GASTRORETENTIVE EFFERVESCENT FLOATING TABLETS (GREFT) OF DRUGS ACTING ON CARDIOVASCULAR DISEASES

SUTAPA BISWAS MAJEE*, TRISHA MISHRA, SOUVIK GUPTI

Division of Pharmacaceutics, Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata-Group of Institutions, 60 B 1 Saha Road, Kolkata-700053, India

*Corresponding author: Sutapa Biswas Majee; *Email: sutapabiswas2001@yahoo.co.in

ABSTRACT

Incidences of Cardio Vascular Diseases (CVDs) are increasing in an alarming proportion in India. Conventional oral dosage forms cannot be retained in the stomach for long owing to gastric emptying. Moreover, drugs which are commonly employed in management of chronic CVDs either have reduced solubility at alkaline pH, undergo colonic degradation, exhibit site-specific absorption or varying bioavailability with combination therapy. Gastro-retentive drug delivery systems (GRDDS) are designed to overcome these challenges. Since 2006, Food and Drug Administration has approved only few GRDDS for treating CVDs. The aim of the present review is to summarize the outcomes of research carried on GRDDS with drugs for CVDs since last 15 y and comprehensive analysis of limitations of such studies due to which no product has been approved or commercialized in over last 18 y. Literature survey includes single unit, multi-particulate, monolayer and bilayer dosage forms with or without effervescence-inducing agents and made of natural and/or synthetic polymers like hydroxypropylmethyl cellulose, natural gums etc. Efforts have been made to compile in vitro buoyancy data such as floating lag time, total floating time, swelling index, release profile and release kinetics. Among various studies reported on monolayer and bilayer Gastro-Retentive Effervescent Floating Tablets, only 3 involved bioavailability studies in human volunteers. Toxicity studies in animals or stability studies are totally lacking. Observation with floating-type multi-particulate GRDDS is more disappointing. Lack of safety, efficacy data, stability data, in vivo imaging studies and in vitro-in vivo correlation data might be actually responsible for lack of commercialization of any GRDDS for drugs acting on CVDs in 21st century.

Keywords: Bilayer tablet, Buoyancy, Cardiovascular diseases (CVDs), Effervescent floating, Floating lag time, Gastro retentive drug delivery systems (GRDDS), Gums, Hydroxypropylmethyl cellulose, Multi-particulate, etc

INTRODUCTION

In 2023, more than 600 million people worldwide are reported to be affected with Cardio Vascular Diseases (CVDs). It is estimated that the number of adults in the United States with symptoms of CVDs who are 25 years of age or older will increase by almost 19% from m 2012 till 2030. In 2021, 10.8 million deaths were caused by hypertension. Up to 76 million mortalities can be avoided globally between 2023 and 2050 if suitable measures and precautions are adopted. CVDs have emerged as India’s major cause of death since the turn of the century, leaving behind malnutrition-related diseases affecting mother and neonates, tropical infectious and communicable diseases. It is alarming that Indian population is at a higher risk of CVDs compared to the rest of the world, and they are affected by CVDs at least 10 years earlier and during peak of their career than persons of European origin [1-4].

Conventional orally administered dosage forms fall to remain in the gastrointestinal tract (GIT) for a sufficient period of time to exert prolonged therapeutic action mainly due to their passage out of the stomach through pyloric sphincter by intrinsic peristaltic movement within maximum 4 h (fed stomach). Gastric retention period can be greatly enhanced by designing appropriate gastro-retentive devices, with an aim of maximizing drug’s bioavailability and minimizing wastage of active pharmaceutical ingredient. Gastro-retentive drug delivery systems (GRDDS) are very suitable for drugs that are degraded in the alkaline pH of the intestines or rendered insoluble or are precipitated at intestinal pH or for drugs having their absorption window in the stomach or meant specifically to treat pathological condition of the stomach itself [5-8].

Advantages of GRDDS as drug delivery systems

1. Significant improvement in the bioavailability with drugs which are absorbed from upper GIT.
2. Reduced frequency of administration with drugs having short elimination half-life, thereby ensuring patient compliance.
3. Minimizing fluctuations in plasma concentration level and achieving ideal steady state for better management of chronic conditions.
4. Reduced risk of toxicities and adverse effects [9-13].

Some of the drugs which are commonly employed in management of chronic CVDs suffer from issues like reduced solubility at alkaline pH (metoprolol, propranolol, verapamil, diltiazem), degradation in colonic environment (captopril), exhibiting site-specific absorption from upper GIT (fresenide) and varying rate and extent of bioavailability with combination therapy.

Till date, only few GRDDS are commercially available with drugs for different arms of CVDs (table 1).

Table 1: Marketed GRDDS of drugs acting on CVDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Manufacturer</th>
<th>FDA approval in</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Hypertension, heart failure and heart attack</td>
<td>Coreg CR®</td>
<td>2006</td>
<td>[14]</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Hypertension</td>
<td>Przaress XL®</td>
<td>1992</td>
<td>[14]</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Angina, unstable angina, hypertension, paroxysmal supraventricular tachycardia (PSVT), prophylaxis, and supraventricular tachycardia (SVT).</td>
<td>Covera HS®</td>
<td>1998</td>
<td>[14]</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Arterial hypertension</td>
<td>Sular®</td>
<td>1995</td>
<td>[14]</td>
</tr>
</tbody>
</table>
The goal of the present review is to focus on the state of research going on currently with GRDDS for drugs acting on CVDs since last 15 years and comprehensive analysis of limitations of such studies in general, which might have contributed to non-availability of any FDA-approved GRDDS for commercial purpose after 2006 with drugs for CVDs, which constitute a considerable risk factor for people globally and which seems to be a very promising market.

The articles for the current review were searched from specialized databases (Range of years: 2009-2024) such as those of Elsevier, Pubmed, and Cambridge using the keywords “Gastro-Retentive Drug Delivery Systems”, “floating type of Gastro-Retentive Drug Delivery Systems”, “natural gums used in development of Gastro-Retentive Drug Delivery Systems”, “Cardio Vascular Diseases”, “floating microspheres” and “gastro-retentive bilayer tablets”. Other selection include articles from Springer, information from Internet and Online published articles from Medscape.

General classification of GRDDS

Prior to delving into studies carried out on the fabrication and characterization of GRDDS developed with anti-hypertensives, anti-hyperlipidemias, diuretics, calcium channel blockers etc., spanning over a period of 15 years, is essential to understand the basis of classification of GRDDS for the current purpose. Here, the conventional basis of classification has not been followed. The aim is to provide a systematic understanding of the various strategies used for design of these GRDDS, such as development of the single unit, bilayer and multi-particulate effervescent or non-effervescent floating type of GRDDS with plethora of natural and synthetic polymers [15-25].

Classification on basis of floating and/or swelling behavior

Effervescent GRDDS

With the help of the effervescence arising out of the reaction between citric/tartaric acid and carbonate/bicarbonate salts, this floating or effervescent delivery system releases CO₂ lowering its density and facilitating it to remain afloat over surface of gastric fluid. Thus, gas-generating agents are essential components of effervescent floating systems. Apart from these effervescence-inducing agents, these dosage forms consist of a polymer matrix, which enables drug release slowly during the period over which it is retained and remains buoyant in the stomach fluid [26-28].

Swellable and expanding GRDDS

Superporous hydrogels and swellable, hydrophilic tablets, which are often referred to as swelling-controlled systems, have the ability to imbibe stomach juices, become porous, swell many times its own volume and can attain buoyancy when the density becomes lower than the stomach fluid. The swollen dosage form thus fails to cross the pyloric sphincter and enter the small intestine and is automatically retained in the stomach. During the process of swelling facilitated by influx of body fluid, drug diffusion occurs in a controlled manner and with time, the dosage form may slowly undergo disintegration and/or dissolution. These systems are sometimes referred to as “plug-type systems” because they have a tendency to form a plug at or block the pyloric sphincter [29-31].

Table 2: GREFT and multi-particulate GRDDS fabricated with combination of natural and synthetic polymers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymers</th>
<th>Type of GRDDS</th>
<th>Floating lag time</th>
<th>Maximum % of drug release</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril maleate</td>
<td>Sodium alginate, HPMC K100M</td>
<td>Monolayer GREFT</td>
<td>58±0.48s</td>
<td>More than 90% in 12h</td>
<td>[44]</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Sodium alginate, HPMC K100M</td>
<td>Monolayer GREFT</td>
<td>01 min 05±0.12</td>
<td>98.23% in 12h</td>
<td>[45]</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Xanthan gum, HPM K4M</td>
<td>Monolayer GREFT</td>
<td>1.52s</td>
<td>99.98% in 12h</td>
<td>[46]</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Karaya gum, HPMC K15M</td>
<td>Monolayer GREFT</td>
<td>20s</td>
<td>87.66 % in 8h</td>
<td>[47]</td>
</tr>
<tr>
<td>Cilnidipine</td>
<td>Gellan gum, HPMC K4M</td>
<td>Monolayer GREFT</td>
<td>9.91s</td>
<td>98% in 12h</td>
<td>[48]</td>
</tr>
<tr>
<td>Propranolol</td>
<td>HPMC K4M, HPM C1.5LV, hydroxypropyl cellulose (HPC), xanthan gum, sodium alginate</td>
<td>Monolayer GREFT</td>
<td>&lt;1 min</td>
<td>92% in 18h</td>
<td>[49]</td>
</tr>
<tr>
<td>Verapamil hydrochloride</td>
<td>Guar gum, xanthan gum and HPM C100M, sodium alginate</td>
<td>Floating type multi particulate</td>
<td>89±1.35%</td>
<td>94% at 12h</td>
<td>[50]</td>
</tr>
</tbody>
</table>

*Indicates in vitro buoyancy (%)
Table 3: Gastro-retentive effervescent floating tablet (GREFT) and multi-particulate GRDDS fabricated with synthetic polymers only

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymers</th>
<th>Type of GRDDS</th>
<th>Floating lag time</th>
<th>Maximum % of drug release</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan Cilexetil</td>
<td>HPMC K100M, ethylcellulose, Gelucire</td>
<td>Monolayer GREFT</td>
<td>25.4±0.22 s</td>
<td>99.5±0.5±% in 12 h</td>
<td>[55]</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>HPMC K15M, HPMC K4M, Carbopol 934P, PVP K30</td>
<td>Monolayer GREFT</td>
<td>25.4±0.22 to 41.7±0.51 s</td>
<td>105.6±0.74% in 7 h</td>
<td>[56]</td>
</tr>
<tr>
<td>Azelnidipine</td>
<td>Polyoxyethylene oxide WSR 303</td>
<td>Monolayer GREFT</td>
<td>37±-178 s</td>
<td>95.1±1.43% in 12 h</td>
<td>[57]</td>
</tr>
<tr>
<td>Ginkgolide</td>
<td>HPMC K4M, HPMC E5L, PVP K30</td>
<td>Monolayer GREFT</td>
<td>20 s</td>
<td>80–90% in 8 h</td>
<td>[58]</td>
</tr>
<tr>
<td>Losartan</td>
<td>HPMC E50, Carbopol 934P</td>
<td>Monolayer GREFT</td>
<td>55.6s</td>
<td>96.3±% in 12 h</td>
<td>[59]</td>
</tr>
<tr>
<td>Nateglinide- Ezetimibe</td>
<td>HPMC K4M, NaCMC</td>
<td>Bilayer GREFT</td>
<td>1 min 50s–4 min 30s</td>
<td>30.9±0.5%</td>
<td>[60]</td>
</tr>
<tr>
<td>Amlodipine besylate immediate release (IR) layer and sustained release (SR) layer of Atenovas calcium hydrochloride</td>
<td>HPMC-K3, Eudragit RSPO, Carbopol 934P</td>
<td>Bilayer GREFT</td>
<td>-</td>
<td>Atenovas for 8h (96.7±%±71) and IR of Amlodipine within 25 min (98.07±%±62)</td>
<td>[61]</td>
</tr>
<tr>
<td>Cilnidipine</td>
<td>HPMC K4M, K15M, E50L</td>
<td>Bilayer GREFT</td>
<td>57s</td>
<td>90% in 12 h</td>
<td>[62]</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Ethylcellulose, polylvinyl alcohol</td>
<td>Floating microsphere</td>
<td>-</td>
<td>87.6±1% in 13 h</td>
<td>[63]</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Cellulose acetate, Eudragit RS100</td>
<td>Floating microsphere</td>
<td>-</td>
<td>77±6.2±12 to 97.5±0.14 % at 12 h</td>
<td>[64]</td>
</tr>
</tbody>
</table>

*indicates in vitro buoyancy (%) and indicates *data not available*

Literature review on studies with different types of GRDDS of drugs acting in CVDs in last 15 y

Effervescent GRDDS

Single unit gastro-retentive effervescent floating tablet (GREFT)

Monolayer GREFT with natural polymers alone or in combination with synthetic polymers

Different studies have been reported on development of GREFT by combining natural polymers like sodium alginate and xanthan gum with synthetic polymers such as hydroxypropyl methylcellulose (HPMC K4M and HPMC K100M) and characterization of in vitro buoyancy parameters like floating lag time, total floating time and in vitro drug release profile. Sodium bicarbonate has been used as an effervescence-inducing agent in the reported studies. Drugs employed include Enalapril maleate, Nifedipine, Perindopril. Floating lag time was found to be 58±0.4 s, 0.1 min: 05±0±.1, 1.52 s and total floating time was found to be >1 h in all cases [47,48]. Extended-release of more than 90% in 12 h could be observed where zero-order kinetics has been followed [44-45] and Higuchi model was followed by the release data in the study reported by Martha et al. [46]. The optimum formulation consisted of sodium alginate and HPMC K100M in the ratio of 1:3.5 and 1:1.5 [44, 45] and drug (Perindopril): xanthan gum (40%) at a ratio of 1: 8 [46].

Dharani et al. employed natural gums like tamarind gum and gum karaya with HPMC K15M for Atorvastatin calcium-loaded GREFT. Optimum formulation with drug and gum karaya (1:7) demonstrated a floating lag time of 20s, total floating duration being more than 12h, swelling index of 76.4±7 and released 87.66 % drug in a very controlled manner over 8 h. Drug release from the formulation was found to follow zero-order kinetics [47].

Gellan gum and HPMC K4M were used in the development of Ciñindipine GREFT. Floating lag time and total floating duration were found to be 9.91s and 12h. Drug release of 98% occurred in 12h. Drug release kinetics followed an anomalous diffusion mechanism, indicating contribution of both diffusion and erosion phenomena. Comparative pharmacokinetic profiling in 10 human subjects (receiving treatment, hypertension patients, and healthy volunteers) revealed that relative bioavailability of Ciñindipine GR tablets was enhanced compared to reference tablets. A stomach radiograph of healthy human volunteers made it clear that the optimized radio-
opaque GREFT remained buoyant in the human stomach for almost 6 h. Addition of hydrophilic gellan gum and HPMC K4M not only improved the aqueous solubility and dissolution profile of Ciñindipine but also produced swelling of tablets. Enhanced in vivo bioavailability was attributed to increased gastro-retention [48].

HPMC K4M, HPMC E 15 IV, hydroxpropyl cellulose (HPC; Klucel HF), xanthan gum, and sodium alginate (Keltose) were evaluated as polymers for designing swellable GREFT of Propranolol. Optimum tablet containing HPMC K4 M (185 mg) and HPC (5 mg) exhibited a floating lag time of 1 min, total floating duration of 24 h and in vitro drug release is 92% in 18h [49].

Thus, above survey indicates that although attempts were made to design GREFT with the combination of natural and synthetic polymers, the optimum formulations in several cases were found to be composed of only natural polymers or only synthetic polymers. Active pharmaceutical ingredient in combination with an appropriate ratio of individual polymer could produce desirable in vitro characteristics of GREFT.

Monolayer GREFT with synthetic polymer only

Vantinita et al. investigated the effect of HPMC K100M, ethylcellulose, Gelucire on in vitro buoyancy and in vitro drug release of Candesartan cilexetil from GREFT. The optimum formulation with Gelucire 54/02(8 mg), Gelucire 43/01(24 mg), HPMC K100M (50 mg), drug (16 mg) and ethyl cellulose (15 mg) released 90±0.09% drug for 12 h and followed Higuchi kinetics [55].

Pandiy et al. investigated the effect of different polymers like HPMC K15M, HPMC K4M, Carbopol 934P and PVP K30 on floating capacity, swelling index, in vitro dissolution of Hydrochlorothiazide from GREFT. Floating lag time and total floating time are reported to be 25±4±0.22 to 41±7±51.5 s and 12 h respectively. Swelling index was 105±0.7±4%. Optimum formulation containing HPMC K 4 M (140 mg), Carbopol 934P (40 mg) and PVP K30 (20 mg) showed in vitro release of 99.5±0.5% in 7 h and followed non-Fickian (anomalous) diffusion [56].

Gaikwad et al. studied the effect of different concentrations of Polyoxyethylene oxide (PEO) WSR 303 as hydrophilic polymer and potassium bicarbonate as gas generating agent on floating lag time, % drug release at 1 h and time required to release 90% of the drug (t90) of Azelnidipine GREFT. Floating lag time varied between 37-
178s and total floating duration was 10-12h. Optimum formulation containing 20 mg PEO WSR released 95.1±1.43% drug for 12 h and followed Korsemeyer-Peppas drug release kinetics [57].

Wang et al. investigated the effect of HPMC K4M, HPMC E50L, PVP K30 on in vitro drug release, floating lag time, total floating duration of Ginkgoide GREFT. Optimum formulation showed in vitro drug release of about 80-90%, in 8h. floating lag time was less than 20s and total floating time was 12h. Release behavior fitted zero order kinetics [58].

Sanjana et al. observed the effect of gas-forming agents such as sodium bicarbonate and citric acid and ratio of gel-forming agents such as HPMC E50 and Carbopol 934P on buoyancy, buoyancy lag time, swelling index and in vitro drug release of Rosuvastatin from GREFT. Optimum formulation with HPMC E50 and Carbopol (2:1 ratio) showed 96.31% drug release at the end of 12 h and exhibited an optimum floating lag time of 55.6 s. Total floating duration is 12h and swelling index was reported as 120%. All formulations best fitted the Higuchi model and non-Fickian drug diffusion was postulated as the mechanism of drug release [59].

Chen et al. observed the effect of swellable and floatable GRDDS tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC) on swelling characteristics and floating capacity of losartan GREFT. The optimum formulation has a floating lag time of 1 min 50s – 4 min 30s and total floating duration was 24 h in simulated gastric fluid. In acidic medium, the release mechanism followed Korsmeyer-Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. Bioavailability from optimum formulation was approximately 164.4±0.3%. The extent of active metabolite formation following administration of GREFT was found to be lower than that from immediate release product in human subjects [60].

Comparison of floating lag time values and maximum % of drug release, release kinetics and mechanism of drug release in 12 h from single unit monolayer GREFT with synthetic polymers only and combination of natural and synthetic polymers revealed synthetic polymers imparted earlier floating or buoyancy to the tablets and released more than 90% drug in 12 h. In most of the instances, the tablets can be assumed to form matrix as they followed either Higuchi kinetics or Korsmeyer-Peppas model. Non-Fickian drug diffusion was reported in most of the studies. However, with GREFT developed with combination of natural and synthetic polymers, comparatively delayed floating was induced and more than 95% drug release occurred in 12 h. These tablets may be predicted to achieve ideal constant plasma drug level as they followed mostly zero-order kinetics with higher % of drug release. In this case also, non-Fickian drug transport was observed. Thus, selection of polymers and choice of drug might influence floating lag time and drug release kinetics. Synthetic polymers primarily formed matrix. Comparative analysis of the effect of polymers on in vitro performance of GREFT can provide valuable inputs to scientists who are in pursuit of GRDDS with drugs for CVDs.

Bilayer GREFT with synthetic polymers only

Parveen et al. reported the effect of Polyox WSR 303, Carbopol 934P, HPMC K4M, Na CMC on in vitro buoyancy, release of Nateglinide from slow-release layer and Ezetimibe from fast-release layer of floating bilayer tablets. The optimum formulation of Nateglinide-Ezetimibe floating formulations showed satisfactory results. Floating lag time was found to be 15.3±2.5s and total floating duration was 12h. Swelling index was reported as 110.4±9.2% in 6 h. Immediate layer released 99.7±1.29% of Ezetimibein 30 min and cumulative % release of Nateglinide is 101.0±3.54% in 12h. Upon obtaining written consent from three fit male volunteers with age between 22 and 26 y, body weight ranging from 64 to 75 kg and height varying from 165 to 173 cm to participate in a study involving in vivo imaging, assessment of residence time in vivo and pharmacoKinetic parameters of bilayer GREFT was performed. To determine the gastrentestinal residence time of GREFT pills, this study employed X-ray with BaSO₄, which was employed to make the tablet opaque to X-ray. mean Residence Time of optimum formulation and that of IR, AUC₁₀⁻₅₅, τ₁/₂ and Cₘ₉₉ were found to differ significantly based on in vivo performance. When compared to reference, immediate release tablets, Nateglinide’s relative bioavailability increased by 1.7 times which suggests that floating dosage forms are preferable for drugs absorbed from the upper GIT [61].

Porwal et al. observed the effect of HPMC K3C, Eudragit RSPO and Carbopol 934P on floating duration, swelling index, and in vitro release from immediate release layer of Amlodipine besylate and sustained release layer of Atorvastatin calcium from optimized capsulated unfolding type gastro-retentive bilayer film. The optimum formulation provided release of Atorvastatin for 8h (96.76±0.71%) and 98.07%±0.62% Amlodipine besylate within 25 min. The swelling index and floating duration for the optimized formulation were 140.48±0.57% and 8.53±0.10h, respectively [62].

Charyulu et al. observed the effect of low-density release retardant polymers like HPMC K4M, K15M, E50L on floating lag time, total floating time, swelling index and in vitro drug release profiles of bilayer floating tablet of Diltiazem hydrochloride. The immediate release layer consisted of gas generating system of sodium bicarbonate and citric acid. The tablets containing HPMC K15M (150 mg) and drug (40 mg) exhibited high degree of swelling with swelling index of 200%. All the formulations remained buoyant up to 10 h. Optimum formulation showed more than 90% drug release in 10h. Floating lag time was 57s and total floating duration was 10h. Data from the optimum formulation best fitted Higuchi model. It was observed that loading dose from all the tablets was released within 30 min from IR layer containing gas-generating agents [63].

Therefore, it was observed that out of 12 studies reported so far on monolayer GREFT and 3 studies on bilayer single unit GREFT with synthetic polymers only and combination of natural and synthetic polymers, only 3 involved bioavailability studies in human volunteers. Moreover, no studies reported stability studies conducted as per ICH guidelines or toxicity studies in animals. Paucity of safety and efficacy data on animals and humans, stability data, assurance of gastric retention in vivo and no studies on in vitro-in vivo correlation might be actually responsible for lack of commercialization of any GRDDS after 2006.

Floating type multi-particulate GRDDS

Multi-particulate GRDDS with combination of natural gums and synthetic polymers

Saravananukumar et al. observed the effect of different polymers like guar gum, xanthan gum and HPMC K100M in the ratios of 1:1, 1:2, 1:3, using sodium alginate as a cross-linking agent on % in vitro buoyancy, % swelling index, and in vitro dissolution profiles of Verapamil hydrochloride from floating microspheres prepared by ionotropic gelation method. The optimum formulation with xanthan gum and drug in the ratio 1:1 showed a maximum release of 94% at 12 h. In vitro buoyancy was reported as 89±1.35% and total floating duration was 12 h [50].

Multi-particulate GRDDS with synthetic polymer only

Jenita et al. investigated the effect of ethyl cellulose, polyvinyl alcohol on in vitro drug release, buoyancy of Fenofibrate from floating microspheres prepared by Taguchi method. The optimum formulation (drug:ethyl cellulose as 1:2) showed cumulative % release of 87.61 in 13 h, 56.61% buoyancy and total floating duration of 24 h. The in vitro release data fitted to Korsmeyer-Peppas model [64].

Cheng et al. reported the effect of cellulose acetate and Eudragit RS100 on floating micro-particulates of Diltiazem prepared by emulsion solvent evaporation technique with respect to in vitro floating and drug release profiles. The formulation with drug and cellulose acetate (1:1) was found to be the optimum with buoyancy of 60.9-84.4%. All the formulations showed good in vitro controlled drug release in the range of 77.62±2.12 to 97.50±1.04 % in 12 h. Drug release was diffusion-controlled and followed zero-order kinetics [65].

None of the studies reported on floating type multi-particulate GRDDS revealed any in vivo studies in animals or humans and stability studies.
Non-effervescent floating type GRDDS

Garse et al. investigated the effect of HPMC K4M CR and HPMC K15M CR along with Poloxamer M127 on in vitro drug release, floating time, floating lag time, swelling of labetalol hydrochloride from non-effervescent sustained release gastro-retentive floating tablet. Optimized formulation with HPMC K 4M CR (180 mg) and Poloxamer (18 mg) showed in vitro drug release of 93.23% in 12 h. Floating lag time was 3% and total floating duration was 17 h. Floating behavior of tablet remained unaffected by the change in osmolarity and pH of the gastric fluid [66].

Future scope

Following up published research on an effervescent and non-effervescent gastro-retentive floating single unit or multi-particulate dosage forms, it can be concluded that few studies exist on bilayer type or multi-particulate type GRDDS with drugs for CVDs either with synthetic polymers or with combination of synthetic and natural polymers although benefits of such delivery systems in treatment of CVDs is galore. Future research should be directed not only to development of these highly promising systems, especially for Cardio Vascular Diseases, but also designing suitable and affordable protocols for assessing their in vivo performance and toxicity in animal models and human volunteers. Stability studies should be routinely adopted in the formulation development process.

CONCLUSION

As a concluding remark, it can be mentioned that scarcity of in vitro stability data, in vivo safety and efficacy data actually contribute to the lack of any new approved and commercialized gastro-retentive effervescent or non-effervescent floating drug delivery system with drugs that are used in management of Cardio Vascular Diseases. Successful translation of investigational dosage forms from bench-side to bedside is possible only when accurate, reproducible and reliable in vivo and stability data are available. Further research needs to be done in the domain of bilayer and multi-particulate gastro-retentive floating dosage forms so that safe and effective quality products reach Indian population at an affordable price to manage this group of highly prevalent non-communicable diseases accounting for considerable proportion of disability and fatality.

ABBREVIATIONS

Cardio Vascular Diseases (CVDs), Gastro-Retentive Drug Delivery Systems (GRDDS), Gastro-Retentive Effervescent Floating Tablets (GREFT), Hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC).

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AUTHORS CONTRIBUTIONS

SBM conceptualized the content of the review article and contributed to final editing of the manuscript; TM and SG collected information and prepared the manuscript draft.

CONFICTS OF INTERESTS

The authors declare no conflicts of interest.

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rosuvastatin tablets by floating drug delivery system


