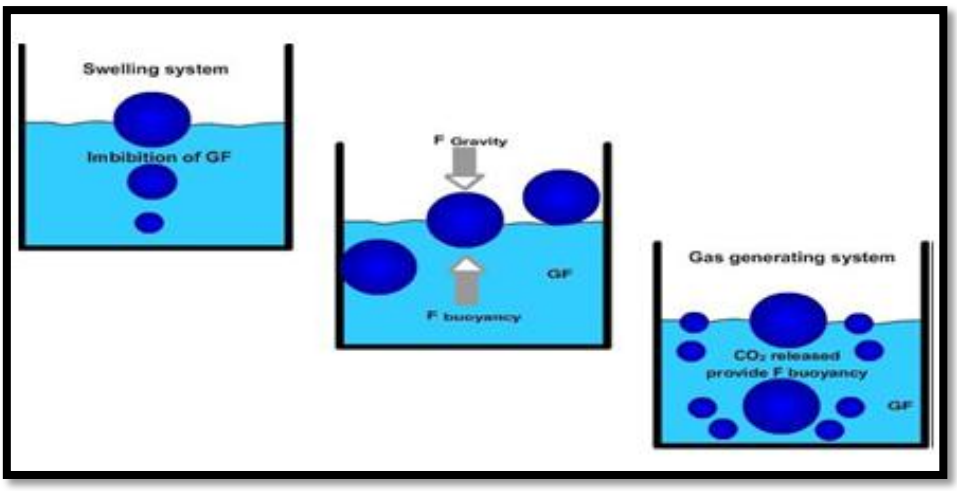

Fig.3: Mechanism of floating systems, GF= Gastric fluid

Methods of preparation of microballoons:

Microballoons are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinylacetate, carbopol, agar, polyethylene oxide and polycarbonate (fig 8).

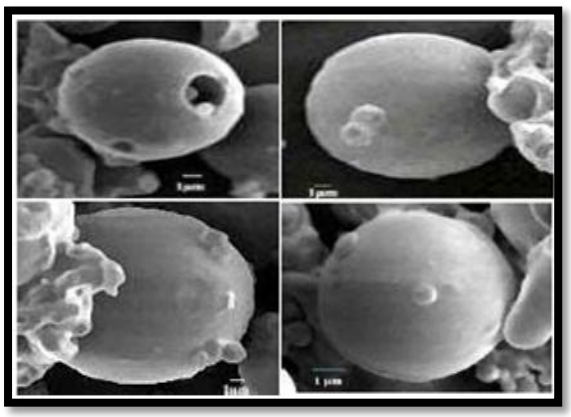

Fig.7: Hollow microspheres

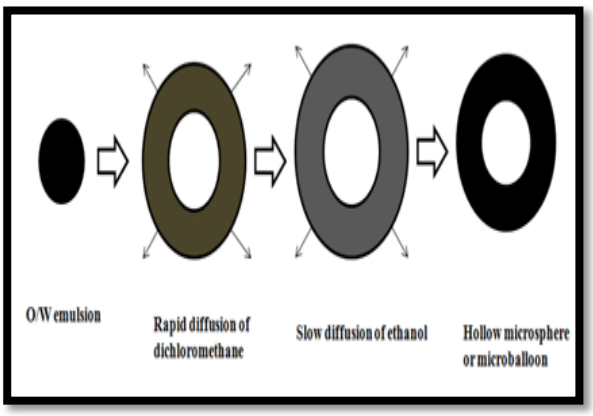

Fig.8: Formulation of floating hollow microsphere or microballoons

Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes [5].

Floating drug delivery system

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side (Fig.3). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [5]. RW or F = F buoyancy – F gravity = (Df - Ds) gV Where, RW = total vertical force, Df = fluid density, Ds= object density, V = volume and g = acceleration due to gravity [6].

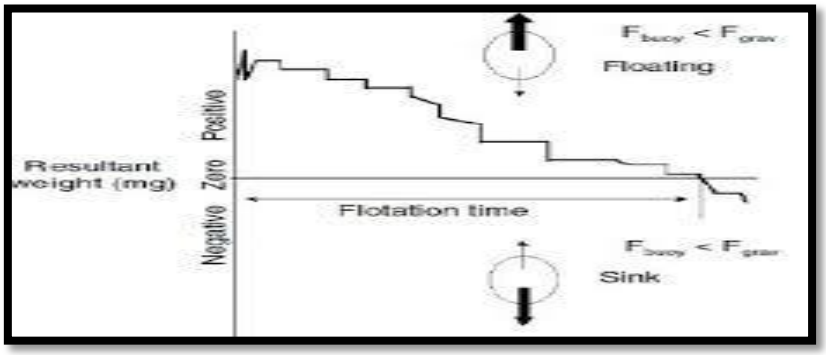

Fig. 3: Effect of resultant weight during buoyancy on the floating tendency of FDDS

Mechanism of floating systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), co adhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric emptying delaying drugs. Among these, the floating dosage forms are the most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system (fig. 4). After release of drug, the residual system is eliminated from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention effect, a minimal level of floating force is also required to maintain the buoyancy of the dosage form on the surface of the meal [7].

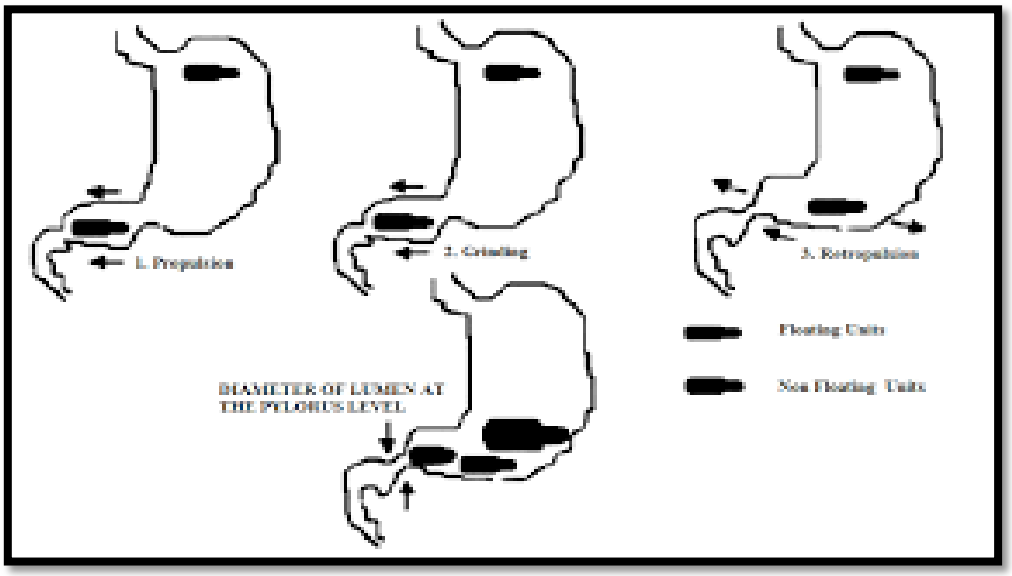

Fig. 4: Intragastric residence positions of floating and non-floating units

Classification

Floating systems can be classified into two systems:

- Effervescent systems
  - Volatile liquid containing systems
  - Gas-generating Systems
- Non-Effervescent Systems

- Colloidal gel barrier systems
- Microporous Compartment System
- Alginate beads
- Hollow microspheres

A. Effervescent Floating Dosage Forms

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate ($NaHCO_3$) or sodium carbonate, and additionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Generally, effervescent systems suffer from the disadvantage not to float immediately after swallowing because the process of gas generation takes some time (fig.5). Therefore, they could be cleared from the stomach before becoming effective. The performance of low-density, floating drug delivery systems is strongly dependent on the filling state of the stomach [8].

B. Non-Effervescent Floating Dosage Forms

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [9].

C. Colloidal gel barrier system

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxy methyl cellulose (NaCMC), poly carbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. (fig. 6) Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [10].

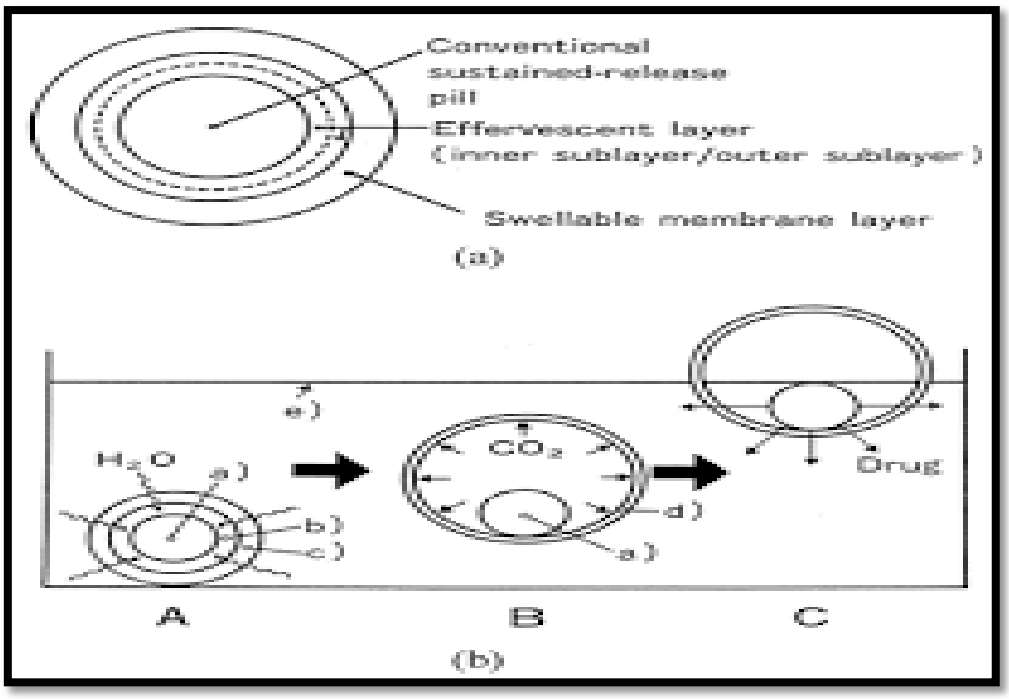

Fig.5: (a) multiple unit oral floating drug delivery system (b) working principle of effervescent floating drug delivery system

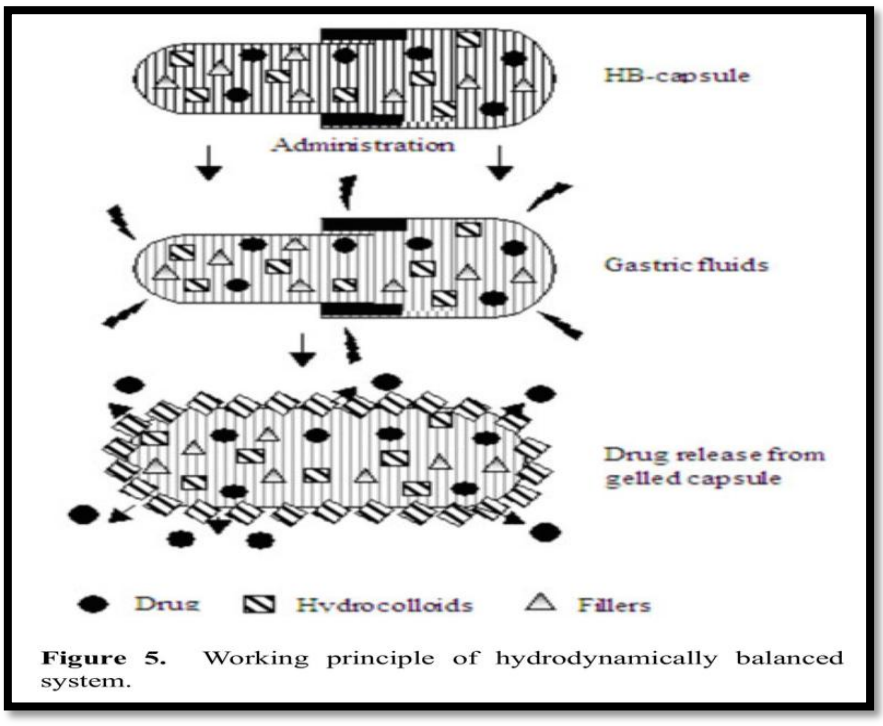

Figure 5. Working principle of hydrodynamically balanced system.

D. Microporous compartment system

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to present any direct contact of the gastricsurface with the undissolved drug. In the stomach containing entrapped air causes the delivery system to float

in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption [11].

E. Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h [12].

F. Hollow Microspheres

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (microballoons) are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 μm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [5]. Hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) of the dosage form with continuously floating over the surface of an acidic dissolution media containing surfactant for >12 h (fig. 7) [13].

Future potential

The control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. It is anticipated that various novel products using gastroretentive drug delivery technologies may enhance this possibility. Further investigations may concentrate on the microballoons concepts:

- Design of an array of gastro retentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of diseases.
- Quantitative efficiency of gastroretentive drug delivery systems in fasted and fed states.
- Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.

Floating multiparticles can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate helicobacter pylori from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. This system allows administration of non-systemic, controlled release antacid formulation containing calcium carbonate and also locally acting anti-ulcer drugs in stomach. Buoyant micro particles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. Floating multiparticulate systems may be used as a carrier for the drugs having narrow absorption windows, for example antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) are absorbed only from very specific regions of GI tract and whose development has been halted due to the lack of pharmaceutical technologies. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin. Floating microparticles of NSAIDs are very effective for reducing their major side effect, gastric irritation as well as for controlled release, e.g. floating microspheres of indomethacin are quite beneficial for rheumatic patients. It is hoped that in near future biopharmaceutically better therapeutic systems in the form of floating multiparticulate systems would be introduced in clinics in greater number [11].

REFERENCES

1. Atyabi, F., Sharma, H.L., Mohammad, H., Fell, J. T., In-vivo evaluation of a novel gastroretentive formulation based on ion exchange resins, J. Control. Rel. 1996; 42: 105-13.
2. Baumgastner, S., Kristel, J., Vreer, F., Vodopivec, P., Zorko, B., Optimization of floating matrix tablets and evaluation of their gastric residence time, Int J Pharm 2000; 195:125 35.
3. Derivative for the treatment of gastritis. Int. J. Pharm. 2008,356,88-94
4. Deshpande, A. A., Shah, N.H., Rhodes, C.T., Malick, W., Development of a novel controlled release system for gastric retention, Pharm. Res. 1997; 14 (6): 815-9.
5. Joshi VK., Jaimini M., Microballons drug delivery system: A review, *AJPRD* 2013; 1:1:07 – 17.
6. Kawatra M., Jain U., Ramana J., Recent advances in Floating microspheres as gastroretentive drug delivery system: A Review, *Int J of Recent Adv in Pharma Res* 2012; 2:3: 5-23.
7. Patel N., Jani D., Nagesh C., Chandrashekhar S., Patel J., Floating drug delivery system: An innovative acceptable approach in Gastro retentive drug delivery, *Asian J. Pharm. Res* 2012; 2:1:07-18.
8. Samaligy SE., Floating Systems for Controlled Drug Delivery, *Tag der mündlichen Prü fung Berlin* 2010.
9. Chandel A., Chauhan K., Parashar B.,Kumar H., Arora S., Floating drug delivery systems: A better approach, *Int Current Pharma* 2012;1:5:110-118.
10. Pattan SR., Wani NP., Shelar MU., Nirmal SA., Chaudhari PD., Gude RS., Scope and significance of floating drug delivery system, *Indian drugs*2012; 49:10:1-8.
11. Dwivedi S., Kumar V., Floating Drug Delivery Systems- A Concept of Gastro retention Dosages Form, *Inter J of Res Pharma Biomed Sci*2011;2:4:1413-1425.
12. Patel DM., Multi Particulate System: Approach in Gastro-Retentive Delivery, *IJAPR* 2011; 2:4:96-106.