A REVIEW OF WORK DONE ON FLOATING DRUG DELIVERY SYSTEM CONTAINING CARDIO VASCULAR DRUGS

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ABSTRACT

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Oral route is the most preferable route of administration but has certain limitations for those drugs which absorb from upper part of GIT tract or having narrow absorption window. The bioavailability of these drugs can be improved by increasing the residence of the dosage form in the stomach. The gastric residence time of the dosage form can be improved by formulating them as floating drug delivery system. The current & recent developments of Stomach Specific cardiovascular drugs formulated as FDDS are discussed in this review.

Key Words: Gastric residence time, Floating drug delivery system, Effervescent, Non-effervescent, Cardiovascular drugs.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. Drug absorption in gastrointestinal (GI) tract may be very short and highly variable in certain Circumstances. Drugs having short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of the medication to achieve therapeutic effect. This results in pill burden and consequently, patient complains. The phenomenon of absorption via a limited part of the GIT has been termed the narrow absorption window; once this dosage form passes the absorption window the drug will be neither bioavailable nor effective. In extreme cases drugs that are insufficiently absorbed due to narrow absorption window cannot be delivered entirely and are either given by the parenteral route or the development of such medication, which deliver the drug in control manner, which is safe.

Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

Oral controlled drug dosage forms for past three decades due to their considerable therapeutic advantages. However, this approach has been suitable for a variety of important drugs, characterized by narrow absorption window in upper part of the gastrointestinal tract, i.e. stomach and upper part of intestine (duodenum).

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a conventional dosage form are as follows:

Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

The above problems can be overcome by the development of effective and safer use of existing drugs through concepts and technique of controlled and targeted drug delivery system. The controlled drug delivery system is one, which delivers the drug at a predetermined rate, locally or systemically for a predetermined period of time.

The advantages of controlled drug delivery system over the conventional dosage form are as follows:

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
5. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing.

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract, and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size.
Hydrodynamically Balanced System or Floating drug

Various approaches have been proposed to increase the duration of oral dosage form in the stomach, including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, Super porous – biodegradable hydrogel systems).

1. Hydrodynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float.11,12,13

2. Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.11,12

3. Swelling type of dosage form are such that after swelling, this product swell to extent that prevent their exit from the stomach through the pylorus. As, a result, the dosage form retained in the stomach for a longer period of time. These systems may be referred to as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters.14

4. Bioadhesive or mucoadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approaches involves the use of bioadhesive polymers that can be adhere to the epithelial surface of the GIT. The proposed mechanisms of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.15

5. Modified shape systems are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the GTT depending on the size, shape and flexural modulus of the drug delivery device.16

6. High density formulations include coated pallets, and have density greater than that of the stomach content (1.004 gm/cm³). This is accomplishing by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antrum.17

7. Another delayed gastric emptying approaches of interest include sham feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release.

Hydrodynamically Balanced System or Floating drug Delivery System

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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. After release of drug, the residual system is emptied from the stomach. This result sin 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 principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Advantages of floating drug delivery system

Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.

3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

4. The gastroretentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of floating drug delivery system

Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

1. These systems require a high level of fluid in the stomach for drug delivery to floats and work efficiently-coat, water.

2. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

3. Some drugs present in the floating system causes irritation to gastric mucosa.

CARDIOVASCULAR DISEASE

Globally, cardiovascular diseases are the number one cause of death and they are projected to remain so. An estimated 17 million people died from cardiovascular disease in 2005, representing 30% of all global deaths.

Of these deaths, 7.2 million were due to heart attacks and 5.7 million due to stroke. About 80% of these deaths occurred in low- and middle-income countries. If current trends are allowed to continue, by 2030 an estimated 23.6 million people will die from cardiovascular disease (mainly from heart attacks and strokes).10

Cardiovascular diseases include:

- Coronary heart disease (heart attacks),
- Cerebrovascular disease,
- Raised blood pressure (hypertension),
- Peripheral arterial disease,
- Rheumatic heart disease,
- Congenital heart disease, and
- Heart failure.

Cardiovascular drugs belong to different category have been found to be good candidate of gastro retentive drug delivery system. The current review deals with the floating drug delivery system that have been develop to improve the therapeutic efficacy of such drugs.
An overview of floating drug delivery system research of cardiovascular drugs

Floating granules
These granules floated for long time in gastric fluid and rate of drug release from the granules was depends upon polymer concentration. Shimpi et al., 2004, prepared floating granules of Diltiazem Hydrochloride using Gelucire 43/01 by melt granulation technique. The granules were retained in stomach for 6 hours and approximately 65 to 85 % drug was released over 6 hours with initial fast release from the surface.21

Floating Microspheres
Soppimuth et al., 2001, prepared hollow microspheres of cellulose acetate loaded with four cardiovascular drugs (Nifedipine, Nicardipine HCl, Verapamil HCl and Dypiridamole) were prepared by a novel solvent diffusion-evaporation method. The O/W emulsion prepared in an aqueous emulsification solvent evaporation technique, using calcium silicate (CS) as porous carrier; (ii) Atenolol, an oral antihypertensive agent; and (iii) Eudragit® S as polymer. The microspheres were found to be regular in shape and highly porous. The prepared microspheres exhibited prolonged drug release and remained buoyant for >10 h. The mean particle size increased and the drug release rate decreased at higher polymer concentrations.24

A.R.Dhole et al., 2011 prepared and evaluation of floating microcarriers of Captorpil as model drug for prolongation of gastric residence time. The microcarriers were prepared by Ionotropic gelation technique using polymers Sodium alginate along with Hydroxyl propymethylcellulose and Ethyl cellulose. The prepared microcarriers exhibited prolonged drug release and remained buoyant for >12 h. The mean particle size increased and the drug release rate decreased as the concentration of polymer increases.25

Streubel et al., 2003, developed low density foam (Polypropylene) based microparticles using diltiazem hydrochloride, theophylline or verapamil hydrochloride as model drug and eudragit RS or polyethyl methacrylate as polymer. The floating micro particle showed a good in-vitro floating behavior and a broad variety of drug release pattern depending upon the drug loading and polymer used.26

Kulkarni et al., 2008, design bilayer floating tablets of diltiazem HCl and lovastatin to give immediate release of lovastatin and controlled release of diltiazem HCl and studied the influence of presence of one drug on the release pattern of other drug. The bilayer tablets consist of sodium starch glycolate as superdisintegrant for lovastatin in the immediate release layer and hydroxypropyl methylcellulose (HPMC) K4M and Xanthan gum as release-retarding agents for diltiazem HCl in the controlled release layer. Sodium bicarbonate was used as the gas generating agent. Dicalcium phosphate was used as the channeling agent. There was significant difference in drug release and floating lag time (P < 0.05). HPMC K4M and Xanthan gum retarded the release of diltiazem HCl for 12 h. The release of one drug remained unaffected in presence of the other drug. In conclusion, such kind of combined dosage forms can effectively be formulated to deliver more than one drug as to have improved patient compliance and better disease management.27

Ling Zhao et al., 2010, hollow microspheres prepared from polymer blends of polyvinyl pyrrolidone (PVP) and ethyl cellulose (EC) could improve the vitro release behavior of the poorly water-soluble drug nifedipine. Hollow microspheres containing nifedipine were prepared by a solvent diffusion-evaporation method using various ratios of PVP and EC co-dissolved with drug in ethanol/ether (5:1, v/v). The hollow microspheres could float in release medium for more than 24 h, prepared using polymer blends of PVP and EC (1.5:8.5, w/w) could be suitable for floating-type controlled-release delivery systems for the oral administration of nifedipine.28

Yogesh S. et al., 2008, has studied formulation and evaluation of floating multiparticulate oral drug delivery system of diltiazem hydrochloride, which can provide sustained release. The aim was to study various parameters affecting the behavior of floating multiparticulate in oral dosage form. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique, using ethyl cellulose and Eudragit RS-100 as the rate controlling polymer. Results show that the mixing ratio of components in the organic phase affected the size, size distribution (199-320

Table 1: Various floating dosage form used in treatment of cardiovascular disease

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Dosage form</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Floating granules</td>
<td>Diltiazem HCl</td>
<td>Shimpi et al.; 2004</td>
</tr>
<tr>
<td>2.</td>
<td>Floating Microspheres</td>
<td>Nifedipine</td>
<td>Soppimuth et al.; 2001</td>
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<td>5.</td>
<td>Floating Microspheres</td>
<td>Captorpil</td>
<td>Dhole R.A. et al.; 2011</td>
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<tr>
<td>6.</td>
<td>Floating Microspheres</td>
<td>Diltiazem HCl</td>
<td>Streubel et al.; 2003</td>
</tr>
<tr>
<td>7.</td>
<td>Floating Microspheres</td>
<td>Nifedipine</td>
<td>Ling Zhao et al.; 2010</td>
</tr>
<tr>
<td>8.</td>
<td>Floating Microspheres</td>
<td>Metropolol</td>
<td>Baskar G.Y. et al.; 2010</td>
</tr>
<tr>
<td>10.</td>
<td>Floating tablet</td>
<td>Nifedipine</td>
<td>Steekanth et al.; 2011</td>
</tr>
<tr>
<td>11.</td>
<td>Floating tablet</td>
<td>Atenolol</td>
<td>Gangadharappa H.V. et al.; 2010</td>
</tr>
<tr>
<td>13.</td>
<td>Floating tablet</td>
<td>Nimodipine</td>
<td>Wu et al.; 1997</td>
</tr>
<tr>
<td>15.</td>
<td>Floating tablet</td>
<td>Sotalol HCl</td>
<td>Ziu et al.; 1999</td>
</tr>
<tr>
<td>17.</td>
<td>Floating beads</td>
<td>Nicardipine HCl</td>
<td>Takka S. et al; 1998</td>
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μm), drug content (59-84%), %yield (57-77%) and drug release of microsphere (45-99%) after 12 h and floating time >12 h. The best results were obtained at the ratio of drug: polymer Eudragit RS-100 (1:3).29

Baskar G.Y. et al, 2010, has developed a floating multiparticulate unit system for metoprolol tartrate, using a porous carrier, with an outcome for delayed gastric emptying. Methods: Dried microparticles of metoprolol tartrate were prepared by solvent evaporation using Eudragit® RS-PO, polypropylene foam powder, and dichloromethane as release-rate modifying polymer, floating aid and solvent respectively. The surface topography of the particles was assessed by SEM while the physical state of the drug within the developed system was characterised by DSC and XRD. Te99m sulfur colloid radio-labelled microparticle formulation was administered to fasting rabbits and their transit behavior was monitored using gamma scintigraphy. The anterior and posterior images recorded were computed to determine the geometric mean counts, enabling quantitative estimation of gastric emptying rate.30

Chen R.N., et al, 2010, has developed an optimal gastro retentive drug delivery system (GRDDS) for administering Losartan. Additionally, the influence of optimized GRDDS on the bioavailability of Losartan and the formation extent of active metabolite E3174 by CYP2C9 polymorphism was investigated. Swellable and floatable GRDDS tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate were prepared at various compression pressures for evaluating swelling characteristics and floating capacity. Then Losartan was incorporated into optimized formulations for in vitro and in vivo characterizations.31

**Floating Tablet**

Sreekanth et al, 2011, designed and evaluated nifedipine floating matrix tablets. Hydroxypropyl methyl cellulose (HPMC K100M) was used as a polymer. About 15-35 % of HPMC can be used as a polymer in the extended release formulations. So, here the polymer was used in the range of 16-36 %. Sodium bicarbonate (40%) is used as a gas generating agent. It can be used in the range of 25-50 %. The granules are prepared by wet granulation method. The drug release follows Korsmeyers – Peppas reaction. The mechanism of drug release is by non-fickian motion. The *in vitro* drug release data indicate that the release of the drug depends upon the proportion of polymer present in the formulation. As the polymer ratio increases the release rate of the drug is prolonged.32

Gangadharappa H.V. et al, 2010, formulated controlled release floating tablets of Atenolol using karaya gum and HPMC as matrix polymers. Atenolol floating tablets based on gas formation technique was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form. It was assumed that this form should reside in the stomach floating for several hours and gradually release the drug in a controlled way. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were prepared by direct compression technique. The effervescent gastric floating drug delivery system was a promising approach to achieve *in vitro* buoyancy and to improve the absorption of Atenolol.33

Patel N Ara et. al, 2011, developed an optimized floating drug delivery system of diltiazem hydrochloride. Diltiazem floating tablets were formulated with different concentrations of two grades of HPMC polymers (HPMC K4M and HPMC K100M) by using wet granulation technique. The maximum percentage of drug release (99.87 %) and prolonged release for time period of about 12 h, thereby improves the bioavailability and patient compliance.34

Wu et al, 1997, developed floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline in in vitro release of nimodipine occurred.35

Moursy et al, 2003, developed sustained release floating capsules of nicardipine HCl. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO2. In vitro analysis of a commercially available 20-mg capsule of nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with16 hours in former case.36

Zia et al.; 1999, optimized Sotalol floating and bioadhesive extended release tablet formulation which posses a unique combination of flotation and bioadhesion for prolong residence in the stomach. A new factor factorial design was employed to optimize the tablet formulation containing 240 mg Sotalol HCl, the ratio of NaCMC to HPMC and the ratio of EC to Crosspovidone. The dependent variable was dissolution, bioadhesive capability, tablet disintegration and required compression force for producing 6 kg hardness tablets.37

Singh S et al.; 2011, The present study was undertaken to prolong the release of orally administer. Captopril in the floating tablets by using different grade of hydroxypropylmethylcellulose. Formulations were optimized using different viscosity grades of hydroxypropylmethylcellulose. Three different viscosity grades of hydroxypropylmethylcellulose namely K100M, K15M and K4M were used as a floating polymer or intention of polymer. It was observed that different viscosities not only influence the drug release from hydrophilic matrix but they also affect the floating properties of tablets. Results revealed that the floating formulation of the Captopril is the best formulation to obtain better therapeutic effect and hydroxypropylmethylcellulose at a concentration of 35% up to some extent it increases the Bioavailability of the drug to retain the dosage form on the desired site for effective period of the time.38

**Floating Beads**

Iannuccelli, et al., 1998, formulated a air compartment multiple unit system and optimized their *in vitro* floating ability. They showed that the floating ability increased with increased in PVA concentration and molecular weight and it was found to be excellent when using PVA 100000 at a concentration of at least 5%.39

Takka S. et al.; 1998, The release rate of nicardipine HCl from various alginate gel bead formulations was investigated. The formulations were prepared by utilizing 23 factorial design. The effect of drug:polymer weight ratio, CaCl2 and sodium-alginate concentration on the time for 50% of the drug release was studied and the results showed a high correlation with the concentration of CaCl2 and sodium-alginate.40

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3. Iannuccelli, et al., 1998, [Formulation of a Air Compartment Multiple Unit System and Optimization of Their In Vitro Floating Ability](#).
drug to be released (≥50%) and the drug entrapment efficiency were evaluated with analysis of variance. The mean particle size and the swelling ratio of the beads were determined. The in vitro release studies were carried out by flow-through cell apparatus in different media (pH 1.2, 2.5, 4.5, 7 and 7.5 buffer solutions). Drug: polymer weight ratio and the interaction of drug: polymer weight ratio and CaCl2 concentration had a significant effect on the drug entrapment efficiency. The release of nicardipine was extended with the alginate gel beads, which were prepared in a ratio of 1:1 (drug: polymer). The release of drug from alginate gel beads took place both by diffusion through the swollen matrix and relaxation of the polymer at pH 1.2-4.5. However, the release was due to the diffusion and erosion mechanism at pH 7-7.5.39

CONCLUSION
One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the gastrointestinal tract is to control the gastric residence time using gastro retentive dosage forms that will provide us with new and important therapeutic options. Floating drug delivery system can provide sufficient gastric retention of cardiovascular drugs which may help to provide sustained release dosage form with enhanced absorption. Number of commercial product and patent issued in this field are evident of it.

REFERENCES