Prospective and New Findings of Hydroxypropyl Methylcellulose (HPMC) as a Potential Carrier for Gastrorententive Drug Delivery Systems

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Abstract: Gastroretentive drug delivery systems are able to prolong the overall gastric residence time and can improve the oral bioavailability of the medicaments that show site specific absorption from the stomach or upper part of the small intestine. Various approaches are currently utilized to retain the dosage form in the stomach including polymeric bioadhesive systems, floating drug delivery systems, swelling and expanding systems, high density systems, biodegradable hydrogel systems and other delayed gastric emptying devices. Among the numerous polymers that are being used for gastroretentive drug delivery systems, hydroxylpropyl methyl cellulose (HPMC), possessing hydrophilic and gel forming properties, is extremely advantageous. It is also nontoxic and biocompatible. In this article, the important properties of HPMC and various techniques used for preparing gastroretentive dosage forms based on HPMC are reviewed. This review also includes the investigation of various classes of drugs used for preparing HPMC based gastroretentive drug delivery system.

Keywords: Hydroxypropylmethylcellulose, Floating gastroretentive tablets, Controlled release, Bioadhesion, Capsules, Pellets.

1. INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of action in the body and to achieve a desire onset of action as well as duration. The most convenient and commonly employed route of drug delivery is peroral. In recent years, sustained or controlled oral delivery systems have drawn more and more attention for their theoretical advantage in reduction of dosing frequency, reduced fluctuations in circulating drug levels, increased patient compliance, and more uniform pharmacological response [1]. However, this approach has not been suitable for a variety of drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract, acting locally in the stomach, degradable in the intestinal environment, and having low solubility at intestinal pH [2]. The absorption capacities of such drugs can be improved by increasing the residence time of the dosage form in the stomach or somewhere in the upper small intestine [3-10].

Gastroretentive systems can remain in the gastric region for several hours and therefore, significantly prolong the gastric residence time of drugs resulting retardation in drug release. Various approaches used to increase the gastric residence time include floating systems [11-13], swelling devices [14, 15], mucoadhesive system [16, 17], modified shape systems [18, 19], high density systems [20], magnetic systems [21], superporous and biodegradable hydrogels [22, 23]. Similarly, various dosage forms like tablets, capsules, microparticles, pellets, granules have been evaluated for gastroretentive systems. Single unit system such as tablet or capsule shows a higher inter and intra-subject variability [20] and is generally unreliable and non-reproducible in prolonging the gastric retention time. However, multiparticulate systems like microparticles and pellets may be more suitable because they show reduced inter subject variability in absorption and also often a better dispersion through the gastrointestinal tract with reduced localized mucosal damage [24]. Both natural and synthetic polymers are generally employed in gastroretentive drug delivery system, targeting the delivery of drug to the stomach. Polymers with pronounced swelling properties have been frequently employed in the formulation of different gastroretentive systems [25]. HPMC is a hydrophilic polymer used for the preparation of oral controlled drug delivery system. It is frequently used in gastroretentive systems due to its high swellability as well as release-retarding characteristic [26-28].

Many review articles have been published on gastroretentive drug delivery system. However, no comprehensive review has yet been published on HPMC based gastroretentive drug delivery system. This article after extensive survey of literatures presents a report on the application and performance of HPMC as a carrier for gastroretentive delivery systems of drugs of different category. This review also provides information on the various dosage forms like microparticles, pellets, granules, tablets and capsules that make use of HPMC as a drug carrier.

2. PHYSICO-CHEMICAL PROPERTIES OF HPMC

Hydroxypropyl methylcellulose is a semi synthetic, inert, viscoelastic polymer. It is a modified form of methyl cellulose with a small amount of propylene glycol ether groups attached to the anhydroglucose of the cellulose Fig. (**1**). The

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dry product contains 19% to 30% of methoxy groups and 3% to 12% of hydroxyl propoxy groups.

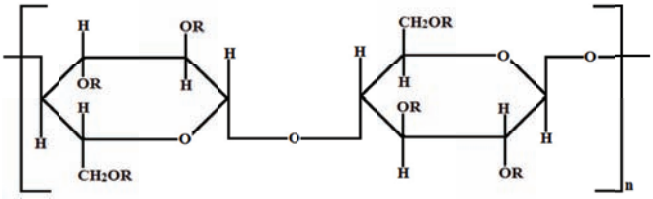

Fig. (1). Chemical structure of HPMC. R= –H, or –CH_3, or –$CH_2CH(CH_3)OH$.

The physicochemical characteristics of HPMC are strongly affected by the methoxy group content, hydroxypropoxy group content, and molecular weight. USP specified four different types of HPMC according to their degree of methoxy and hydroxypropoxy substitution. These are HPMC 1828, HPMC 2208, HPMC 2906 and HPMC 2910. The first two numbers indicate the percentage of methoxy groups, the last two numbers the percentage of hydroxypropoxy groups, determined after drying at 105°C for 2 hours. HPMC in an aqueous solution exhibits a thermal gelation property. When the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule. The mechanisms by which HPMC retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluids [29]. The drug is released from the matrix mainly by diffusion through water filled pores.

3. HPMC BASED GASTRORETENTIVE DOSAGE FORMS

Various gel forming polymers such as HPMC, carbopol (CP), xanthan gum, alginate, guar gum, and pectin etc. were used to retain the dosage form in the stomach and to increase gastric residence time, resulting in prolonged drug delivery in stomach. Among the various polymers, HPMC was widely used in gastroretentive dosage forms due to its swelling as well as release retarding characteristics. Various HPMC based formulation like tablets, capsules, granules, pellets, and microparticles etc. was prepared and evaluated as gastroretentive drug delivery system.

3.1. HPMC based Tablets for Gestroretentive Drug Delivery

Chavanpatil *et al.* [30] developed ofloxacin tablet composed of release retarding polymers like HPMC K100M and psyllium husk for gastroretentive drug delivery system. They observed that the burst drug release was decreased as the concentration of HPMC K100M was increased. They postulated that the increased polymer concentration could have increased the diffusion path length for the drug which could have retarded the drug release from the formulations. Bioadhesive properties of developed formulation showed significant bioadhesion in combination as compared to HPMC K100M and psyllium husk alone. Oral floating matrix tablets of diltiazem hydrochloride were prepared by direct compression technique to prolong gastric residence time and increase its bioavailability [31]. It has been observed that the concentration of methocel K100MCR or Compritol 888ATO decreases the rate of release of diltiazem hydrochloride from matrix tablet. The optimized formulation containing highest concentration of Methocel K100M C R and Compritol 888ATO gives the best result in terms of the required lag time (4.4 minutes) and floating duration of 24 hours, and drug release was in accordance with the USP dissolution criteria. Floating matrix tablets were prepared using HPMC and/ or sodium alginate as release retarding polymer(s) by effervescent technique for controlled release of ciprofloxacin hydrochloride [32]. It was observed that the drug release retarded by increasing the concentration of HPMC K15M since higher viscosity of polymer would promote the formation of highly viscous gels upon contact with aqueous fluids. Abdominal X-ray imaging of tablet loaded with barium sulfate in healthy volunteers indicated that a mean gastric retention period of 5.5 hours. In another study, intragastric floating tablets containing HPMC, CP, and xanthan gum as gel forming polymers were prepared for controlled release of verapamil HCl [33]. The *in vitro* dissolution studies indicated that the higher initial drug dissolution in tablets containing HPMC K4M and HPMC K15M as compared to tablets containing CP 934P and CP 940P. This was due to rapid hydration of HPMC than CP in the presence of 0.1 N HCl. The tablet composed of 3:2 ratio of HPMC K4M to xanthan gum, showed satisfactory result with 95.39% drug release in 24 hours and tablet remained buoyant for greater than 24 hours.

Jagdale *et al.* [34] studied the effect of various polymers such as HPMC K4M, HPMC E15LV, hydroxypropyl cellulose (HPC), CP, and xanthan gum on the floating abilities of tablet as well as the release of drug from the tablet. Tablet formulations containing HPMC K4M showed the best floating abilities among all the formulations and also gave the best *in vitro* release of 92% drug in 18 hours. *In vitro* study by X-ray technique indicated that tablet was remained in the stomach for 4 hours. However, tablets containing HPC, sodium alginate, and HPMC E15LV failed to produce matrix of required strength. A new reservoir type floating multilayer coated tablet based on gas formation were prepared by Sungthongjeen *et al.* [35]. The drug loaded core tablets were prepared and consecutively coated with a protective layer of HPMC, a gas forming layer of sodium bicarbonate using HPMC as binder and a gas-entrapped membrane Fig. (**2**).

It was observed that the polymeric film with Eudragit® RL30D compared to Eudragit® RS30D and NE30D had high capability to entrap generated CO_2 and subsequent good floating properties. It was also observed that the floating properties and the drug release from the tablets were dependent on the core preparation method, the amount of a gas forming agent (ratio of $NaHCo_3$ to HPMC) and the level of gas- entrapped membrane. Oliveire *et al.* [36] developed assembled modules technology in which two differently cylindrical base curved matrix/modules, identified as female and male, were assembled to form a void configuration system for site specific prolonged delivery of norfloxacin. It has been observed that the assembly exhibited *in vitro* floatation

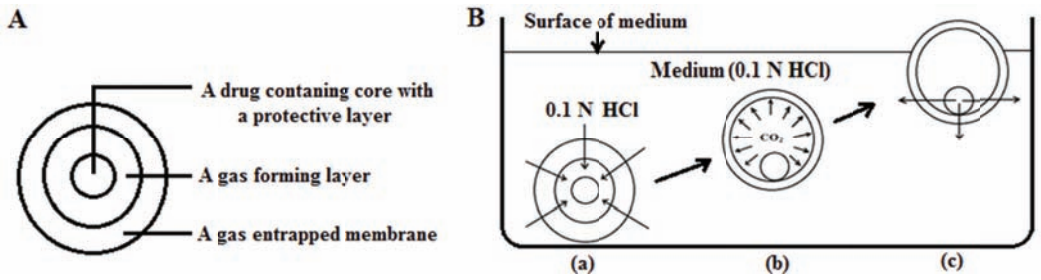

Fig. (2). (**A**) A floating multilayer coated tablet. (**B**) Stages of floating mechanism of a multilayer coated tablet. (**a**) penetration of medium. (**b**) generation of gas (CO_2) and floating. (**c**) release of drug [Adopted from reference 35].

up to 240 minutes. However, the individual male and female modules never floated.

Krogel *et al.* [27] developed and evaluated a multifunctional drug delivery system based on HPMC matrix tablet placed within an impermeable polymeric cylinder (open at both ends). They investigated three different configurations of multifunctional drug delivery system by placing one or two HPMC-tablets within a hollow impermeable poly (propylene) cylinder Fig. (**3**).

It has been observed that the configuration 1 systems released drug slower than the free tablets because of the restricted surface area. Moreover, the release of drug from configuration 1 systems containing tablets prepared with the higher viscosity HPMC grades was slower compared to tablets prepared with the low viscosity HPMC grade. The configuration 2 system floated immediately after immersion into the release medium and sunk after complete erosion of at least one tablet. Configuration 3 systems consisted of an impermeable capsule half filled with drug and excipients and closed with a drug free HPMC matrix tablet and the drug was released in a pulsatile fashion.

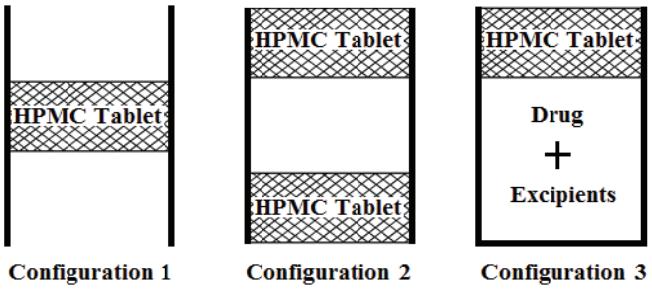

Fig. (3). Different configuration of multifunctional drug delivery system [adopted from reference 27].

3.2. HPMC based Capsules for Gastroretentive Drug Delivery

About 25-30% of a normal dose of supplemental calcium can be absorbed through conventional oral dosage form due to incomplete absorption [37-38]. The active transport process of calcium mainly occurs at duodenum and proximal jejunum, and a non-saturable concentration gradient dependent passive absorption process of calcium occurs predominately in the distal jejunum and ileum [39]. Therefore, if the gastric residence time of calcium containing formulation could be prolonged then the oral bioavailability of calcium might be increased. Li *et al.* [40] investigated the effect of HPMC and CP on the release and floating properties of floating capsule using calcium carbonate as a model drug. It has been observed that HPMC viscosity, the presence of CP and their interaction had significant impact on the release and floating properties of the delivery system. Moreover, polymer with lower viscosity was shown to be beneficial then higher viscosity polymer in improving the floating properties of capsules.

Hydrodynamically balanced system (HBS) containing one or more gel forming hydrophilic polymers. The polymer is mixed with drug and usually administered in a gelatin capsule. The hydrogel shell maintains a relative integrity of shape and a bulk density less then 1gm/cm^3. The drug is slowly released in the stomach by diffusion through the hydrogel barrier and erosion of the surface of the dosage form. Dorozynski *et al.* [41]' prepared and evaluated HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule. Upon contact with gastric fluid, the capsule shell dissolves; the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time until all the drug was released Fig. (**4**). They observed that the densities of the resultant HBS systems in 0.1 M hydrochloric acid ranged from 0.37 g/cm^3 to 0.71 g/cm^3. It was also observed that the HPMC and sodium alginate formulation reached maximum floating force within half an hour after immersion.

In vitro and *in vivo* evaluation of HBS system of metformin as a single unit floating capsule was carried out by Ali *et al.* [42]. *In vitro* release study revealed that the capsules prepared with HPMC K4M and ethyl cellulose gave the best result. *In vivo* studies indicated that the optimized HBS capsule remained buoyant during 5 hours of study in rabbits. Moreover, the pharmacokinetic study showed an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation.

3.3. HPMC based Granules for Gastroretentive Drug Delivery

Single unit system such as tablets or capsules are more subjected to the gastric emptying variability, as generally unreliable and non reproducible residence times in the stomach are observed after their oral administration. However, multiunit dosage forms such as granules may be more suitable because they claim to reduce the inter subject variability in absorption. Jain *et al.* [43] developed and evaluated repa-

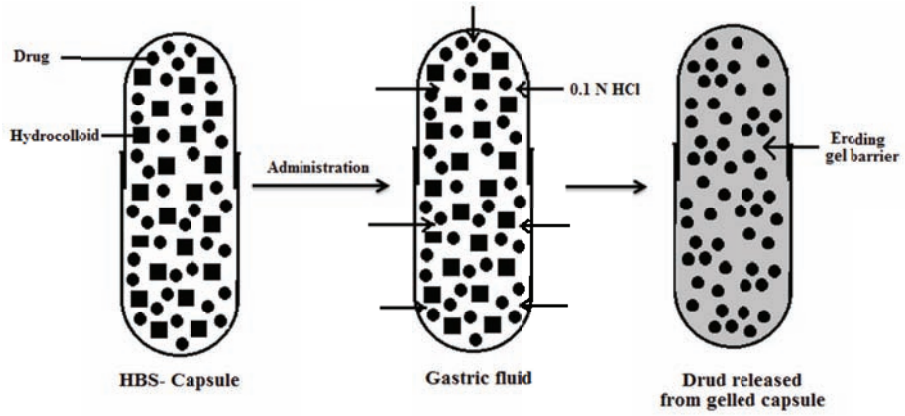

Fig. (4). Working principle of hydrodynamically balanced system (HBS).

glinide floating granular delivery system composed of highly porous carrier material like calcium silicate and matrix forming polymer such as HPMC K4M, ethyl cellulose, and CP 940. They observed that the floating ability of the granules and the release rate of the drug from the granules can be controlled by changing the polymer type as well as the composition ratio of HPMC K4M, ethyl cellulose, and CP 940 in the polymer solution. Gamma scintigraphic images during the *in vivo* study in rabbits clearly indicated that the optimized formulation remained buoyant and uniformly distributed in the stomach for the study periods of 6 hours. Moreover, the relative bioavailability of optimized formulation was found to be increased about 3.8 fold times in comparison to that of its marketed preparation. In another study, Jain *et al.* [44] prepared and evaluated calcium silicate based floating granular delivery system of ranitidine hydrochloride with matrix forming polymers such as HPMC K4M and ethyl cellulose. The *in vivo* study in albino rats showed the higher plasma concentration throughout the study period from the floating granules of ranitidine hydrochloride. Moreover, bioavailability and elimination half life was found to be enhanced in the resultant formulation. Similarly, ranitidine hydrochloride floating lipid granules were prepared by the melt granulation technique using ethyl cellulose, methyl cellulose, and HPMC as release rate modifiers [45]. They observed that the moderate amount of Gelucire 43/01 and ethyl cellulose provides desired release of ranitidine hydrochloride from a floating system. Jain *et al.* [46] prepared and evaluated an intragastric floating granular delivery system of orlistat using calcium silicate as porous carrier and HPMC K4M, ethyl cellulose, and CP 940 as matrix forming polymers. It was observed that the optimized formulation showed favorable *in vitro* floating and release characteristics.

3.4. HPMC based Microparticles for Gastroretentive Drug Delivery

Single unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. However, microparticulate dosage form has all the advantages of a single unit form and also is devoid of the above mentioned disadvantages of single unit formulations. Shishu *et al.* [47] developed multiple unit oral floating dosage form of 5-flurouracil (5-FU) to prolong gastric residence time, target stomach cancer, and increase drug bioavailability. The floating beads were prepared by dispersing 5-FU together with calcium carbonate into a mixture of sodium alginate and HPMC K15M solution and then dipping the dispersion into an acidified solution of calcium chloride. The optimized formulation exhibited the sustained release of drug ($t_{80\%}$ = 15.06 hours) with excellent floating properties. *In vivo* antitumor studies revealed that the floating beads reduced the tumor incidence in mice by 74%, while the conventional tablet dosage form reduced this incidence by only 25%. Similarly, multiple unit floating beads were prepared by dispersing nevirapine together with calcium carbonate in a mixture of sodium alginate and HPMC solution and then dipping the dispersion into an acidified solution of calcium chloride [48]. The beads containing higher amounts of calcium carbonate showed excellent floating ability over a period of 24 hours. However, increasing the coating level of the gas entrapped membrane increased the time to float and slightly retard the drug release.

A novel floating mucoadhesive beads of clarithromycin based on alginate and HPMC was developed for the treatment of *Helicobacter pylori* (*H.pylori*) infection [49]. X-ray radio imaging study in rabbits and *in vitro* mucoadhesion study using rat stomach mucosal membrane indicated that the alginate HPMC beads may be suitable floating mucoadhesive drug delivery system for delivering clarithromycin to treat stomach ulcers. To improve efficacy of narrow absorption window drugs, the floating microspheres of carbidopa and levodopa were prepared by the o/w emulsion solvent diffusion method using polymers HPMC K15M and ethyl cellulose [50]. The prepared microspheres were spherical and smooth surfaced with encapsulation efficiency ranging from 43% to 86%. Moreover, the prepared microspheres exhibited prolonged drug release (approximately 10 hours) and remained buoyant for >12 hours. Srinatha and pandit [51] studied the effect of additives such as gellan, HPMC, starch and chitosan on ciprofloxacin release from multi unit floating beads prepared by simultaneous external and internal gelation method. They observed that the *in vitro* release of ciprofloxacin from the beads in simulated gastric fluid was influenced significantly by the properties and concentration of additives. Among the polymers used HPMC provided an extended release over 7 hours.

Another promising multi unit drug delivery floating system is hollow microspheres (microballoons) that are designed to float on gastric juice with a specific density of <1. Sato *et al.* [52] prepared microballoons by emulsion solvent diffusion method using HPMC and Eudragit® S100 by dissolving in a mixture of dichloromethane and ethanol Fig. (**5**). A solution of polymer and drug in ethanol and dichloromethane mixture is poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around the dichloromethane droplets. The subsequent evaporation of the entrapped dichloromethane leads to the formation of internal cavities with entrapped air within the microparticles. The entrapped air in the microparticles lessens the density of the particles, ensuring buoyancy of the microballoons. They investigated that the particle size and HPMC ratio in the formulation influenced the buoyancy of microballoons. Moreover, riboflavin release was affected by the HPMC ratio.

4. DIFFERENT CATEGORIES OF DRUGS INCORPORATED INTO HPMC BASED GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive dosage forms prepared using HPMC are being extensively investigated for various classes of drugs. In this section, incorporation of various drugs in HPMC based gastroretentive dosage forms are reviewed with examples from literature.

4.1. Gastrointestinal Agents

4.1.1. Famotidine

It is a potent histamine H_2-receptor antagonist and not absorbed uniformly throughout the gastrointestinal tract. Elmoafy *et al.* [53] formulated single unit floating matrix tablets of famotidine by a direct compression method. They observed that the matrix integrity, swelling, *in vitro* drug release, and kinetics of release data were shown to depend on the type and composition of the polysaccharides or blends with cellulose ethers. Moreover, the optimized formulations were able to sustain drug release over 6 hours. Similarly, famotidine floating tablets were prepared using two different grades of methocel K100 and methocel K15M by effervescent technique [54]. It was observed that the tablets containing methocel K100 found to float for long duration as compared with formulations containing methocel K15M. Release of drug from the tablets was sufficiently sustained.

4.1.2. Ranitidine Hydrochloride

Ranitidine hydrochloride is a histamine H_2 receptor antagonist. It is widely used in active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease, and erosive esophagitis. Patel *et al.* [45] developed ranitidine hydrochloride lipid granules by the melt granulation technique and evaluated for *in vitro* floating and drug release characteristics. They studied the effect of various drug release modifiers such as ethyl cellulose, methyl cellulose, and HPMC on drug release from granules. Ethyl cellulose was found to be the most effective in retarding the drug release among the three release rate modifiers. Kumar *et al.* [55] developed gastroretentive drug delivery system of ranitidine hydrochloride consisted of osmotic core, coated with semipermeable membrane which is then further coated with compression coating of gelling agent (HPMC K4M) containing gas generating agent. The entire developed tablet showed floating lag time of less than 2 minutes and were floated for more than 12 hours. Dave *et al.* [56] studied the effect of citric acid and stearic acid on drug release profile and floating properties of gastroretentive drug delivery system of ranitidine hydrochloride. They used 3^2 full factorial designs to optimize the drug release profile. The results of the 3^2 factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation.

4.1.3. Metronidazole

Cedillo-Ramirez *et al.* [57] developed metronidazole floating tablets with varied proportions of sodium bicarbonate (SB) and pharmatose DCL11 and two polymers methocel K4M and CP 971P NF. Tablets containing methocel matrices floated more than 8 hours with SB proportions up to 24%. However, tablets containing CP matrices floated more than 8 hours with SB proportions only up to 12%. Moreover, methocel matrices showed greater hydration volumes and greater drug dissolution compared to CP matrices. Similarly, a novel metronidazole sustained release and floating matrix tablets were developed for eradication of *H.pylori* in peptic ulcer diseases [58]. The resultant tablet formulations were able to float immediately and showed buoyancy for at least 8 hours. Moreover, sustained profiles of drug release were also obtained.

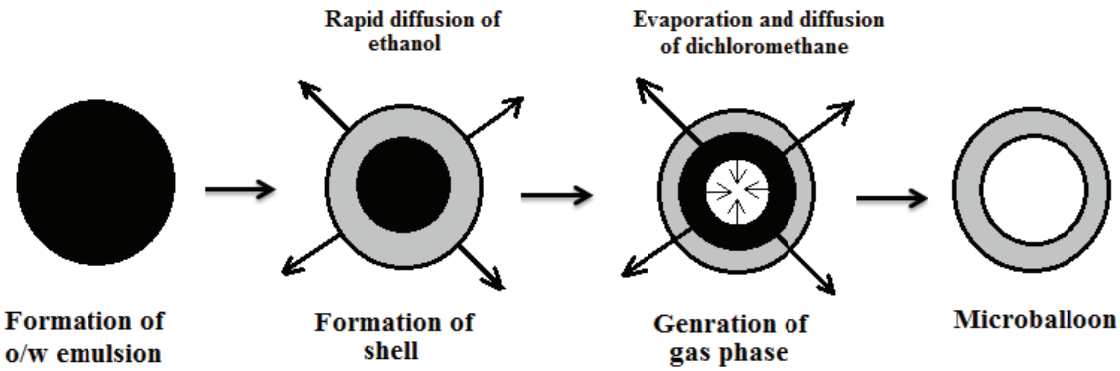

Fig. (5). Preparation technique of microballoone by emulsion solvent diffusion method.

4.1.4. Metoclopramide Hydrochloride

Singh *et al.* [59] prepared gastroretentive floating matrix tablets of metoclopramide hydrochloride using the polymers guar gum, karaya gum, HPMC E15 alone and in combination with HPMC K15M and gas generating agents such as calcium carbonate and citric acid. Tablets with gas generating agents and HPMC K15M floated for 24 hours without complete erosion and showed slower drug release. Further increase in the concentration of HPMC K15M from 10 mg to 40 mg resulted in decrease in release rate of drug. Differential scanning calorimetry and fourier transform infrared spectrophotometric study indicated no interaction between drug and polymers.

4.2. Antidiabetic Agents

4.2.1. Metformin

It is an antidiabetic agent which improves glucose tolerance in type II diabetes. The main site of its absorption is proximal small intestines and biological half life is 1.5-1.6 hours. HBS system of metformin as a single unit floating capsule was prepared for gastroretentive drug delivery system [42]. It was observed that the optimized formulation containing 500 mg of metformin granulated with 5% of ethyl cellulose and 150 mg of HPMC K4M gave the best *in vitro* release of 97% in 12 hours in simulated gastric fluid at pH 3.

4.3. Antibiotics

4.3.1. Tetracycline

Tetracycline, metronidazole, and bismuth salt loaded triple layer tablets for stomach specific delivery were prepared for the treatment of *H.pylori* associated peptic ulcers [60]. HPMC and poly (ethylene oxide) were used as rate controlling polymeric excipients. It has been observed that sustained delivery of tetracycline and metronidazole over 6-8 hours can be easily achieved while the tablet remained a float.

4.3.2. Ofloxacin

The bioavailability of ofloxacin is strongly dependent on the local physiology in the gastrointestinal tract and which is readily soluble and absorbed in the acidic environment of the stomach. Sustained release gastroretentive tablet of ofloxacin was prepared using different polymers such as psyllium husk, HPMC K100M, crospovidone and its combinations [61]. The optimized formulation was found to be bioequivalent to the marketed product (zenocin). Moreover, the percent relative bioavailability of optimized formulation was found to be 97.55%. Ofloxacin loaded HBS capsules were prepared by physical mixing of various grades of HPMC and poly (ethylene oxide) alone as well as in combination for increased local action in gastric region against *H.pylori* infection [62]. The *in vitro* release was found to be 96.02% in 12 hours.

4.3.3. Clarithromycin

Clarithromycin is a macrolide antibiotic widely used in *H.pylori* mediated peptic ulcers. The biological half life of the drug is ~3-5 hours. Floating tablets of clarithromycin were prepared by wet granulation method for the treatment of *H.pylori* mediated peptic ulcer [63]. It has been observed that the developed formulation containing 66.2% clarithromycin, 12 % HPMC K4M polymer, and 8% sodium bicarbonate gave floating lag time less than 3 minutes with a floating time of 12 hours. *In vivo* radiographic studies on healthy human volunteers revealed that tablets remained in the stomach for 220 ± 30 minutes. Similarly floating matrix tablets of clarithromycin were prepared for the treatment of *H.pylori* [64]. The optimized formulation gave floating lag time <30 minutes with a total floating time >10 hours. Moreover, the *in vitro* release profile very near to the target *in vitro* release profile and follows anomalous diffusion as well as zero order pattern of release.

4.3.4. Ciprofloxacin Hydrochloride

Ciprofloxacin hydrochloride is a broad spectrum, fluoroquinolone antibiotic. It is more absorbed from the stomach and the proximal part of the small intestine. Arora *et al.* [65] formulated and evaluated swellable and floating gastroretentive ciprofloxacin hydrochloride tablets for the delivery of drug to the stomach and the proximal parts of the small intestine by increasing the mean residence time in the stomach. The radiographic pictures of healthy volunteers indicated the *in vivo* buoyancy in the stomach for 320 minutes. Furthermore, a combination of HPMC K100M, crospovidone, and sodium carbonate showed the good swelling, drug release, and floating characteristics than the marketed product CIFRAN OD®. Ciprofloxacin floating bioadhesive tablets were prepared by effervescent technique using HPMC, sodium carboxymethyl cellulose, polyacrylic acid, polymethacrylic acid, citric acid, and sodium bicarbonate. The resultant tablets floated for 23-24 hours and showed a Higuchi, nonfickian release mechanism.

4.3.5. Norfloxacin

Norfloxacin floating matrix tablets were prepared by the wet granulation method using polymers such as HPMC K4M, HPMC K100M, and xanthan gum [66]. The resultant tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. The *in vivo* radiographic studies by incorporating $BaS0_4$ indicated that the tablets remained in the stomach for 180 minutes in fasting human volunteers.

4.3.6. Cefuroxime axetil

Cefuroxime axetil loaded intragestric floating tablets were prepared by direct compression method [67]. The 3^2 full factorial designs were employed to evaluate the effect of HPMC K4M to HPMC K100LV ratio and sodium lauryl sulfate on drug release from tablets. It was observed that polymer blend and sodium lauryl sulfate significantly affect the time required for 50% of drug release, percentage drug release at 12 hours, release rate constant, and diffusion component.

4.4. Cardiac Agents

4.4.1. Diltiazem Hydrochloride

Diltiazem hydrochloride is a calcium channel blocker and widely used for the treatment of hypertension and angina. It is more absorbed from the upper intestinal tract and biological

half life of 3.5 hours. Kulkarni and Bhatia [68] developed bilayer floating tablets of diltiazem hydrochloride and lovastatin to get immediate release of lovastatin and controlled release of diltiazem hydrochloride. The tablets were prepared using sodium starch glycolate as superdisintegrant for lovastatin in the immediate release layer and HPMC K4M and xanthan gum as release retarding agents for diltiazem hydrochloride in the controlled release layer. It was observed that HPMC K4M and xanthan gum retarded the release of diltiazem hydrochloride for 12 hours. Oral floating matrix tablets of diltiazem hydrochloride were also prepared by direct compression method using polymers such as HPMC and/ or compritol 888 ATO [31].

4.4.2. Propranolol Hydrochloride

Propranalol hydrochloride is a beta adrenergic receptor blocking agent and widely used as anti hypertensive, antianginal, and antiarrhythmic. It has an elimination half life of 3-4 hours and peak plasma concentration occur about 1 to 4 hours after an oral dose. Floating tablet of propranolol hydrochloride was prepared using various polymers such as HPMC, HPC, xanthan gum, and sodium alginate [34]. The optimized formulation showed good drug release and floating abilities.

4.4.3. Atenolol

Atenolol is a cardioselective beta 1 adrenoreceptor blocker. It is poorly absorbed from the lower gastrointestinal tract. Srivastava *et al.* [69] prepared floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared using polymers such as HPMC K15M, HPMC K4M, guargum, and sodium carboxymethyle cellulose alone or in combination by direct compression method. It was observed that the type of polymer affects the drug release rate and the mechanism.

4.4.4. Captopril

Captopril is an angiotensin converting enzyme inhibitor and widely used for the treatment of congestive heart failure and hypertension. Nur and Zhang [70] prepared captopril floating and/or bioadhesive tablets using two viscosity grades of HPMC (HPMC 4000 and 15000) and CP 934P. All tablet formulations tested showed a sustained release pattern of Captopril over 24 hours with varying cumulative percentage released. Tablets containing HPMC 4000 showed the highest drug release rate, whereas tablets containing HPMC 15000 exhibited the lowest release rate.

4.4.5. Trimetazidine Dihydrochloride

Trimetazidine dihydrochloride is a clinically effective antianginal agent and widely used for the treatment of angina pectoris. Floating tablet of Trimetazidine dihydrochloride were prepared using different hydrophilic matrix forming polymers sush as HPMC4000, CP971P, polycarbophil, and guar gum [71]. All floating tablet formulations showed <0.5 minutes of floating lag time, more than 12 hours of floating duration, and extended biological half-life. The optimized floating tablet indicated a great enhancement in the drug bioavailability compared to immediate release tablets (Vastarel® 20 mg)

4.4.6. Metoprolol Tartrate

Metoprolol tartrate loaded bilayer tablet was developed and optimized for gastric floating drug delivery system [72]. 2^3 full factorial design was employed two optimize the formulation with total polymer content to drug ratio, polymer to polymer ratio, and different viscosity grades of HPMC as independent variables and percentage of drug release at 8 hours, $t_{50\%}$, diffusion coefficient, and floating time as dependent variable. The full factorial design results demonstrated that total polymer content to drug ratio and polymer to polymer ratio significantly affected the floating time and release properties. However, the effect of different viscosity grades of HPMC was nonsignificant.

4.5. Antihypertensive Agent

4.5.1. Phenoporlamine Hydrochloride

Phenoporlamine hydrochloride is a novel compound that is widely used for the treatment of hypertension. It has an elimination half life of 22 hours. Xiaoqiang *et al.* [73] prepared phenoporlamine hydrochloride loaded floating tablet composed of HPMC K4M, CP 971P NF, and gas forming agent. It was observed that the floating matrix tablet containing more CP was capable of releasing the drug for longer periods with increased bioavailability. *In vivo* studies in healthy male human volunteers indicated that the tablet formulation containing 25% CP 971PNF, 8.3% HPMC K4M showed the best bioequivalence to the reference tablet (the relative bioavailability was 1.11).

4.5.2. Labetalol Hydrochloride

Labetalol hydrochloride is a nonselective alpha, beta adrenoreceptor antagonist that is widely used in the treatment of hypertension. Ganse *et al.* [74] formulated and evaluated labetalol hydrochloride loaded gastroretentive floating tablets using various grades of HPMC and poloxamer. The resultant tablets showed negligible floating lag time with a total floating time over 12 hours with complete release.

4.6. Others

4.6.1. Levodopa

New multiple unit levodopa sustained- release minitablets were prepared by melt granulation and subsequent compression [75]. The optimized formulation floated after only one minute and remained buoyant more than 13 hours. Moreover the release of drug was extended for more than 8 hours.

4.6.2. Acyclovir

Acyclovir loaded floating tablets were prepared by wet granulation method using psyllium husk and HPMC K4M as the polymers and sodium bicarbonate as a gas generating agent [76]. It was observed that the resultant formulations having floating lag time below 3 minutes and constantly floated on dissolution medium for more than 24 hours. Furthermore, the optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be

anomalous type, controlled by diffusion through the swollen matrix. Similarly, acyclovir loaded floating matrix tablets were prepared by direct compression technique using polymers such as HPMC 4000 and compritol 888 [77]. The results indicated that a high level of both HPMC 4000 and compritol favors the preparation of floating controlled release of acyclovir tablets. Garg and Gupta [78] prepared floating effervescent tablets of acyclovir by various materials like HPMC K4M, HPMC K15M, psyllium husk, swelling agent like crospovidone and microcrystalline cellulose and gas generating agent like sodium bicarbonate and citric acid. It was observed that most of the formulations showed fickian type of drug release mechanism.

4.6.3. Liquorice Extract

Liquorice extract loaded floating tablets were prepared using HPMC K100M as hydrophilic polymer and sodium bicarbonate as gas generating agent by direct compression method for the treatment of *H.pylori* and gastric ulcers [79]. The floating lag time of all tablet formulations was less than 5 minutes and tablet remained in floating condition throughout the study. Moreover, the optimized formulation released 98.3% of drug in 8 hours *in vitro.*

4.6.4. Fenoverine

Bandari *et al.* [80] prepared biphasic gastroretentive drug delivery system of fenoverine consisted of a loading dose tablet and a floating multiple matrix tablet by the direct compression process. The drug release from biphasic system was sustained over 12 hours with buoyant properties.

4.6.5. Theophylline

Swain *et al.* [81] investigated the influence of various viscosity grades and contents of HPMC on theophylline release from a gastroretentive floating drug delivery system using a 3^2 full factorial design. It was observed that all nine experimental batches showed less than 2 minutes floating lag time and floatation time of more than 12 hours. 3^2 full factorial design results indicated that both viscosity and content of HPMC statistically influenced the floating time and drug release properties. Similarly, theophylline loaded gastroretentive floating tablets were prepared using methocel K100M and methocel K15M or as hydrophilic polymers and sodium bicarbonate and citric acid as gas generating agents by direct compression technique [82]. It was observed that polymer content and amount of floating agent significantly affected the mean dissolution time and percentage drug release after 8 hours.

4.6.6. Domperidone

Prajapati *et al.* [83] designed and optimized gastric floating matrix tablets of domperidone by using Box-Behnker design. They selected HPMC K4M, CP 934P, and sodium alginate as independent variables and floating lag time, total floating time, $t_{50\%}$, and diffusion component as dependent variables. It was found that HPMC significantly affecting floating properties and CP controlling the release rate of the drug.

4.6.7. Carbamazepine

Carbamazepine loaded floating tablets were prepared using HPMC, guar gum, and CP as polymers and sodium bicarbonate as the gas generating agent [84]. It was observed that the carbamazepine release from the floating dosage forms was uniform and followed a zero order release. Tablets containing higher proportions of HPMC (high viscosity) showed slower release than those containing lower proportions.

4.6.8. Cisapride

Cisapride loaded two-layer floating tablet was prepared using HPMC and sodium bicarbonate [85]. *In vitro* release of drug was controlled by the amount of HPMC in the drug loading layer. Moreover, *in vitro* drug dissolution in simulated gastric fluid (SGF) was faster than in simulated intestinal fluid (SIF) since cisapride has greater solubility in SGF than SIF.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable process. Prolonging gastric residence time of a dosage form means extension of the time for drug absorption. Gastroretentive drug delivery systems are used for this purpose. Various natural polymers have been explored for their promising potential in stomach specific drug delivery. HPMC, a derived natural polymer, has been successfully used by many researchers for developing various stomach specific drug delivery systems. Its most important characteristics is the high swellability, which has a significant effect on the release of an incorporated drug from stomach specific dosage forms. Moreover, the release of drug can be modulated by using different viscosity grades of HPMC as well as concentration. A number of *in vitro* and *in vivo* studies favor the suitability of HPMC for efficient stomach-specific drug delivery. This may encourage more utilization of HPMC in developing stomach specific drug delivery systems with better therapeutic efficacy and target specificity.

CONFLICT OF INTEREST

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REFERENCES

[1] Handani, J.; Moes, A.J.; Amighi, K. Devlopment and *in vitro* evaluation of a novel floating multiple unit dosage form obtained by melt pelletization. *Int. J. Pharm.* **2006**, 322, 96-103.

[2] Dorozynski, P.; Kulinowski, P.; Mendyk, A.; Jachowicz, R. Gastrorentetive drug delivery systems with L-dopa based on carrageenans and hydroxypropylmethylcellulose. *Int. J. Pharm.* **2011**, 404, 169-175.

[3] Pandya, N.; Pandya, M.; Bhaskar, V.H. Preparation and *in vitro* Characterization of Porous Carrier-Based Glipizide Floating Microspheres for Gastric Delivery. *J. Young. Pharm.* **2011**, 3(2), 97-104.

[4] Setthacheewakul, S.; Kedjinda, W.; Maneenuan, D.; Wiwattanapatapee, R. Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS). *AAPS. Pharm. Sci. Tech*., **2011**, 12(1), 152-164.

[5] Boldhane, S.P.; Kuchekar, B.S. Development and optimization of metoprolol succinate gastroretentive drug delivery system. *Acta. Pharm*. **2010**, 60(4), 415-425.

[6] Baki, G.; Bajdik, J.; Pintye Hodi, K. Evaluation of powder mixtures and hydrophilic gastroretentive drug delivery systems containing zinc acetate and sodium bicarbonate. *J. Pharm. Biomed. Anal*. **2011**, 54(4), 711-716.

[7] Hascicek, C.; Rossi, A.; Colombo, P.; Massimo, G.; Strusi, O.L.; Colombo, G. Colombo, G. Assemblage of drug release modules: effect of module shape and position in the assembled systems on floating behavior and release rate. *Eur. J. Pharm. Biopharm*. **2011**, 77(1), 116-121.

[8] Sahasathian, T.; Praphairaksit, N.; Muangsin, N. Mucoadhesive and floating chitosan-coated alginate beads for the controlled gastric release of amoxicillin. *Arch. Pharm. Res*. **2010**, 33(6), 889-899.

[9] Hu, L.D.; Xing, Q.B.; Shang, C.; Liu, W.; Liu, C.; Luo, Z.L.; Xu, H.X. Preparation of rosiglitazone maleate sustained-release floating microspheres for improved bioavailability. *Pharmazie*. **2010**, 65(7), 477-480.

[10] Bhardwaj, P.; Chaurasia, H.; Chaurasia, D.; Prajapati, S.K.; Singh, S. Formulation and in-vitro evaluation of floating microballoons of indomethacin. Acta. *Acta. Pol. Pharm*. **2010**, 67(3), 291-298.

[11] Rouge, N.; Cole, E.T.; Doelker, E.; Buri, P. Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs. *Dev. Technol*. **1998**, 3, 73-84.

[12] Yusa, H.; Takashima, Y.; Kanaya, T. Studies on the development of intragastric floating and sustained release preparation I Application of calcium silicate as a floating carrier. *Chem. Pharm. Bull*. **1996**, 44, 1361-1366.

[13] Lee, J.H.; Park, T.G.; Choi, H.K. Development of oral drug delivery system using floating microspheres. *J. Microencapsul*. **1999**, 16, 715-729.

[14] Mamajek, R.C.; Moyer, E.S. Drug dispensing device and method. *US Patent 4*. **1980**, 207, 890.

[15] Urquhart, J.; Theeuwes, F. Drug delivery system comprising a reservoir containing a plurality of tiny pills.*US Patent 4*. **1984**, 434,153.

[16] Wang, J.; Tabata, Y.; Bi, D.; Morimoto, K. Morimoto, K. Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres. *J. Control. release*. **2001**, 73, 223-231.

[17] Tamburic, S.; Craig, D.Q.M. The effects of aging on the rheological, dielectric and mucoadhesive properties of poly (acrylic acid) gel systems. *Pharm. Res*. **1996**, 13, 279-283.

[18] Fix, J.A.; Cargill, R.; Engle, K. Controlled gastric emptying III: gastric residence time of a non- disintegrating geometric shape in human volunteers. *Pharm. Res*. **1993**, 10, 1087-1089.

[19] Fedzierewicz, F.; Thouvenot, P.; Lemut, J.; Etinine, A.; Hoffonan, M.; Maincene, P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. *J. Control. Release.* **1999**, 58, 195-205.

[20] Hwang, S.J.; Park, K. Gastric retentive drug delivery systems. *Crit. Rev. Ther. Drug .Carrier .Syst.* **1998**, 15, 243-284.

[21] Groning, R.; Berntgen, M.; Georgarakis, M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracoporal magnets to control gastrointestinal transit. E *Eur. J. Pharm. Biopharm*. **1998**, 46, 285-291.

[22] Chen, J.; Blevins, W.E.; Park, H.; Park, K. Gastric retention properties of superporous hydrogel composites. *J. Control. Release*. **2000**, 641-3, 39-51.

[23] Chen, J.; Park, K. Synthesis and characterization of superporous hydrogel composites. *J .Control. Release*. **2000**, 651(2), 73-82.

[24] Singh, B.N.; Kim, K.H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J. Control. Release*. **2000**, 63, 235-259.

[25] Chourasia, M.K.; Jain, S.K. Polysaccharides based colon-specific drug delivery, In: Jain NK, Progress in controlled and novel drug delivery systems.1st Edn.,CBS Publishers, New Delhi,2004,405-432.

[26] Baumgartner, S.; Kristl, J.; Vrecer, F.; Vodopivec, P.; Zorko, B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm*. **2000**, 195, 125-135.

[27] Krogel, I.; Bodmeier, R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. *J. Control. Release*. **1999**, 61, 43-50.

[28] Velasco, M.V.; Ford, J.L.; Rowe, P.; Rajabi-Siahboomi, A.R. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. *J. Control. Release*. **1999**, 57, 75-85.

[29] Mandal, T.K. The influence of binding solvents on drug release from hydroxypropyl methylcellulose tablets. *Drug. Dev. Ind. Pharm*. **1995**, 21, 1389-1397.

[30] Chavanpatil, M.D.; Jain, P.; Chaudhari, S.; Shear, R.; Vavia, P.R. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *Int. J. Pharm.* **2006**, 316, 86-92.

[31] Gambhire, M.N.; Ambade, K.W.; Kurmi, S.D.; Kadam, V.J.; Jadhav, K.R. Development and *in vitro* evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. *AAPS. Pharm.Sci.Tech.* **2007**, 8(3), E1-E9.

[32] Tadros, M.I. Controlled release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro- in vivo* evaluation in healthy human volunteers. *Eur. J. Pharm. Biopharm*. **2010**, 74, 332-339.

[33] Patel, A.; Modasiya, M.; Shah, D.; Patel, V. Development and *in vivo* floating behavior of verapamil HCL intragastric floating tablets. *AAPS. Pharm.Sci.Tech*. **2009**, 10(1), 310-315.

[34] Jagdale, S.C.; Agavekar, A.J.; Pandya, S.V.; Kuchekar, B.S.; Chabukswar, A.R. Formulation and evaluation of Gastroretentive drug delivery system of propranolol hydrochloride. *AAPS. Pharm.Sci.Tech.* **2009**, 10(3), 1071-1079.

[35] Sungthongjeen, S.; Sriamornsak, P.; Puttipipatkhachorn, S. Design and evaluation of floating multi-layer coated tablets based on gas formation. *Eur. J. Pharm. Biopharm.* **2008**, 69, 225-263.

[36] Oliveira, P.R.; Bernardi, L.S.; Strusi, O.L.; Mercuri, S.; Marcos, A.; Silva, S.; Colombo, P.; Sonvico, F. Assembled modules technology for site specific prolonged delivery of norfloxacin. *Int. J. Pharm*. **2011**, 405, 90-96.

[37] Schaafsma, G. Bioavailability of calcium and magnesium. *Eur. J. Clin. Nutr*. **1997**, 51, S13-S16.

[38] Bronner, F.; Pansu, D.; Stein, W.D. An analysis of intestinal calcium transport across the intestine. *Am. J. Physiol*. **1986**, 250, 561-569.

[39] Pansu, D.; Bellaton, C.; Bronner, F. Effect of Ca intake on Saturable and nonsaturable components of duodenal Ca transport. *Am. J. Physiol*. **1981**, 240, 32-37.

[40] Li, S.; Lin, S.; Daggy, B.P.; Mirchandani, H.L.; Chien, Y.W. Effect of HPMC and CP on the release and floating properties of gastric floating drug delivery system using factorial design. *Int. J. Pharm*. **2003**, 253, 13-22.

[41] Dorozynski, P.; Jachowicz, R.; Kulinowski, P.; Kwiecinski, S.; Szybinski, K.; Skorka, T.; Jasinski, A. The macromolecular polymers for the preparation of hydrodynamically balanced systems. *Drug Dev. Ind. Pharm*. **2004**, 30(9), 947-957.

[42] Ali, J.; Arora, S.; Ahuja, A.; Babbar, A.K.; Sharma, R.K.; Khar, R.K.; Baboota, S. Formulation and development of hydrodynamically balanced system for metformin: *In vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.* **2007**, 67, 196-201.

[43] Jain, S.K.; Agrawal, G.P.; Jain, N.K. Porous carrier based floating granular delivery system of repaglinide. *Drug Dev. Ind. Pharm*. **2007**, 33, 381-391.

[44] Jain, A.K.; Jain, S.K.; Yadav, A.; Agrawal, G.P. Controlled release calcium silicate based floating granuler delivery system of ranitidine hydrochloride. *Curr. Drug. Deliv*. **2006**, 3(4), 367-372.

[45] Patel, D.M.; Patel, N.M.; Patel, V.F.; Bhatt, D.A. Floating granules of ranitidine hydrochloride-gelucire: formulation optimization using factorial design. *AAPS. PharmSciTech*. **2007**, 8(2), 30.

[46] Jain, S.K.; Agrawal, G.P.; Jain, N.K. *In vitro* evaluation of porous carrier-based floating granular delivery system of orlistat. *PDA J Pharm Sci Technol.* **2008**, 62(4), 292-299.

[47] Shishu.; Gupta, N.; Aggarwal, N. Stomach specific drug delivery of 5- fluorouracil using floating alginate beads. *AAPS. PharmSciTech*. **2007**, 8(2), E1-E7.

[48] Vedha, H.B.; Brahma, R.A.; Samyuktha, R.B. Floating drug delivery of nevirapine as a gastroretentive system. *J. Young. Pharm*. **2010**, 2(4), 350-355.

[49] Gattani, S.G.; Savaliya, P.J.; Belgamwar, V.S. Floating- mucoadhesive beads of clarithromycin for the treatment of H.pylori infection. *Chem. Pharm. Bull.* **2010**, 58(6), 782-787.

[50] Choudhary, H.; Agrawal, A.K.; Malviya, R.; Yadav, S.K.; Jaliwala, Y.A.; Patil, U.K. Evaluation and optimization of preparative variables for controlled-release floating microspheres of levodopa/carbidopa. *Pharmazie*. **2010**, 65(3), 194-198.

[51] Srinatha, A.; Pandit, J.K. Multi-unit floating alginate system: effect of additives on ciprofloxacin release. *Drug Deliv*. **2008**, 15(7), 471-476.

[52] Sato, Y.; Kawashima, Y.; Takeuchi, H.; Yamamoto, H. *In vitro* and *in vivo* evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy humans. *Int. J. Pharm*. **2004**, 275, 97-107.

[53] Elmowafy, E.M.; Awad, G.A.S.; Mansour, S.; El hamid, A.; El shamy, A. Release mechanisms behind polysaccharides based famotidine controlled release matrix tablets. *AAPS. PharmSciTech.* **2008**, 9(4), 1230-1239.

[54] Jaimini, M.; Rana, A.C.; Tanwar, Y.S. Formulation and evaluation of famotidine floating tablets. *Curr. Drug. Deliv*. **2007**, 4(1), 51-55.

[55] Kumar, P.; Singh, S.; Mishra, B. Gastroretentive drug delivery system of ranitidine hydrochloride based on osmotic technology: development and evaluation. *Curr. Drug. Deliv*. **2008**, 5(4), 332-342.

[56] Dave, B.S.; Amin, A.F.; Patel, M.M. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation. *AAPS. PharmSciTech*. **2004**, 5(2), e34.

[57] Cedillo-Ramirez, E.; Villafuerte-Robles, L.; Hernandez-Leon, A. Effect of added pharmatose DCL 11 on the sustained- release of metronidazole from Methocel K4M and CP 971NF floating matrices. *Drug Dev. Ind. Pharm*. **2006**, 32(8), 955-965.

[58] Asnaashari, S.; Khoei, N.S.; Zarrintan, M.H.; Adibkia, K.; Javadzadeh, Y. Preparation and evaluation of novel metronidazole sustained release and floating matrix tablets. *Pharm. Dev. Technol.* **2011**, 16(4), 400-407.

[59] Singh, S.; Singh, J.; Muthu, M.S.; Balasubramaniam, J.; Mishra, B. Gastroretentive drug delivery system of metoclopramide hydrochloride: formulation and *in vitro* evaluation. *Curr. Drug. Deliv*. **2007**, 4(4), 269-275.

[60] Yang, L.; Eshraghi, J.; Fassihi, R. A new intragastric delivery system for the treatment of H.pylori associated gastric ulcer: *in vitro* evaluation. *J. Control. Release*. **1999**, 57, 215-222.

[61] Chavanpatil, M.; Jain, P.; Chaudhari, S.; Shear, R.; Vavia, P. Development of sustained release gastroretentive drug delivery system for ofloxacin: *In vitro* and *in vivo* evaluation. *Int. J. Pharm*. **2005**, 304, 178-184.

[62] Ali, J.; Hasan, S.; Ali, M. Formulation and development of gastroretentive drug delivery system for ofloxacin. *Exp. Clin. Pharmacol*. **2006**, 28(7), 433-439.

[63] Nama, M.; Gonugunta, C.S.R.; Veerareddy, P.R. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. *AAPS .PharmSciTech*. **2008**, 9(1), 231-237.

[64] Patel, S.S.; Ray, S.; Thakur, R.S. Formulation and evaluation of floating drug delivery system containing clarithromycin for H.pylori. *Acta. Pol. Pharm*. 2006, 63(1), 53-61.

[65] Arza, R.A.K.; Gonugunta, C.S.R.; Veerareddy, P.R. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. *AAPS. PharmSciTech*. **2009**, 10(1), 220-226.

[66] Bomma, R.; Swamy Naidu, R.A.; Yamsani, M.R.; Veerabrahma, K. Development and evaluation of gastroretentive norfloxacin floating tablets. *Acta. Pharm*. **2009**, 59(2), 211-221.

[67] Patel, V.F.; Patel, N.M. Intragastric floating drug delivery system of cefuroxime axetil: *in vitro* evaluation. *AAPS. PharmSciTech*. **2006**, 7(1), E17.

[68] Kulkarni, A.S.; Bhatia, M.S. Design of floating bilayer tablets of diltiazem hydrochloride and lovastatin. *PDA. J. Pharm. Sci. Technol*. **2008**, 62(5), 344-352.

[69] Srivastava, A.K.; Wadhwa, S.; Ridhurkar, D.; Mishra, B. Oral sustained delivery of atenolol from floating matrix tablets formulation and *in vitro* evaluation. *Drug Dev. Ind. Pharm.* **2005**, 31, 367-374.

[70] Nur, O.A.; Zhang, J.S. Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev. Ind. Pharm*. **2000**, 26(9), 965-969.

[71] Abdelbary, A.; Elgazayerly, O.N.; Elgendy, N.A.; Ali, A.A. Floating tablet of trimetazidine dihydrochloride: an approach for extended release with zero order kinetics. *AAPS. PharmSciTech*. **2010**, 11(3), 1058-1066.

[72] Narendra, C.; Srinath, M.S.; Babu, G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. *AAPS. PharmSciTech*. **2006**, 7(2), E34.

[73] Xiaoqiang, X.; Minjie, S.; Feng, Z.; Yiqiao, H. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: *In vitro* and *in vivo* evaluation in healthy volunteers. *Int. J. Pharm*. **2006**, 310, 139-145.

[74] Garse, H.; Vij, M.; Yamgar, M.; Kadam, V.; Hirlekar, R. Formulation and evaluation of a gastroretentive dosage form of labetalol hydrochloride. *Arch. Pharm. Res*. **2010**, 33(3), 405-410.

[75] Goole, J.; Vanderbist, F.; Amighi, K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. *Int. J. Pharm*. **2007**, 334(1-2), 35-41.

[76] Kharia, A.A.; Hiremath, S.N.; Singhai, A.K.; Omray, L.K.; Jain, S.K. Design and optimization of floating drug delivery system of acyclovir. *Indian. J. Pharm. Sci*. **2010**, 72(5), 599-606.

[77] El Gamal, S.S.; Naggar, V.F.; Allam, A.N. Factorial design analysis and physiochemical characterization studies. *Drug Dev. Ind. Pharm*. **2011**, 37(7), 855-867.

[78] Garg, R.; Gupta, G.D. Preparation and evaluation of gastroretentive floating tablets of acyclovir. *Curr. Drug. Deliv*. **2009**, 6(5), 437-443.

[79] Ram, H.N.; Lachake, P.; Kaushik, U.; Shreedhara, C.S. Formulation and evaluation of floating tablets of liquorice extract. *Pharmacognosy. Res*. **2010**, 2(5), 304-308.

[80] Bandari, S.; Eaga, C.M.; Thadishetty, A.; Yamsani, M.R. Formulation and evaluation of multiple tablets as a biphasic gastroretentive floating drug delivery system for fenoverine. *Acta. pharm*. **2010**, 60(1), 89-97.

[81] Swain, K.; Pattnaik, S.; Mallick, S.; Chowdary, K.A. Influence of hydroxypropyl methylcellulose on drug release pattern of a gastroretentive floating drug delivery system using a 3(2) full factorial design. *Pharm. Dev. Technol*. **2009**, 14(2), 193-198.

[82] Khan, F.; Ibn Razzak, S.M.; Khan, Z.R.; Azad, M.A.; Chowdhury, J.A.; Reza, S. Theophylline loaded gastroretentive floating tablets based on hydrophilic polymers: preparation and *in vitro* evaluation. *Pak. J. Pharm. Sci.* **2009**, 22(2), 155-161.

[83] Prajapati, S.T.; Patel, L.D.; Patel, D.M. Gastric floating matrix tablets: design and optimization using combination of polymers. *Acta. Pharm*. **2008**, 58(2), 221-229.

[84] Kar, M.; Reddy, M.S. Design and *in vitro* evaluation of floating drug delivery system for an antipsychotic agent: a technical report.*PDA .J. Pharm. Sci. Technol*. **2006**, 60(6), 389-394.

[85] Wei, Z.; Yu, Z.; Bi, D. Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug. *Drug Dev. Ind. Pharm*. **2001**, 27(5), 469-474.

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