Overview on Recent Researches on Floating Microspheres

Manish Negi*, Vikash Kumar Shukla, T. S. Easwari

IIIMT College of Medical Sciences, Mawana Road, Meerut-250001, (U.P.), India

Abstract

Conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. The floating or hydrodynamically controlled drug delivery systems are useful in such application. Floating microspheres are especially suitable for achieving sustained or delayed release oral formulations with flexibility of blending to attain different release patterns, low risk of dose dumping as well as reproducible and short gastric retention time. The floating microspheres produces controlled delivery of drug and also enhance the bioavailability of drug. Floating microsphere is especially gaining attention due to their wide applicability in the targeting of drugs to the stomach. These floating microspheres have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the vagaries of gastric emptying retention time of drugs. This review provides an overview of scientific work done in the formulation and development of various drug for floating microspheres.

1 Introduction

The conventional oral dosage forms offer no control over drug delivery, leading to fluctuations in plasma drug level. These have a disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the Gastro intestinal transit (GIT) to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Various approaches have been worked out to improve the retention of oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, bioadhesive systems, high density systems.

Floating microspheres is the one best approach to minimize the disadvantages of conventional oral dosage forms. Floating microspheres belongs to gastro-retentive drug delivery systems. It floating is based on effervescent and non-effervescent technique. The size of microspheres should be less than 200 mm, and are free flowing powders. It is prepared by proteins or synthetic polymers. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug from microsphere released slowly at desired rate leading in enhanced gastric retention with reduced fluctuations in plasma drug concentration. The floating microsphere decreases the dosing frequency, and it improves the patient compliance. It also enhanced the therapeutic effects of drug which have short half-life. The microsphere also enhanced drug absorption which solubilize in stomach.

There are various techniques are available for the preparation of microsphere such as single emulsion technique, double emulsion technique, polymerization techniques, phase separation coacervation technique, spray drying and spray congealing and solvent extraction.

Floating microspheres are evaluated by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose, scanning electron microscopy, *in vitro* floatability studies, *in vivo* floatability studies in dogs, *in vitro* drug release studies and stability studies etc.

The various scientific attempts have been done by researchers to develop floating microspheres to retain the dosage form in the stomach as a way of increasing retention time.

2 Scientific approaches to Floating microspheres

Bhadouriya *et al.* (2014) formulated and to characterized a floating drug delivery system for clopidogrel bisulphate to improve bioavailability and to minimize the side effects of the drug such as gastric bleeding and drug resistance development. Clopidogrel floating tablets were prepared by direct compression technique by...
the use of three polymers xanthan gum, hydroxypropyl methylcellulose (HPMC) K15M and HPMC K4M in different concentrations (20%, 25% and 30% w/w). Sodium bicarbonate (15% w/w) and microcrystalline cellulose (30% w/w) were used as gas generating agent and diluent respectively. Studies were carried out on floating behavior and influence of type of polymer on drug release rate. All the formulations were subjected to various quality control and in-vitro dissolution studies in 0.1 N hydrochloric acid (1.2 pH) and corresponding dissolution data were fitted to popular release kinetic equations in order to evaluate release mechanisms and kinetics. All the clopidogrel floating formulations followed first order kinetics, Higuchi drug release kinetics with diffusion as the dominant mechanism of drug release. As per Korsmeyer-Peppas equation, the release exponent "n" ranged 0.452-0.654 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. The drug release rate of clopidogrel was found to be affected by the type and concentration of the polymer used in the formulation (P < 0.05). As the concentration of the polymer was increased, the drug release was found to be retarded. Based on the results, clopidogrel floating tablets prepared by employing xanthan gum at concentration 25% w/w (formulation F2) was the best formulation with desired in-vitro floating time and drug dissolution

Bhadouriya et al. (2013) prepared floating microspheres of atenolol as prolonged release multiparticulate system and evaluate it using novel multi-compartment dissolution apparatus. Atenolol loaded floating microspheres were prepared by emulsion solvent evaporation method using 3² full factorial design. Formulations F1 to F9 were prepared using two independent variables (polymer ratio and % polyvinyl alcohol) and evaluated for dependent variables (particle size, percentage drug entrapment efficiency and percentage buoyancy). The formulation (F8) with particle size of 329 ± 2.69 μm, percentage entrapment efficiency of 61.33% and percentage buoyancy of 96.33% for 12 h was the optimised formulation (F8). The results of factorial design revealed that the independent variables significantly affected the particle size, percentage drug entrapment efficiency and percentage buoyancy of the microspheres. In vitro drug release study revealed zero order release from F8 (98.33% in 12 h). SEM revealed the hollow cavity and smooth surface of the hollow microspheres

Shahi et al. (2013) developed the Verapamil hydrochloride sustained-release floating matrix tablets using gas-generation approach to prolong the gastric residence time. Floating tablets were prepared using hydroxypropyl methylcellulose K4M (HPMC) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and Citric Acid as floating assistant agent. A 3² factorial design was used to select the optimised formulation wherein HPMC K4M (X1) and Citric Acid (X2) were taken as independent variables and

Floating lag time (FLT), amount of drug release after 24hrs. (Q₂₄) were taken as dependent variables. The release data were evaluated by the model-dependent (curve fitting) method using PCP Disso v2.08 software. Optimisation studies were carried out by using the Design Expert software (version 8.0.1). The floating tablets were evaluated for uniformity of weight, hardness, thickness, swelling index, friability, drug content, FLT, and in vitro release. The in vitro drug release followed Hixon-Crowell model and mechanism of drug release was found to be anomalous or non-Fickian type. The optimized formulation was F3 containing HPMC K4M 15%, and Citric acid 3% having minimum FLT and maximum drug release after 24 hrs

Aejaz et al. (2013) prepared floating microspheres of clarithromycin designed as gastroretentive dosage form for the treatment of Helicobacter pylori. The floating microspheres were prepared using different polymers like HPMC - ethyl cellulose, HPMC, eudragit S - 100, eudragit L - 100, by solvent evaporation/diffusion methods which offer advantage of short processing time, lack of exposure of the ingredients to high temperature and gives high encapsulation efficiency. Formulations were characterized for their particle size, practical yield, entrapment efficiency, in vitro buoyancy, drug polymer compatibility (IR), scanning electron microscopy (SEM) and in vitro drug release. Scanning electron microscopy shows that spherical microspheres with porous surface were formed. The optical microscopic studies revealed that the practical yield was more than 61.35% with a particle size range of 105.61 - 325.15 μm. The percent entrapment efficiency is about 62.68% and more in larger particle as compared to smaller particle. The percent buoyancy was more than 71. 40% up to 12 hours. The particle size, percent yield, percent drug entrapment and percent was increased significantly with increase in polymer concentration. The in vitro release was significantly decreased with in polymer concentration. The release obeys first order kinetics model and the drug release rate was diffusion controlled with Fickian or non – Fickian transported depending upon the polymers. The prepared floating microspheres were stable. Hence it can inferred that the floating microsphere of clarithromycin as a gastroretentive dosage form may prolong the drug release thereby improving the bioavailability

Goudanavar et al. (2013) prepared and evaluated the floating microspheres of Esomeprazole magnesium trihydrate as a model drug for prolongation of the gastric retention time for oral delivery. EMT is a proton pump inhibitor which acts by irreversibly blocking the (H+K+) - ATPase enzyme system of the gastric parietal cell. Its half life is 1 - 1.5 hrs. EMT poor absorption may be because of degradation in gastric acid which can be prevented by incorporation of sodium bicarbonate which is a systemic antacid and act as buffer. The EMT floating microspheres were prepared by double emulsion
solvent diffusion method by using Ethyl cellulose and different grades of HPMC like K4M, K15M, using Dichloromethane and alcohol solvent systems. EMT Floating microspheres were evaluated for micromeritic properties, particle size, % yield, In-vitro buoyancy, incorporation efficiency and drug release. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 10 hrs and the particle sizes of microspheres were found to be in the range of 67.24±4.57 μm to 106.35±5.67 μm. Incorporation efficiency was found in the range of 54.75±3.51 to 83.97±2.54. In-vitro release profile of optimized formulations follows first order non-Fickian (Anomalous) release indicates diffusion and dissolution controlled release. FT-IR and DSC studies revealed the absence of any chemical interaction between drug and polymers used. During the stability period selected microspheres were found to be stable with respect to Entrapment efficiency and drug release characteristics.

Bhattacharjee et al. (2013) developed once daily sustained release floating dosage form of salbutamol sulfate. The study involves the preparation of floating microspheres of salbutamol sulfate coated with Eudragit L100 using solvent evaporation method and its in vitro characterization. Three batches (F1, F2 & F3) of microspheres were prepared taking three drugs: polymer ratios (1:1, 1:2 & 1:3). The entrapment efficiency was increased with the increment in polymer concentration. The microspheres remained buoyant in acidic medium containing surfactant for 8-12 hours in vitro. The mean particle size increased and the drug release rate decreased at higher polymer concentration. The surface morphology of microspheres characterized by SEM showed microspheres with smooth surface. The in-vitro drug release studies were carried out for 12 hours both in 0.1N HCl (pH 1.2) and pH 6.8 buffers. The release studies showed the drug release was faster in intestinal pH as compared to gastric pH due to the polymer solubility in pH from 6.9.

Pawar et al. (2013) developed a gastroretentive floating tablet of Atenolol and investigate the effects of both hydrophilic and hydrophobic retardant on in vitro release. Atenolol is an antihypertensive drug with an oral bioavailability of only 50% because of its poor absorption from lower gastrointestinal tract. The floating tablets of Atenolol were prepared to increase the gastric retention, to extend the drug release, and to improve the bioavailability of the drug. The floating tablets were formulated using hydrophilic polymers as Hydroxy propyl methyl cellulose (HPMC K4M and HPMC K15M), hydrophobic retardant as a hydrogenated cottonseed oil (HCSO), and sodium bicarbonate as a gas generating agent to reduce floating lag time. The formulated tablets were evaluated for the quality control tests such as weight variation, hardness, friability, swelling index, floating lag time, and total floating time. The in-vitro release study of the tablets was performed in 0.1N HCl as a dissolution media. The results of the present study clearly indicates the promising potential of Atenolol floating system as an alternative to the conventional dosage and other sustained release formulations. The study also revealed the effectiveness of HCSO as retardant in combination with HPMC.

Hafeez et al. (2013) prepared floating microspheres to increase the residence time in stomach with lesser direct contact with gastric mucosa. Floating microspheres of Ethyl cellulose (EC), blend of Ethyl cellulose and Hydroxypropyl methyl cellulose (HPMC) (in a ratio of 1:1) loaded with ketoprofen were prepared using emulsion solvent diffusion method. Shape and surface characteristics were analyzed using optical and scanning electron microscopy respectively. They found to be sufficiently buoyant over simulated gastric fluid for more than 4 hrs. Entrapment of the drug in polymer matrix was found to be increased with an increase in amount of polymer. In-vitro release study was done in phosphate buffer (pH 7.4, 6.8) for 6 hrs and the prepared microspheres exhibit prolonged drug release. The mean particle size increased and the drug release rate decreased at higher polymer concentration.

Goswami et al. (2012) developed floating microspheres of VCH to localise the drug at upper part of GIT, for improved absorption. Floating microspheres were prepared by W/O emulsification solvent evaporation method using Ethylcellulose (EC) as polymer. Particle size and % EE were 550.02±0.241 μm, 79.88±2.236% respectively. In vitro and in vivo floatability studies confirmed floating behaviour of microspheres. VCH loaded floating microspheres can be a suitable alternative to the conventional formulation, by localizing the drug at upper GIT.

Durgavale et al. (2012) prepared and evaluated floating microsphere of Captopril as model drug for prolongation of gastric residence time. The different gas forming agents are used such as sodium bicarbonate and calcium carbonate. The microspheres were prepared by Ionotrop gelation technique using polymers Sodium alginate along with HPMC (K4M) and Ethyl cellulose. The microsphere was evaluated for angle of repose, bulk density, tapped density, Carr’s index, Hausner’s ratio, percent yield and drug entrapment. The shape and surface morphology of prepared microsphere were characterized by optical and scanning electron microscopy, respectively. In-vitro drug release studies were performed by using an USP dissolution test apparatus (type II) at 37±0.5°C and 50 rpm speed. To study the release behaviour, kinetic analyses were performed on the optimized formulation. The dissolution data were fitted to zero order, first order, matrix, Hixson-Crowell, Peppas model. The prepared microsphere exhibited prolonged drug release (~ 12 hr) and remained buoyant for > 12 hr. The optimized formulations H3, H6 were kept for short term stability study. The conditions for stability study were 40°C and relative Hafeez et al. (2013) developed floating microspheres to increase the residence time in stomach with lesser direct contact with gastric mucosa. Floating microspheres of Ethyl cellulose (EC), blend of Ethyl cellulose and Hydroxypropyl methyl cellulose (HPMC) (in a ratio of 1:1) loaded with ketoprofen were prepared using emulsion solvent diffusion method. Shape and surface characteristics were analyzed using optical and scanning electron microscopy respectively. They found to be sufficiently buoyant over simulated gastric fluid for more than 4 hrs. Entrapment of the drug in polymer matrix was found to be increased with an increase in amount of polymer. In-vitro release study was done in phosphate buffer (pH 7.4, 6.8) for 6 hrs and the prepared microspheres exhibit prolonged drug release. The mean particle size increased and the drug release rate decreased at higher polymer concentration.

Negi et al. (2013) developed once daily sustained release floating dosage form of salbutamol sulfate. The study involves the preparation of floating microspheres of salbutamol sulfate coated with Eudragit L100 using solvent evaporation method and its in vitro characterization. Three batches (F1, F2 & F3) of microspheres were prepared taking three drugs: polymer ratios (1:1, 1:2 & 1:3). The entrapment efficiency was increased with the increment in polymer concentration. The microspheres remained buoyant in acidic medium containing surfactant for 8-12 hours in vitro. The mean particle size increased and the drug release rate decreased at higher polymer concentration. The surface morphology of microspheres characterized by SEM showed microspheres with smooth surface. The in-vitro drug release studies were carried out for 12 hours both in 0.1N HCl (pH 1.2) and pH 6.8 buffers. The release studies showed the drug release was faster in intestinal pH as compared to gastric pH due to the polymer solubility in pH from 6.9.

Pawar et al. (2013) developed a gastroretentive floating tablet of Atenolol and investigate the effects of both hydrophilic and hydrophobic retardant on in vitro release. Atenolol is an antihypertensive drug with an oral bioavailability of only 50% because of its poor absorption from lower gastrointestinal tract. The floating tablets of Atenolol were prepared to increase the gastric retention, to extend the drug release, and to improve the bioavailability of the drug. The floating tablets were formulated using hydrophilic polymers as Hydroxy propyl methyl cellulose (HPMC K4M and HPMC K15M), hydrophobic retardant as a hydrogenated cottonseed oil (HCSO), and sodium bicarbonate as a gas generating agent to reduce floating lag time. The formulated tablets were evaluated for the quality control tests such as weight variation, hardness, friability, swelling index, floating lag time, and total floating time. The in-vitro release study of the tablets was performed in 0.1N HCl as a dissolution media. The results of the present study clearly indicates the promising potential of Atenolol floating system as an alternative to the conventional dosage and other sustained release formulations. The study also revealed the effectiveness of HCSO as retardant in combination with HPMC.

Hafeez et al. (2013) prepared floating microspheres to increase the residence time in stomach with lesser direct contact with gastric mucosa. Floating microspheres of Ethyl cellulose (EC), blend of Ethyl cellulose and Hydroxypropyl methyl cellulose (HPMC) (in a ratio of 1:1) loaded with ketoprofen were prepared using emulsion solvent diffusion method. Shape and surface characteristics were analyzed using optical and scanning electron microscopy respectively. They found to be sufficiently buoyant over simulated gastric fluid for more than 4 hrs. Entrapment of the drug in polymer matrix was found to be increased with an increase in amount of polymer. In-vitro release study was done in phosphate buffer (pH 7.4, 6.8) for 6 hrs and the prepared microspheres exhibit prolonged drug release. The mean particle size increased and the drug release rate decreased at higher polymer concentration.

Goswami et al. (2012) developed floating microspheres of VCH to localise the drug at upper part of GIT, for improved absorption. Floating microspheres were prepared by W/O emulsification solvent evaporation method using Ethylcellulose (EC) as polymer. Particle size and % EE were 550.02±0.241 μm, 79.88±2.236% respectively. In vitro and in vivo floatability studies confirmed floating behaviour of microspheres. VCH loaded floating microspheres can be a suitable alternative to the conventional formulation, by localizing the drug at upper GIT.

Durgavale et al. (2012) prepared and evaluated floating microsphere of Captopril as model drug for prolongation of gastric residence time. The different gas forming agents are used such as sodium bicarbonate and calcium carbonate. The microspheres were prepared by Ionotrop gelation technique using polymers Sodium alginate along with HPMC (K4M) and Ethyl cellulose. The microsphere was evaluated for angle of repose, bulk density, tapped density, Carr’s index, Hausner’s ratio, percent yield and drug entrapment. The shape and surface morphology of prepared microsphere were characterized by optical and scanning electron microscopy, respectively. In-vitro drug release studies were performed by using an USP dissolution test apparatus (type II) at 37±0.5°C and 50 rpm speed. To study the release behaviour, kinetic analyses were performed on the optimized formulation. The dissolution data were fitted to zero order, first order, matrix, Hixson-Crowell, Peppas model. The prepared microsphere exhibited prolonged drug release (~ 12 hr) and remained buoyant for > 12 hr. The optimized formulations H3, H6 were kept for short term stability study. The conditions for stability study were 40°C and relative
humidity of 75% from the study; it was observed that there is no significant change in drug entrapment and drug release rate.\(^\text{13}\)

Jani \textit{et al.} (2012) developed controlled release (CR) floating multiparticulate drug delivery system of tolperisone hydrochloride. Microspheres were prepared by nonaqueous solvent evaporation technique consisting of porous calcium silicate (Florite or FLR) as porous carrier, tolperisone hydrochloride (API), Ethyl cellulose (EC), and HPMC 15 cPs as rate controlling polymers. Full factorial design was applied for optimization of formulation. The effect of various formulation and process variables on the particle morphology, micromeritic properties, in vitro floating behavior, entrapment efficiency, and \textit{in vitro} drug release were studied. The size of microspheres was varied from 300 to 500 μm. The microspheres were found to be highly porous and regular in shape. All the formulations showed excellent flow properties. The percentage entrapment efficiency of all batches was greater than 80%. The percentage buoyancy varied from 85% to 98% at the end of 12 h. The release rate was determined in simulated gastric fluids. The formulation demonstrated favorable \textit{in vitro} floating and release characteristics. Different kinetic models were applied to study the release mechanism. All formulations followed Higuchi model, which indicates the diffusion control release of water soluble drug from polymer matrix. Multiple regression analysis was applied for study of the effect of independent variables on the dependent variables.\(^\text{14}\)

Srikanth \textit{et al.} (2011) formulated gastroretentive floating drug delivery system (GRFDDS) of ofloxacin by using synthetic and natural polymers. Formulations were prepared by wet granulation technique and sodium bicarbonate (10% w/w) was incorporated as gas generating agent. Tablets were evaluated for hardness, \textit{in vitro} buoyancy, drug content and \textit{in vitro} drug release studies. Release data obtained was subjected to analysis using different mathematical models namely – zero order flux, first order, erosion plot, Higuchi and Korsmeyer Peppas equations. All formulated tablets irrespective of polymer used had hardness and friability values >5.0kg/cm\(^2\) and <0.68%. The \textit{in vitro} lag time and total buoyancy time for all the formulations were between 45 to 183secs and 5 to 16 hours respectively. As the concentration of the polymers in the formulations increased the drug release decreased. Formulations made with gum karaya exhibited first order kinetics, non- fickian diffusion and the formulations like OGK3 and OGK4 followed first order and erosion mechanism. Whereas polyethylene oxide based formulations OP2,OP4 and OP5 exhibited zero order, non fickian diffusion and remaining formulations followed first order, erosion mechanism. GRFDDS of ofloxacin using synthetic (polyethylene oxide) and natural polymer (gum karaya) with drug to polymer ratio 1:0.5 and 1:0.625 respectively were final optimized formulations. These were further characterized by Fourier Transform Infrared Spectroscopy (FTIR) which indicated that there was no interaction between drug and polymers.\(^\text{15}\)

Padminavathy \textit{et al.} (2011) outlined a systematic approach for designing and development of ofloxacin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of ofloxacin have shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by wet granulation technique using HPMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lag time, total floating time, swelling index and \textit{in vitro} drug release. It was found that the hardness of the tablets affects the buoyancy characteristic of the dosage form. All six formulations possessed good floating properties with total floating time between 8 – 12 hrs. The \textit{in vitro} cumulative percentage drug release of the formulations F1A, F1B, F2A, F2B, F3A and F3B were 102.85%, 101.32%, 100.2%, 99.98%, 99.28% and 97.25%.\(^\text{16}\)

Patil \textit{et al.} (2011) carried out a study on development of floating tablets of Ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC K100M as swelling polymers, with sodium bicarbonate as gas generating agent and were evaluated for parameters such as weight variation, hardness, friability, drug content, swelling index, \textit{in vitro} buoyancy study & \textit{in vitro} drug release study. All the formulation showed compliance with pharmacopeia standards. Based on the evaluation results, F3 and F6 formulations were selected as the best formulations and were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release profile of the best formulations was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation.\(^\text{17}\)

Yadav \textit{et al.} (2011) prepare floating microballoons consisting of (i) calcium silicate as porous carrier; (ii) propranolol hydrochloride (PRH), an oral anti-hypertensive agent; and (iii) Eudragit S as polymer, by solvent evaporation method and to evaluate their gastroretentive and controlled release properties. The effect of various formulation and process variables on the particle morphology, micromeritic properties, \textit{in vitro} floating behavior, percentage drug entrapment, and \textit{in vitro} drug release was studied. The gamma scintigraphy of the optimized formulation was performed in albino rabbits to monitor the transit of floating microballoons in the
gastrointestinal tract. The propanolol hydrochloride-loaded optimized formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters of propanolol hydrochloride from floating microballoons. The microballoons were found to be regular in shape and highly porous. Microballoons formulation CS4, containing 200 mg calcium silicate showed the best floating ability (89 ± 4% buoyancy) in simulated gastric fluid as compared with other formulations. Release pattern of propanolol hydrochloride in simulated gastric fluid from all floating microballoons followed Korsmeyer model and Peppas-Korsmeyer model. Prolonged gastric residence time of over 6 h was achieved in all rabbits for calcium silicate based floating microballoons of propanolol hydrochloride. The enhanced elimination half life observed after pharmacokinetic investigations in the present study is due to the floating nature of the designed formulations18.

Semalty et al. (2010) The floating microspheres of ofloxacin were formulated to develop gastroretentive formulation. These floating microspheres release the drug in the stomach and upper gastrointestinal tract and thereby improve the bioavailability. In the present study, six formulations of ofloxacin hydrochloride were prepared as floating microspheres by solvent diffusion technique using polymers such as ethyl cellulose, polyvinyl pyrrolidone K-90 and polyvinyl alcohol in different ratios. The prepared microspheres were evaluated for different physicochemical tests such as particle size, percent drug entrapment, drug content uniformity, SEM, buoyancy test, and in vitro drug release studies. The results of all the physicochemical tests of all formulations were found to be satisfactory. In vitro floatability studies revealed that most of the microspheres (52.5% to 95.5%) were floatable. The in vitro drug release was found to be in the range of 39.64 to 93.64 % at the end of 6 hours. It is concluded that these floating microspheres can be selected for the development of gastroretentive drug delivery system of ofloxacin hydrochloride for potential therapeutic uses19.

Gupta et al. (2010) prepared floating tablets of Acyclovir containing polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose (HPMC) as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time and tablets were prepared by wet granulation method. On the basis of evaluation parameter formulation AV4 selected as developed formulation20.

Durgapal et al. (2010) prepared floating microparticle drug delivery system of ofloxacin. In the present study ofloxacin floating microsphere as oral controlled system were prepared by the different techniques like non aqueous solvent evaporation technique, Different polymers like ethyl cellulose (EC), acrycoat L100, acrycoat S100, hydroxy propyl methyl cellulose (HPMC) were used in individually or in combination for the preparation of microspheres21.

Chandiran et al. (2010) were investigated the use of biodegradable polymers for microencapsulation of aceclofenac using solvent evaporation technique.Poly lactic acid was selected as a retardant polymer and Four different batches of microspheres were prepared by varying the concentration of polymer. The microspheres were characterized for drug content, percentage yield and encapsulation efficiency, particle size analysis and surface morphology. Microsphere prepared with high drug content produces higher percentage yield and encapsulation efficiency values. It was observed the increase in concentration of the polymer, increases the mean particle size of the microspheres. The effect of polymer concentration on the in vitro release of aceclofenac from the microspheres was also studied. It can be seen that by increasing the polymer concentration, decreases the rate of drug release from the microspheres dramatically. The kinetics of drug release from F1 and F2 microspheres predominantly follows Higuchi pattern followed by zero order and then first order. The release kinetics of F3 and F4 predominantly follows zero order followed by Higuchi and then first order22.

Deepa et al. (2009) developed floating microspheres of cefpodoxime proxetil in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The microspheres were prepared by non-aqueous solvent evaporation method using polymers such as hydroxyl propyl methyl cellulose (HPMC K 15 M), ethyl cellulose in different ratios and cefpodoxime proxetil in each formulation. In vitro drug release were performed by USP apparatus type I and the microspheres were characterized by polymer compatibility by using FT-IR. The yield, particle size, Buoyancy percentage, drug entrapment efficiency, and in vitro drug release were studied. The result showed that microspheres yielded 50.5-72.2%. The particle size was distributed between75-600 μm, drug entrapment efficiency was 14.1-28.2%, and Buoyancy percentage was 70.1-88.3%. The best drug release profiles were seen with formulation 2 at the ratio of drug to polymer of 1:223.

Yadav et al. (2009) developed floatable hollow microspheres of ofloxacin designed to increase its residence time in the stomach without contact with the mucosa having potential for intragastric sustained drug delivery. Floating microspheres were prepared using emulsion-solvent diffusion method, which involved co-dissolution of drug and Eudragit RS-100 & Eudragit S-100 in various ratios in ethanol: dichloromethane mixture (1:1 v/v), which was finely dispersed in the aqueous medium. In vitro testing revealed that the hollow microspheres floated continuously over the surface for more
than 24 hours. The drug release profiles from floating microspheres reflected their enteric behavior.

Abhishek et al. (2009) studied preparation and evaluation of floating microspheres using famotidine (FM) as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the solvent evaporation technique, using polymers such as hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum. The best formulation (F4) was selected based on in vitro drug release studies and the drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration on the size of the microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (18 h) and remained buoyant for more than 12 h. The mean particle size increased and the drug release rate decreased at a higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. In vitro studies demonstrated a diffusion-controlled drug release from the microspheres. Chi-square test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. In vitro data obtained for floating microspheres of FM showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

Bomma et al. (2009) developed to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by the wet granulation technique, using polymers such as hydroxypropyl methylcellulose and xanthan gum. The best formulation (F4) was selected based on in vitro characteristics and was used in vivo radiographic studies by incorporating BaSO4. These studies revealed that the tablets remained in the stomach for 180 ± 30 min in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs. Optimized formulations F4 and F9 with HPMC floated with a lag time of less than 1 minute and continued to float for 24 h. Formulation F16, with xanthan gum, floated with a lag time of 9 min and continued to float for 24 h. Floating lag time of xanthan gum tablets was reduced by using lactose. In vivo radiographic studies revealed that F4 tablets remained in the stomach for 180 ± 30 min, which indicated that GRT was increased by the floating principle and was considered desirable for improving bioavailability of the absorption window drugs.

Prabu et al. (2009) encapsulated aceclofenac within biodegradable polymer rosin and evaluated the effect of different formulation variables such as concentration of drug, polymer, polyvinyl alcohol and solvent. Microencapsulation is a useful method which prolong the duration of drug effect significantly and improves patient compliance. The meaning of microencapsulation is converting liquids to solids, altering colloidal and surface properties, providing environmental protection and controlling the release characteristics by using the coating materials. Emulsion solvents, phase-separation method and spray drying method are commonly used for the preparation of microspheres. The prepared batches were characterized for microspheres particle size distribution, encapsulation efficiency, and in vitro release behavior. The study reveals that drug:polymer ratio had a considerable effect on the entrapment efficiency, however particle size distribution of microspheres was more dependent on the volume of dichloromethane and polyvinyl alcohol concentration rather than on the drug:polymer ratio. Drug, polymer concentrations were varied to obtain optimum release profile for sustaining the action of the drug.

Bhowmik et al. (2009) carried out the development and characterization of microencapsulated bioadhesive vaginal gel (MBVG). Metronidazole encapsulated microcapsules were prepared by thermal change method using ethyl cellulose as rate controlling polymer in different ratios. The microcapsules were found to be discrete, spherical with free flowing properties. The selected microcapsule formulation MC3, containing drug: polymer ratio 1:4 was incorporated in gels with a variety of bioadhesive polymers. The MBVGS were evaluated for pH, spreadability, extrudability, viscosity, vaginal irritation test, in vitro drug release, drug release kinetics, bioadhesion test, accelerated stability of selected gel formulation. In vitro drug release rate for selected MBVG (F5 gel, containing 1% w/w of drug loaded microcapsules and 0.6% w/w of carbopol 974) was found to sustain metronidazole over 36 h obeying zero order kinetic with a good bioadhesion quality. The results were compared statistically and found with satisfactory correlation. Thus in conclusion preparation protocol of MBVG studied may be adopted for a successful development of newer drug delivery system of other drugs for administration to vagina.

Thakkar et al. (2008) developed floating levofloxacin tablets and to understand the kinetics of drug release by applying mathematical and model-dependent approaches. Nine formulations of floating tablets were prepared by the direct compression method using Gelucire (hydrophobic) and hydroxypropylmethylcellulose (hydrophilic) polymer in different ratios. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content,
**in vitro** buoyancy and **in vitro** release studies. Various models were used to estimate kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness-of-fit test and lowest sum of square residual and Fischer’s ratio. **In vitro** release study reveals that the release rate of drug was decreased by increasing the proportion of Gelucire 43/01, 5 to 40%. The release rate of levofloxacin hemihydrates from matrices was mainly controlled by the hydrophilic and hydrophobic polymer ratio. Matrix tablet containing 25% HPMC K4M and 15% Gelucire 43/01 showed a release as target profile. Novel mathematical approach was applied to determine the deviation in area under the curve between predicted and observed dissolution data which found to be lowest in optimal batch.

Garg et al. (2008) showed that controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method in which used ingredient are ethanol/dichloromethane, poly vinyl alcohol. Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window.

Mayavanshi et al. (2008) studied that gastric emptying is a complex process and in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 hours. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, pop rice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxyl propyl cellulose depending on the type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration: Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs.

Tanwar et al. (2007) prepared floating microspheres of verapamil hydrochloride for improving the drug bioavailability by prolongation of gastric residence time. Cellulose acetate, acrycoat S100 and eudragit S100 microspheres loaded with verapamil hydrochloride were prepared by solvent diffusion-evaporation method. The yield of the microspheres was up to 70.51% and cellulose acetate microspheres entrapped the maximum amount of the drug. Scanning electron microscopy confirmed their hollow structures with sizes in the range 251.80 to 350.75 µm Radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulphate floated on the gastric fluid for about 3.2 h. In vitro release studies demonstrated non-Fickian diffusion of drug from the microspheres.

Jain et al. (2006) studied to prepare floating microspheres consisting of calcium silicate as porous carrier; orlistat, an oral anti-obesity agent; and Eudragit S as polymer, by solvent evaporation method and to evaluate their gastro-retentive and controlled-release properties. The effect of various formulation and process variables on the particle morphology, micromeritic properties, in vitro floating behavior, percentage drug entrapment, and in vitro drug release was studied. The gamma scintigraphy of the optimized formulation was performed in albino rabbits to monitor the transit of floating microspheres in the gastrointestinal tract. The orlistat-loaded optimized formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters of orlistat from floating microspheres. The microspheres were found to be regular in shape and highly porous. Microsphere formulation CS4, containing calcium silicate, showed the best floating ability in simulated gastric fluid as compared with other formulations. Prolonged gastric residence time of over 6 hours was achieved in all rabbits for calcium silicate-based floating microspheres of orlistat. The enhanced elimination half-life observed after pharmacokinetic investigations in the present study is due to the floating nature of the designed formulations.

Dashora et al. (2006) concluded that the processing variables; polymer: drug ratio, agitation speed and stirring time affects the preparation of sustained release nimesulide microparticles by an emulsion solvent evaporation process. Micro particulate systems of nimesulide (NIM) were prepared by modified solvent evaporation method using different variables such as polymer: drug (NIM) ratios (ethyl cellulose, EC: nimesulide, NIM) (1:9, 1:6 and 1:3), agitation speeds (500-1000 rpm) and stirring time (5-15 min).

Barhate Shashikant et al. (2005) developed multi particulate gastroretentive drug delivery system of Ketorolac trometamol. The gastro retentive drug delivery system can be prepared to improve the absorption and bioavailability of ketorolac trometamol by retaining the system into the stomach for prolonged period of time.
floating drug delivery system of ketorolac trometamol was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100 polymers in varying concentration.\textsuperscript{35}

Shrivastava et al. (2005) reported that the present study involves preparation and evaluation of floating microspheres with cimetidine as model drug for prolongation of gastric residence time. The microspheres were prepared by the solvent evaporation method using polymers hydroxyl propyl methyl cellulose and ethyl cellulose. Microspheres were prepared using a gradually increasing EC concentration in combination with a fixed concentration of HPMC to assess the effect of polymer concentration on the size of microspheres. In vitro data obtained for floating microspheres of cimetidine showed excellent floatability, good buoyancy and prolonged drug release.\textsuperscript{36}

3 Conclusions

From above discussion it has been observed that the gastro retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of various drugs.

4 References


