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Review

Decades of research in drug targeting using gastroretentive drug delivery systems for antihypertensive therapy

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The limitations in absorption of drugs with narrow absorption window, or those unstable in the intestinal pH or those exhibiting low solubility at high pH are primary candidates for gastroretentive drug delivery systems (GRDDS). The delivery system has been widely explored for its commercial potential for a wide variety of therapeutic agents. GRDDS offer clinical therapeutics for acute and chronic management. Hypertension is a chronic disease that requires long term treatment and its management by patient compliant dosage forms would be clinically useful. Antihypertensives belonging to different classes have proved good candidates for the formulation of GRDDS. The review aims to discuss various GRDDS researched for antihypertensive drugs to increase the gastric residing time, bioavailability, henceforth to reduce the dose of the drug, dosing frequency and increase patient compliance. It also explores various marketed products and the patents filed/granted for GRRDS of antihypertensives. The GRDDS investigated include effervescent and non-effervescent floating drug delivery systems, swelling and expanding systems and bio/mucoadhesive systems. Many other systems that provided research platforms include high density systems, raft forming systems and osmotic delivery systems. In clinical context, wherein combination of antihypertensives is indicated, dual release delivery systems may also be explored.

Keywords: Antihypertensive drugs. Gastroretention delivery systems/absorption. Floating systems. Expanding and swelling systems, Bio/mucoadhesive systems.

INTRODUCTION

The drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems and site-specific delivery systems have been extensively explored due to their significant therapeutic advantages. The current controlled release technology has made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years (Sato *et al.,* 2003; Streubel, Siepmann, Bodmeier*,* 2006). However, this benefit has not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, and/ (iv) exhibit low solubilities at high pH values (Streubel, Siepmann, Bodmeier*,* 2006; Rocca, Omidian, Shah, 2003). These limitations promoted the development of gastroretentive drug delivery systems (GRDDSs). Besides being able to continually and sustainably deliver drugs to the small intestinal absorption window, the improvements provided by GRDDSs include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora (Sarojini, Manavalan, 2012). The prolongation of gastric residing time is expected to maximize drug absorption from GRDDSs due to increased dissolution of drug and prolonged residence in the gastric region. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility of those that are less soluble in a high pH environment. Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juices in the stomach. The problem arises when the

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stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. A prolonged stay in the stomach is not desirable for drugs that (i) cause gastric lesions (e.g., NSAIDs); (ii) are unstable in the acidic pH of the stomach; or (iii) undergo a significant first-pass effect (i.e., metabolism in the liver prior to entering the systemic circulation; e.g., nifedipine) (Streubel, Siepmann, Bodmeier, 2006).

Different techniques used for gastric retention (Arora *et al.,* 2005; Prinderre, Sauzet, Fuxen, 2011; Adebisi, Conway, 2011) are compiled as a schematic chart (Figure 1). These systems have been researched for a wide variety of therapeutic categories including antiulcer drugs, antibiotics, anti-diabetic drugs, cardiovascular drugs, drugs for gout and NSAIDS.

Hypertension and its therapy

Hypertension is the term used to describe high blood pressure. Normal blood pressure is below 120/80 mmHg; blood pressure between 120/80 mmHg and 139/89 mmHg is called "pre-hypertension", and a blood pressure of 140/90 mmHg or above is considered high. An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), eye damage, and stroke (brain damage). These complications of hypertension are often referred to as end-organ damage because damage of these organs is the result of chronic (long duration) high blood pressure. To nullify its impact, the diagnosis of high blood pressure is important so that efforts can be made to normalize blood pressure and prevent complications (MedlinePlus, 2015; Macgill, 2016). The treatment approaches include diuretics, ACE inhibitors, angiotensin antagonists, β-adrenergic blockers, α-adrenergic blockers, calcium channel blockers and vasodilators (Table I). Most anti-hypertensive medications can be used either alone or in combination: some are used only in combination (amlodipine with lisinopril); some are preferred over others in certain specific medical situations; and some are not to be used (contraindicated) in specific situations. Combination therapy is advocated when monotherapy fails or is not tolerated. In practice, a large majority of hypertensives ultimately require 2 or more drugs. Even initial treatment of mild to moderate hypertension with a low dose combination is being advocated as an alternative strategy. (Tripathi, 2003).

Need for GRDDS of antihypertensive drugs

Hypertension is one of the most common conditions in primary care and one of the key risk factors, along with hyperlipidemia, hyperglycemia, obesity and smoking etc that contribute to other diseases like myocardial infarction, stroke, renal failure and death. Joint National committee VIII (United States) estimates suggest more than 1 billion hypertensive patients world-wide. As per WHO report on World Health Statistics 2012, one in every three adults has raised blood pressure (Arora *et*

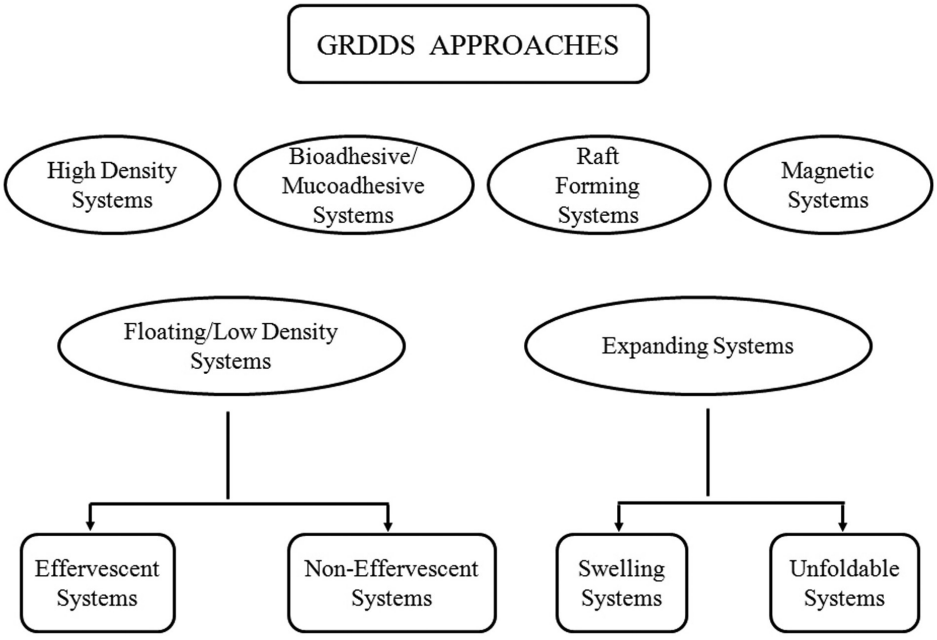

FIGURE 1 - General approaches to gastric retention.

TABLE I - The commercial dosage forms of antihypertensive drugs

Category	Drug	Dosage forms
Diuretics		
Thiazides	Hydrochlorthiazide,	Tablets
	Chlorthalidone	Tablets
Loop acting	Furosemide,	Tablets, injection
	Terosemide	Tablets
K^+ sparing drugs	Spironolactone,	Tablets
	Triamterene	Tablets
ACE inhibitors	Captopril,	Tablets
	Enalapril,	Tablets
	Lisinopril	Tablets
	Quinapril	Tablets
Angiotensin antagonist	Losartan,	Tablets
	Candesartan	Tablets
β-adrenergic blockers	Propranolol,	Tablets, injection
	Metoprolol,	Tablets, injection
	Atenolol	Tablets
α-adrenergic blockers	Prazosin,	Tablets
	Terazosin	Tablets
β + α Adrenergic blockers	Labetalol,	Tablets, injection
	Carvedilol	Tablets
Calcium Channel Blockers	Nifedipine,	Tablets, Capsules
	Felodipine,	Tablets
	Amlodipine	Tablets
	Nicardipine,	Capsules, injection
	Verapamil,	Tablets, injection
	Diltiazem,	Tablets, injection
	Nitrendipine	Tablets, injection
Vasodilators	Hydralazine,	Tablets, injection
	Minoxidil,	Lotion, Solution, spray

al., 2015). This becoming a chronic disease requires long term treatment. GRDDS can be a viable option for management of hypertension management as several antihypertensive drugs are associated with (a) narrow absorption window {e.g. furosemide (Pawar *et al.,* 2012; Davis, 2005; Darandale, Vavia, 2012), atenolol, diltiazem (Srikanth *et al.,* 2011)}; (b) short half-life {e.g. losartan (Chen *et al.,* 2010), furosemide (Darandale, Vavia, 2012)}, (c) instability {e.g. captopril (Streubel, Siepmann, Bodmeier*,* 2006; Pawar *et al.,* 2012)} at high pH values; (d) low solubility {e.g. verapamil (Streubel, Siepmann, Bodmeier*,* 2006; Niranjanbhai *et al.,* 2012), furosemide (Streubel, Siepmann, Bodmeier*,* 2006), propranolol (Chinta *et al.,* 2009)} at high pH, and (e) degradation in the colon {e.g. metoprolol (Srikanth *et al.,* 2011)}. GRDDS is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper GIT for local or systemic effects. This site-specific drug delivery reduces undesirable side effects of administered drug as it can minimize the counter activity of the body leading to higher drug efficiency. This review aims to discuss various GRDDS of antihypertensive drugs to increase the gastric residence time, bioavailability, henceforth to reduce the dose of the drug, dosing frequency and increased patient compliance.

GRDDS FOR ANTIHYPERTENSIVE DRUGS

Gastroretentive systems using polymers have been extensively investigated for various antihypertensive drugs and the findings are summarized in a classified manner in the following sections.

Floating Systems

Effervescent systems

Floatability can be achieved by generation of gas bubbles. CO_2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid- either the natural gastric acid or co-formulated as citric or tartaric acid. An alternative is to incorporate a matrix with entrapped liquid, which forms a gas at body temperature. Drug and excipients can be formulated independently and the gas generating unit can be incorporated into any of the layers. Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO_2. The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer (Bardonnet *et al*., 2006).

Chen *et al*. (2010) formulated gastroretentive tablets based on effervescence/swelling mechanism using polymers sodium carboxymethyl cellulose, hydroxyethyl cellulose and sodium bicarbonate for losartan. To evaluate swelling and effervescent properties, tablets were prepared with different compression pressure. The optimized formulation floated for more than 16 h with a swollen diameter of 2 cm within 3 h in the simulated gastric fluid. Also, the formulations showed pH-dependent drug release with an extension for 24 h. Clinical trials of the optimized GRDDS were assessed on the bioavailability of losartan and the formation extent of active metabolite E3174 by CYP2C9 polymorphism. Trials in healthy human volunteers showed an enhanced bioavailability of approximately 164% as compared to the immediate release marketed formulation Cozaar®. As expected, the developed GRDDS showed favourable pharmacokinetic parameters: increased mean residence time whereas, T_{max}

and C_{max} were lower as compared to Cozaar® concluding the enhancement in bioavailability due to gastroretention.

Ozdemir, Ordu and Ozkan (2000) designed floating bilayer tablets with controlled release for furosemide. To enhance the poor solubility of furosemide in the gastric medium, its inclusion complex with beta-cyclodextrin in a 1:1 proportion was prepared by kneading method. The first layer constituted of HPMC 4000, HPMC 100, and CMC and the drug. The second layer was composed of the effervescent mixture of sodium bicarbonate and citric acid. The *in vitro* floating studies inferred that lesser the compression force the shorter was the time of onset of floating. For tablets compressed at 15 MPa, floatation was initiated in 20 min whereas at a force of 32 MPa the time was prolonged to 45 min. *In vivo* studies on six healthy male volunteers revealed gastroretention of 6h when monitored by radiography. Pharmacokinetic studies showed that the bioavailability of the drug from the floating tablets was 1.8 times than that of the conventional tablets. These findings suggested that the delivery of furosemide from floating bilayer tablets resulted in sustained antihypertensive effect.

Another study on furosemide, by Meka *et al.* (2009) reports formulation of polymer coated mini tablets as multiple unit gastroretentive floating systems. A core containing a solid dispersion of furosemide in polyvinyl pyrrolidone with other excipients was prepared by direct compression. The core was coated first with an effervescent layer (sodium bicarbonate) and a second coat with polymethacrylates (Eudragit RL30D) was affected. Interestingly, with an increase in the amount of the effervescent agent and decrease in the coating level of the polymer, the time to float was decreased. The in vivo gastric residence time examined by radiograms revealed gastroretention of about 6 h that would be helpful in drug release sustainment. The stability samples showed no significant change in dissolution profiles.

In a research endeavour, Elkheshen, Yassin and Alsuwayeh (2004) formulated and evaluated floating effervescent sustained release tablets of verapamil hydrochloride from granules containing mixtures of a forming matrix (HPMC, HPC, EC/carbopol) together with sodium bicarbonate and anhydrous citric acid. *In vivo* X-ray imaging experiments conducted on fasted beagle dogs to abolish the effect of food, showed that the gastric emptying time of the floating tablets could be more than 4 h and less than 5 h. Results demonstrated that the optimized formulation delayed the gastric emptying time under fasted conditions. While fed state is the primary requirement for gastroretention in vivo studies so the fed state would prove useful.

Directly compressed floating tablets of verapamil hydrochloride have also been reported by Dawange, Khadabadi and Saboo (2015). A variety of polymers and effervescent properties (HPMC K15M, sodium alginate, sodium bicarbonate and citric acid) were utilized to optimize the desired disposition profile by 3^2 factorial design. It was found that the levels of HPMC K4M, sodium alginate and their interaction had significant influence on both the drug release and floating lag time of the delivery system. *In vitro* drug release studies showed sustained release for 12 h and that followed Korsemeyer Peppas model.

A similar formulation approach was used by Rahman, Ali and Khar (2006) for formulating a bilayer floating tablet of captopril using direct compression technology. First layer consisted of HPMC K-grade and a mixture of citric acid and sodium bicarbonate. Second layer contained captopril and various polymers like HPMC K15M, PVP-K30 and Carbopol 934P. The optimized formulation released 95% of drug in 24 h *in vitro*, while the floating lag time was 10 min and the formulation remained floatable throughout the study. The release kinetics followed the Higuchi model. X-ray imaging method used to evaluate the buoyancy behaviour of captopril bilayer-floating tablet in 10 human subjects showed that the tablets remained in the stomach for about 6.4 h. Thus, the optimized formulation showed gastroretention due to buoyancy conferred by the porous structure formed due to entrapment of CO_2. In a mechanistic study, Martinez, Ramirez and Robles (2010) studied the effect of antioxidant metolose SH 4000 SR on drug release from floating matrix tablets of captopril. It was concluded that the higher levels of gas forming agent caused hindrance on drug release, as carbon dioxide bubbles obstructed the diffusion path and decreased the matrix coherence. The developed dosage form remained buoyant for a period of more than 8 h. An increase in polymer concentration resulted in decreased drug release rate due to an increasing tortuosity and length of the diffusion path through the matrix.

Barmpalexis, Kachrimanis and Georgarakis (2011) developed an effervescent controlled release floating tablets of nimodipine-PEG solid dispersions. The mixture proportions of PEG, HPMC, PVP, effervescent agents and nimodipine were optimized in relation to drug release ($t_{60\%\ min}$ and $t_{90\%}$) and floating properties (tablet's floating strength and duration), employing a 25-run D-optimal mixture design combined with artificial neural networks and genetic programming. Results showed that nimodipine existed as mod I microcrystals in the solid dispersions and was stable for at least a three-month period. The tablets

showed good floating properties and controlled release profiles, with drug release proceeding via swelling and erosion of the polymer matrix. The floatation duration varied from 1 to 20 h with a lag time of less than 3 min. The researchers concluded enhancement in solubility and gastroretention to improve site specific bioavailability of the drug.

Apart from research reports on tablets, the literature also cites gastroretentive capsules of antihypertensive drugs. Moursy *et al.* (2003) formulated sustained release floating capsules of nicardipine HCl. A hydrocolloid of high viscosity grade was used for the floating systems, and for aiding buoyancy sodium bicarbonate was added to allow evolution of CO_2. In vitro evaluation showed an increase in floating duration with an increase in proportion of hydrocolloid. The optimized sustained release floating capsules were evaluated *in vivo* in comparison to MICARD (commercially available conventional 20 mg capsule of nicardipine hydrochloride capsules) by using it on rabbits. Drug determination in rabbit plasma revealed a prolonged sustained drug release of 16 h over the conventional "MICARD" capsule (8 h).

Non-effervescent systems

This type of system, after swallowing, swells via imbibitions of gastric fluid to an extent that prevents their exit from the stomach. The formulation methods of such type of dosage forms involve the mixing of the drug with a gel, which swells when it comes in contact with gastric fluid 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 provides buoyancy to these dosage forms (Sarojini, Manavalan, 2012).

In an attempt to develop non-effervescent GRDDS of antihypertensives, Sultana, Bhavna and Iqbal (2009) formulated gastroretentive microspheres of lacidipine using chitosan as polymer and glutaraldehyde as the cross-linking agent. The effect of independent variables such as concentration of polymer, glutaraldehyde volume, stirring speed and cross-linking time was evaluated on the dependent variables: mucoadhesion and entrapment efficiency using central composite design. It was found that the polymer concentration and glutaraldehyde volume had pronounced effect on dependent variables.

Shimpi *et al.* (2004) explored the application of gelucire 43/01 for designing floating granules of a highly water-soluble drug diltiazem HCl. The granules were prepared by melt granulation technique and evaluated for pharmaceutical characteristics. The results of *in vivo* gamma-scintigraphy in healthy human volunteers showed that the granules retained in stomach for 6 h and 65–80% of drug was released over 6 h with an initial fast release from the surface. It was concluded that hydrophobic lipid, gelucire 43/01, can be considered as an effective carrier for design of a multi-unit floating drug delivery system of diltiazem HCl. Additionally, a polymer based multiunit floating system of diltiazem hydrochloride was developed by Ma *et al.* (2008). Floating alginate microspheres were developed by ionotropic gelation method using calcium carbonate as floatation aid. Experiments were conducted to enhance the drug encapsulation efficiency by adding chitosan into the gelation medium and the drug release was delayed by coating with Eudragit. Both uncoated and coated microspheres were able to continuously float over the simulated gastric fluid for 24 h *in vitro.* Gamma scintigraphy technique was used to compare gastrointestinal transit of optimized floating sustained release microspheres with that of the non-floating system manufactured from the same material, in healthy human volunteers. It was observed that the gastric-retention time of the optimized floating microspheres was prolonged for over 5h and was 2.5h for non-floating system. Alginate based floating beads of diltiazem HCl have also been reported by Saxena *et al.* (2016). The floating beads were prepared by ionotropic external gelation technique using $CaCl_2$ as cross-linking agent. The authors however attempted to improve both the entrapment efficiency and drug release by incorporating low methoxy pectin and sunflower oil as co-polymers along with sodium alginate. SEM images of beads showed sponge like nature with little droplets of oil that imparted buoyancy to the beads. This report paves way for experimenting with many more biological macromolecules and low density food grade oils for preparation of floating beads.

In this context, Patel *et al.* (2006) formulated and evaluated floating chitosan microspheres of propranolol hydrochloride. Microspheres were prepared by chemical denaturation using glutaraldehyde as a cross-linking agent. A 3^2 full factorial design was used to study the effect of independent variables like drug: polymer ratio and volume of cross-linking agent on dependent variables, such as drug entrapment efficiency, floating lag time, $T_{80\%}$, particle size and similarity factor. *In vivo* study in healthy rabbits demonstrated sustained antihypertensive effect of floating microspheres of propranolol hydrochloride over a 12 h period due to slow release of the drug. In another research, Strubing, Metz and Mader (2008) prepared a single unit floating Kollidon SR matrix tablets of propranolol HCl and characterized it for the floating strength of tablets and the drug release profiles. The tablets remained buoyant for 24 h with a very short lag time and the floating strength was inferred to be dependent upon the level of Kollidon

SR and improved with high polymer/drug ratio. The drug release kinetics followed Fickian diffusion. While the results concluded the floating and sustained release properties, the viability of single unit system over the reported multiparticulate system is debatable especially in the absence of in vivo studies.

An interesting report by Chinta *et al.* (2009) explores a novel spray-dried tableting excipient made of chitosan (all three grades) and lactose for developing GRDDS of propranolol HCl. Specific amount(s) of chitosan was dissolved in an aqueous solution of citric acid and mixed with aqueous solution of lactose and the drug. The resultant solution was spray dried to get granules that were directly compressed with sodium bicarbonate. The tablets showed their 50% drug release between 30 and 35 min. Another report on propranolol HCl by Porwal, Swami and Saraf (2011) describes preparation of sustained release microballoons for increasing its bioavailability by increasing gastroretention. Microballoons were prepared by the non-aqueous O/O emulsion solvent diffusion evaporation method using Eudragit RSPO as polymer. It was found that preparation temperature determined the formation of cavity inside the microballoon and this in turn determined the buoyancy. The microballoons presented spherical and smooth morphologies and remained buoyant for >12 h with favourable *in vitro* release characteristics. *In vitro* release kinetics followed Higuchi model mainly controlled by diffusion; and showed a biphasic pattern with an initial burst release, followed by sustained release for 12 h. A single unit floating system of propranolol HCl has also been described by Srikanth *et al.* (2012) Gastric floating tablet was developed by using central composite design and the effects of formulation variables on drug release and the buoyancy properties were investigated. The independent variables were polyethylene oxide WSR coagulant and sodium bicarbonate. Mathematical modelling of the responses demonstrated significant effects of independent variables on floating lag time, drug release at 1h and $t_{90\%}$. *In vivo* studies in human volunteers demonstrated buoyancy in gastric fluid and the gastric residence time was enhanced in the fed in comparison to the fasted state.

Poorly water soluble antihypertensive drugs have also been developed as non-effervescent GRDDS. Iannuccelli *et al*. (2000) used solid dispersion of furosemide inpolyvinylpyrrolidone (PVP) to prepare floating multiple unit system. The complete dose release over the actual intra-gastric residence time of the system (about 8 h) was achieved by loading both the core and the membrane forming the units with a 1:5 furosemide/PVP solid dispersion. XRD showed a decrease in crystallinity of furosemide in solid dispersion, which lead to the improved solubility and dissolution rate of the drug, that further led to desired release profile from the floating units.

Further, Sahu, Singh and Verma (2011) formulated non-effervescent floating matrix tablets of furosemide using chitosan and HPMC. The tablets were evaluated for floating capability and in-vitro drug release kinetics. The drug release followed non-Fickian diffusion. On combining HPMC with chitosan in various mixtures, it was observed that formulations followed zero-order kinetics with floatation period of >8 h.

ElMeshad and El-Ashmoony (2012) prepared buoyant beads enclosing furosemide by cross-linking chitosan with dioctyl sodium sulphosuccinate and characterized. The spherical beads floated for over 12 h in simulated gastric fluid and affected retarded release of the drug as compared to pure drug powder and Lasix tablets. The beads remained buoyant in the stomach of dogs for 6 h. The results concluded that chitosan floating beads as effective carrier for furosemide, maximizing its therapeutic effect at the site of absorption in a controlled release pattern.

In another research endeavour, Streubel, Siepmann and Bodmeier (2002; 2003; 2003a) prepared microparticles of verapamil containing polypropylene foam powder and different polymers (Eudragit RS, EC, polymethyl methacrylate) by o/w solvent evaporation method. They also formulated a monolithic floating drug delivery system based on highly porous polypropylene and matrix-forming polymers. The highly porous foam powder provided low density tablets which could float for at least 8 h in 0.1N HCl. Drug release characteristics were modified according to the ratio of matrix-forming polymer and foam powder and were also strongly related to drug chemistry.

Coated minitablets of the verapamil formulated by Sawicki (2002) were assessed for their *in vivo* performance in healthy human volunteers. An increase in AUC was observed for testing minitablet against the immediate release formulation. However, the results could not conclude the gastric retention because of the indirect link between pharmacokinetics and the gastrointestinal position.

In another study on verapamil, Eldeen, Alsara and Mohizea (2006) designed gastroretentive beads using chitosan as polymer and glutaraldehyde as a cross-linking agent. Internal structure of dried beads confirmed encapsulation of verapamil into the bead cores. The beads prepared by using medium molecular weight chitosan showed good floating characteristics and floating lag time was found to be 5 min with total buoyancy duration of >6 h. The formulations exhibited a kinetic model of

combined mechanism(s) of diffusion, partially through a swollen matrix and partially through water-filled pores. Floating microspheres (251.80 to 350.75 µm) of verapamil HCl by solvent-diffusion evaporation method using cellulose acetate, Acrycoat S100 and Eudragit S100 have been prepared by Tanwar, Naruka and Ojha (2008). The microspheres showed prolonged drug release and remained buoyant for more than 12 h that is nearly two times the value reported for gastroretentive beads reported by Eldeen *et al*. (2006). *In vitro* release study demonstrated non-Fickian diffusion of the drug and radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulphate floated on the gastric fluid for about 3.2 h. The hollow structure of the microspheres was responsible for the floating properties.

A similar formulation approach was used by Soppimath *et al*. (2006) to study the effect of co-excipients on drug release profile and floating property of the hollow microspheres of nifedipine. The drug was incorporated into cellulose acetate hollow microspheres prepared by solvent diffusion/evaporation technique in the presence of co-excipients like polyethylene glycol, dibutyl phthalate and poly(-caprolactone) by using ethyl acetate as a dispersing solvent. An increase in polymer concentration resulted in an increase in the size of the microspheres. The microspheres remained buoyant in simulated gastric fluid for over 12 h. The presence of co-excipients affected the buoyancy of the microspheres. The cellulose acetate-polyethylene glycol microspheres had lower buoyancy that increased with increasing concentration of polyethylene glycol (PEG). However, on increasing the PEG concentration from 10% to 40%, the buoyancy decreased from 51.3% to 11.8%. Better buoyancy (62–82%) was observed for microspheres made with water-insoluble plasticizer dibutyl phthalate due to its hydrophobic nature that prevented wetting as well as water uptake. The drug release was in a controlled manner that was amenable to modification by the process variables.

Floating gastroretentive microspheres of carvedilol using EC and HPMC have been reported by Zhang *et al.* (2016). The formulations were screened for drug loading (74.62±2.05 to 95.02±1.02%), particle size (270.04±10.30 to 356.30±10.60 µm), floating time (4.5 to 9.12 h) and swelling at the end of 4h (67.25±1.67 to 93.64±3.05%). The *in vitro* drug release in pH 1.2 after 6 h was found in the range of 64.45±1.41 to 88.07± 1.74%. The optimized formulation (containing EC=1.0% and HPMC=0.5%) was significantly effective in promptly lowering the systolic blood pressure as compared to that of conventional tablet in hypertensive patients.

Using a polymeric blend of hydroxyethylcellulose and chitosan, and sodium bicarbonate Chen *et al*. (2013) developed gastroretentive drug delivery systems of losartan by combining floating and swelling approaches. They found that formulations containing equivalent ratio of hydroxyethylcellulose and chitosan with 20 mg sodium bicarbonate began floating within 1 min and floated for more than 16 h, exhibiting a swelling ratio of 2 (due to polymeric blend) to achieve an adjustable sustained release profile.

Similarly, Nur and Zhang (2000) designed captopril floating tablets using HPMC (4000 and 15000 cps) and Carbopol 934P. In vitro buoyancy studies exhibited that tablet with hardness of 2 kg/cm^2, after immersion floated immediately whereas the tablets with hardness of 4 kg/cm^2 displayed a lag time of 3 to 4 min. Tablets in both cases remained floating for 24 h. No floating capability was found in the tablet with 8 kg/cm^2 hardness. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the porosity of the tablets. A prolonged release for 24h from the floating tablets and the release kinetics fitted Korsemeyer and Peppas equation was followed by first order kinetics.

In another research, Wu *et al.* (1997) prepared floating sustained release tablets of nimodipine using HPMC and PEG 6000. Before formulating floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. Formulations were optimized using uniform design and variables affecting nimodipine release from matrix were studied. In vitro release followed zero-order kinetics and it was observed that an increase in HPMC and decrease in the PEG 6000 content resulted in decrease in the *in vitro* release of nimodipine. *In vivo* studies in healthy volunteers showed that the optimized formulation could remain floating on gastric fluid for more than 10 h. Relative bioavailability of floating tablets was 391.46% and MRT was more than twice the conventional tablets. Thus, floating tablets of nimodipine loaded solid dispersion results in tremendous increase in the bioavailability of the drug.

Hydrophilic cellulose and pH-independent acrylic polymer based directly compressible controlled release floating matrix tablets of nicorandil were designed and developed by Nath and Ahmed (2016). The optimized formulation was evaluated for stability study and *in vivo* absorption in rabbits to compare the pharmacokinetic parameters with commercially available immediate release tablet of nicorandil. *In vivo* gamma scintigraphy studies revealed that the system was floated for a period of 6-7 h

in the stomach and *in vivo* absorption studies showed a significant increase in the AUC and MRT.

Expanding and swelling systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable and swellable systems have been investigated. Unfoldable systems are made of biodegradable polymers. The idea is to make a carrier, such as a capsule, incorporating a compressed system that extends in the stomach. Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids. The bulk enables gastric retention and maintains the stomach in a "fed" state, suppressing housekeeper waves (Bardonnet *et al*., 2006).

Darandale and Vavia (2012) developed and characterized a gastroretentive dosage form suitable for controlled drug release of furosemide. It consists of a drug loaded polymeric film made up of a bilayer of immediate and controlled release layers which was then folded (zig-zag folding; Figure 2) into a hard gelatin capsule. The bilayer film consists of hydroxypropyl-β-cyclodextrin in both layers and Carbopol ® 971P NF, Eudragit RLPO and HPMC E4M in the controlled release layer. The film was shown to unfold and swell under acidic conditions and provide immediate release of the drug for 1h and controlled release for up to 12 h in acidic medium. Unfolding and swelling of the film and its bioadhesion to the gastric mucosa forms the key to gastroretention.

A similar approach was used by Sathish *et al*. (2013) for the preparation of a novel expandable gastroretentive dosage form based on an unfolding mechanism. They prepared a bilayer polymeric film of captopril folded into a hard gelatin capsule, which achieved gastric retention due to unfolding of the dosage form within 15-20 min. Films were formulated by solvent-casting technique using EC, HPMC E15 and Eudragit RLPO as polymers and dibutyl phthalate as the plasticizer in both the layers. Apart from routine technical parameters, the bilayer films were evaluated for unfolding behaviour based on the mechanical shape memory of polymers. The capsulated zigzag folded film was shown to unfold in the gastric juice and provided

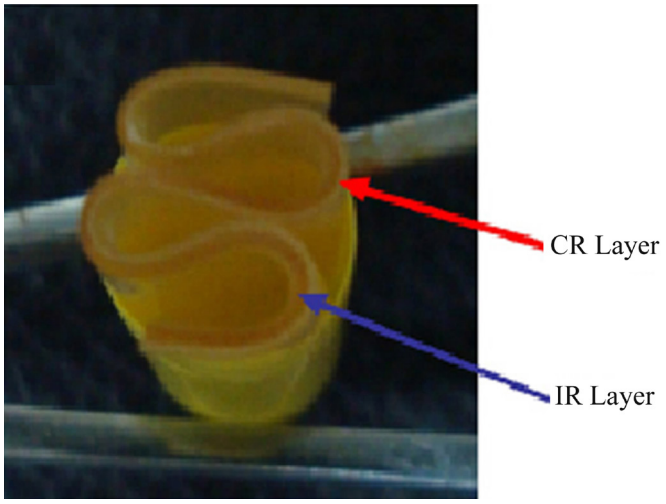

FIGURE 2 - Folding pattern of film for gastroretentive bilayer film of furosemide. (Darandale, Vavia, 2012.)

drug release up to 12 h in the simulated gastric fluid. The X-ray study revealed that the GRDDS was retained in the stomach for up to 6± 0.5 h in fasting condition and 8 h in fed state validating the design.

In an effort to design a controlled-release, expandable GRDDS; Biswas *et al*. (2014) fabricated a drug delivery system of carvedilol using HPMC and psyllium. Mass swelling ratios at equilibrium were higher for batches containing psyllium which rendered them buoyant in the simulated gastric fluid within 9 min and maintained the structural integrity for a maximum period of 23.8±0.97 h. The batch with HPMC K15M and psyllium in the ratio 2:1 exhibited Fickian type swelling mechanism. The drug diffused out through the gel barrier around the swollen matrix slowly via diffusion/relaxation controlled transport. Release retardant effect of psyllium was manifested in high values of $t_{50\%}$ and $t_{80\%}$ of 7.8 0.59 and 16.1±0.26 h, respectively, for the optimized batch.

Bio/Mucoadhesive systems

They bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems (Sarojini, Manavalan, 2012).

Pathak, Mishra and Mishra (2013) developed gastroretentive mucoadhesive films of captopril by using polymers like EC, HPMC and carbopol 934P and glycerine(plasticizer) for treatment of hypertension. The release kinetics followed Korsmeyer-Peppas model.

The optimized formulation showed best mucoadhesive strength and a drug release of 99.06% at 24th hour. In another report on captopril; Pawar, Lalitha and Ruckmani (2015) prepared gastroretentive captopril loaded alginate beads by ionotropic gelation method using sodium alginate in combination with natural gums containing galactomannans (Senna tora seed gum, guar gum and locust bean gum) in the presence of calcium chloride. From the entrapment efficiency and drug release studies, it was concluded that galactomannans in combination with sodium alginate show sustained release property. The optimized formulation showed satisfactory sustained release for 12 h and the release was governed by swelling of the polymer followed by drug diffusion through the swollen polymer and slow erosion of the beads.

Lemieux, Gosselin and Mateescu (2015) prepared microspheres from carboxymethyl starch powder and investigated the influence of degree of substitution (0.1 to 1.5) on the physicochemical, drug release and mucoadhesion properties as well as interactions with gastrointestinal tract epithelial barrier models. Placebo and furosemide loaded microspheres were obtained by emulsion-crosslinking with sodium trimetaphosphate. The degree of substitution impacted the equilibrium water uptake and modulated drug release properties of the microspheres according to the surrounding pH. The drug release, permeability enhancement and mucoadhesive properties of the microspheres suggested that the microspheres made with carboxymethyl starch powder with degree of substitution between 0.6 and 1.0, were suitable excipient for GRDDS.

Using isabgol as an excipient for developing GRDDS of lisinopril was experimented by Semwal, Semwal and Semwal (2014) and its gastroretentive ability was enhanced by addition of sodium bicarbonate as a gas-generating agent while its mucoadhesive property was enhanced by incorporation of HPMC K4M. The drug, sodium bicarbonate and HPMC K4M were imbibed on isabgol husk, dried and filled in a hard gelatin capsule. The drug released through isabgol was delayed by 12 h in comparison to commercially available formulation of lisinopril which released the drug completely in 0.5 h. The drug release study from the formulation followed first order kinetics using a diffusion controlled mechanism. The results from the present study concluded that isabgol can be used as a potential excipient for the formulation of GRDDS in future.

Formulation of gastroretentable mucoadhesive patch of lercanidipine HCl has been reported by Pandey *et al*. (2013). The patch consisted of a rate controlling film (Eudragit RSPO and RLPO) and a mucoadhesive film of various hydrophilic polymers. The bilayered patch was prepared by using the layering method. The film was folded into a hard gelatin capsule and evaluated for in vitro drug release in pH 1.2 containing 0.2% (w/v) sodium lauryl sulphate, and in vivo bioavailability in rabbits. The patches showed controlled drug release up to 12 h and optimal mucoadhesion (4.05±0.4 to 4.52±0.12 N). *In vivo* bioavailability results revealed that the gastroretentive patch system provided a novel way to retain the drug matrix for the longer period of time in stomach, enhance drug absorption and thereby offer a promising strategy for gastroretentive mucoadhesive drug delivery for the lercanidipine HCl.

COMMERCIALIZATION AND PATENTS

The commercial potential of GRDDS has already been proven. Commonly used drugs in formulation of gastroretentive dosage forms and the marketed products of antihypertensives available as GRDDS can be found in Table II and Table III respectively. While to the best of our knowledge only four products could be found, twice the number of patents was documented in literature as compiled in Table IV. This definitely offers wide vistas for researchers to explore the less trodden area. A few of the patents have been described briefly in the following text.

Dudhara, Dharmadhikari and Dhayse (2004) patented a gastric retention controlled drug delivery system comprising: (a) a controlled release core comprising a drug, a highly swellable polymer and a gas generating agent, said core being capable of swelling and achieving floatation rapidly while maintaining its physical integrity in gastrointestinal fluids for prolonged periods and (b) a rapidly releasing coat so that the system provides a biphasic release of the drug in gastrointestinal fluids.

Ogorka *et al.* (2009) has been assigned a patent for an extended release GRDDS of valsartan containing a release portion of valsartan, a gastroretentive portion for retaining the drug delivery system in the stomach and an optional secondary portion for delivering a secondary pulse of valsartan. In another embodiment, a swellable unfolding membrane comprising Valsartan for sustained administration of Valsartan has been provided to the upper GI tract of a patient.

Mullen, Stevens and Eccleston (2011) got patented an invention in which an active agent is designed to be released in a prolonged manner at a point of time some time after administration of the active agent. The present invention is particularly suitable for administering an agent that may be released while the subject is sleeping, shortly before waking up and continues to administer

TABLE II - Summarized compilation of antihypertensive drugs explored for various GRDDS

Dosage forms	Antihypertensive drugs
Tablets	Losartan (Chen, 2010), propranolol (Chinta, Graves, Pamujula, 2009; Srikanth *et al.*, 2012), furosemide (Ozdemir, Ordu, Ozkan, 2000; Sahu, Singh, Verma, 2011), verapamil (Elkheshen, Yassin, 2004; Sawicki, 2002), captopril (Martinez, Ramirez, Robles, 2010; Nur, Zhang, 2000), nimodipine (Barmpalexis, Kachrimanis, Georgarakis, 2011; Wu *et al.*, 1997), nicorandil (Nath, Ahmed, 2016), quinapril (Mali, Bathe, 2015), amlodipine (Ramasubramaniyan *et al.,* 2015), atenolol (Charan, Meher, Pochaiah, 2013), metoprolol (Ratnaparkhi, Garje, Chaudhari, 2013)
Microspheres	Lacidipine (Sultana *et al.*, 2009), diltiazem (Ma *et al.*, 2008), propranolol (Adebisi, Conway, 2011; Patel *et al.*, 2006), furosemide (Iannuccelli *et al*., 2000), verapamil (Tanwar, Naruka, Ojha, 2008), nifedipine (Soppimath *et al.*, 2006), carvedilol (Zhang *et al.*, 2016)
Capsules	Nicardipine (Moursy *et al.,* 2003), lisinopril (Semwal's, 2014), lercanidipine (Pandey *et al*., 2013)
Granules	Diltiazem (Shimpi *et al.*, 2004)
Films	Furosemide (Darandale, Vavia, 2012), captopril (Sathish *et al*., 2013; Pathak, Mishra, 2013)
Beads	Diltiazem (Saxena *et al.*, 2016), furosemide (ElMeshad, El-Ashmoony, 2012), verapamil (Eldeen, Alsara, Mohizea, 2006), captopril (Pawar, Lalitha, Ruckmani, 2015)

TABLE III - Marketed products of GRDDS for antihypertensive drugs (Srikanth, 2011; Awasthi, Kulkarni, 2016)

Drug	Technology	Brand name	Manufacturer
Prazosin HCl	Effervescence and swelling based floating system.	Prazopress XL®	Sun Pharma, India
Carvedilol	Osmotic system	Coreg CR®	Glaxosmithkline, USA
Verapamil HCl	OROS	Covera HS®	DURECT Corporation, USA
Nisoldipine	Geomatrix™	Sular®	Skyepharma, Shionogi Pharma Inc. UK

the drug during the early waking hours. The invention treats certain conditions by a particular regime, as well as provides novel formulations for a delayed, followed by a prolonged release of drug.

FUTURE PERSPECTIVE

A controlled drug delivery system with prolonged residence time in the stomach can be of great importance for antihypertensive drugs with select pharmacokinetic features. The systems developed include gastroretentive tablets, capsules, microspheres, granules and beads. Many other systems can be explored for developing GRDDS of antihypertensive drugs. These may be osmotically regulated systems that offer the possibility of varying the formulation variables and exploring various designs. Unfolding bilayer system, raft based and ion exchange resin systems may be utilized depending upon the physicochemical properties of the drug. The bilayer unfolding and raft forming systems need to be explored extensively as scarce reports can be found in literature that offer most promising GRDDS. Through bilayer unfolding systems both sustained as well as immediate release can be obtained, and sustained release can be increased up to 24 h. At the same time, small size of the folded system makes it easy to administer and on reaching the stomach it will unfold and swell to prolong gastric retention thereby increasing gastric emptying time as well as increasing bioavailability. More research is required on this system that has potential for exhibiting excellent results in controlling hypertension.

The ion-exchange resin complexes can be prepared from both acidic and basic drugs and have immense commercial potential. Salts of cationic and anionic exchange resins are insoluble complexes in which drug releases from exchange of bound drug ions by ions normally present in body fluids; in this case the gastric fluid (Guo, Chang, Hussain, 2009). However, judicious selection of the ion-exchange resins and the drug are of utmost importance. Another significant system that has been reported for its gastroretentivity is based on floatation and is microsponges. In a report by Arya and Pathak (Arya, Pathak, 2014), the viability of microsponges as GRDDS was assessed in delivering curcumin for the treatment

TABLE IV - Patents on grdds of antihypertensive drugs

Patent/Application number (year of issue/publication) & Drug	Original assignee/ Applicant	Comment	Ref.
US20040180088A1 (2004) Antihypertensives	Dudhara KM, Dharmadhikari NB, Dhayse VV.	Provides a gastric retention controlled drug delivery system comprising: (a) a controlled release core comprising a drug, and (b) a rapidly releasing coat so that the system provides a biphasic release of the drug in gastrointestinal fluids.	(Dudhara, Dharmadhikari, Dhayse, 2004)
EP2061438 A1 (2009) Valsartan	Novartis AG	Invented an extended release GRDDS of valsartan containing a release portion of valsartan, a gastroretentive portion for retaining the drug delivery system in the stomach and an optional secondary portion for delivering a secondary pulse of valsartan.	(Ogorka *et al.,* 2009)
WO2009087665 A2 (2009) Propranolol	Vishwanath SN	Claimed a novel GRDDS that floats over the simulated physiological fluids owing to its low density. The system comprises inert core, polymers and plasticizer.	(Vishwanath, 2009)
US7776345 B2 (2010) Antihypertensives	Sun Pharma Advanced Research Company Ltd	A GRDDS comprising a controlled release core of the, a highly swellable polymer and a gas generating agent, and (b) a rapidly releasing coat such that the system provides a biphasic release of the drug.	(Dudhara, Dharmadhikari, Dhayse, 2010)
WO2011107750 A2 (2011) Antihypertensives	University of Strathclyde	Discloses an invention in which an active agent is designed to be released in a prolonged manner at a time point some time after administration of the active agent.	(Mullen, Stevens, Eccleston, 2011)
WO2013051036 A1 (2013) verapamil, propranolol, captopril, diltiazem	Council of Scientific & Industrial Research, India	The invention discloses a GRDDS comprising a drug in the core and coated with a coating of a pH sensitive polymer. The system can release the drug in both sustained and pulsatile manner.	(Kolhe, Kulkarni, 2013)
WO2013054285 A1 (2013) ACE inhibitors	Ranbaxy Laboratories, New Delhi, India	Invented a floating capsule which releases the drug without any lag time and which remains buoyant for a sufficient period of time in the stomach.	(Kumar, Ahmad, Singh, 2013)
US8586083 B2 (2013) Metoprolol	Euro-Celtique S.A.	The invention is produced by extrusion. The use of extrusion enables the product to take many useful forms. The product may comprise a sheet of hydratable polymer, the hydrated sheet being of a size which will not pass out of the stomach, for example a shaped sheet or a roll.	(Mohammad, 2013)

of gastric cancer. The *in vitro* permeation capability of curcumin along with favourable pharmaceutical and pharmacokinetic characteristics of the optimized formulation affirmed the capability of microsponges as efficient GRDDS.

Over the last few decades majority of the work was done on the GRDDS of antihypertensives reports development of novel systems by using single drug. Clinically, for chronic hypertensive cases, dual drug therapy is advised that presents a new area of research

focussing on dual drug release systems. One can find few reports on drug delivery systems based on dual release mechanism and an interesting design has been reported recently by Rajput Singh and Pathak (2014) though not for antihypertensives. Briefly, the authors developed a bifunctional single unit capsular system comprising uniquely shaped gastroretentive fanicular cylindrical system for immediate release of granules of ranitidine HCl and controlled delivery of clarithromycin (Figure 3). The fanicular cylindrical system of clarithromycin exhibited synergistic gastroretention due to its floating and bioadhesive features. This system can be extrapolated/ modified version can serve as a lead for development of bifunctional /dual release systems of antihypertensive drugs.

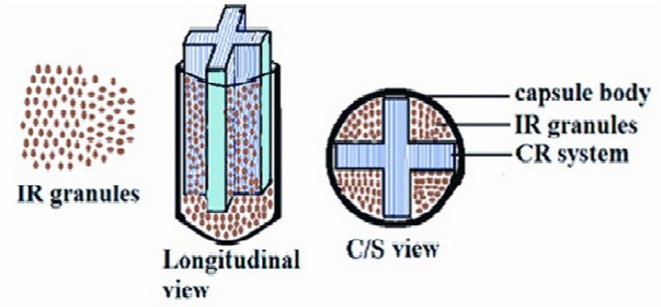

FIGURE 3 - Bifunctional capsular dosage form consisting of CR gastroretentive system of clarithromycin and IR granules of ranitidine HCl.

CONCLUSION

Adequate control of the gastric residence time combined with controlled drug release patterns can significantly improve the bioavailability of the drug. To achieve this goal, floating, bioadhesive, expanding/ swelling and raft forming systems have depicted promising potential. However, various other systems need to be explored for achieving maximum therapeutic efficacy. While many systems have proven their efficacy, *in vitro* and *in vivo*, clinical intricacies need to be resolved before the novel GRDDS can be put into commercial use.

DECLARATION OF INTEREST

None

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