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Solvent evaporation technique: An innovative approach to increase gastric retention

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Abstract
Floating dosage forms are emerging as a promising novel dosage forms, these can be retained in the stomach for a prolonged period of time and release the active ingredient in a predetermined manner. In exploration of this avenue, different novel strategies have been undertaken for the designing of floating systems including floating microspheres. Polymeric floating microspheres are ideal vehicles for many controlled delivery applications due to their ability to encapsulate a variety of drugs, biocompatibility, high bioavailability and prolonged drug release characteristics. To achieve these goals various techniques have been developed for preparation of floating microsphere, among them solvent evaporation is an effective approach. Present review addresses the general description of the floating system, floating microspheres, solvent evaporation process, various research findings based on solvent evaporation technique.

Keywords: Floating drug delivery system, G.I.T., Floating microsphere, Solvent evaporation technique

1. Introduction
The pharmaceutical industry and the medical profession in association with progress and innovation in the field of technology are making efforts to develop controlled release dosage forms for many drugs [1, 2]. Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To overcome these drawbacks, the oral controlled release formulations have been extensively used to enhance therapy with better bioavailability [3-5]. However, such oral drug delivery devices have a physiological limitation of short gastric retention time (GRT), variable and short gastric emptying time can result in incomplete drug release from the drug delivery system in the absorption zone (stomach or upper part of the small intestine), leading to diminished efficacy of the administered dose [6]. Moreover, the transit time of a drug delivery system along the GI tract is the most limiting physiological factor in the development of a controlled release dosage forms. In addition, the physical state of the drug delivery system, either a solid or a liquid, also influences the transit time through the GI tract [7].
Control over placement of a drug delivery system in a specific region of the GI tract offers numerous advantages; especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of drug delivery system with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption [8, 9]. Various attempts have been made to prolong the retention time of the dosage form in the stomach. One such approach is the preparation of a device that remains buoyant in the stomach contents due to its lower density than that of the gastric fluids; therefore gastroretentive systems have been developed [10].
Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems. These systems can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site [11]. Controlled gastric retention of solid dosage forms helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [12]. An effective approach of achieving this is through the prolongation of the gastric residence time employing several gastroretentive drug delivery mechanisms such as the use of floating systems, high density systems, magnetic systems, mucoadhesive systems, swelling/expanding systems, superporous hydrogels and the inclusion of gastric motility retarding agents with biocompatible polymeric materials [13-17]. Among the various approaches employed to increase the retention time of an oral dosage form, floating drug delivery system is considerably easy and logical approach in the development of gastro retentive drug delivery systems [18].

2. Floating drug delivery systems (FDDS)
Floating dosage forms also referred to as low density systems because these systems have a bulk density less than the gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time with the potential for continuous release of the drug. While the system is floating on the gastric content, the drug is released slowly at the desired rate and after release of the drug; the system is eliminated from the body. This results in an increased GRT and a better control of fluctuations in plasma drug concentrations [19-23]. The most commonly used excipients are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers [24]. Various approaches have been used for the design of floating dosage forms such as a single unit and multiple unit floating systems [25].
However, many floating systems reported in literature are single-unit systems which are unreliable in prolonging the gastric residence time owing to their ‘all-or-nothing’ emptying process and, thus, may result in high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple-unit dosage forms can be formulated in various forms such as

microspheres, granules, pellets, beads etc. [26]. In these systems, the dosage of the drug is divided on a plurality of the subunit, typically consisting of thousands of spherical particles and each discrete unit exhibiting some desired characteristics [27]. After oral administration, multiple unit systems retain their structure in GIT and each unit acts as an individual entity [28]. Multiple unit systems are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. Recently, much emphasis has being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, low risk of local irritation and predictable gastric emptying [29].

Floating microspheres

Floating controlled release dosage forms cover a wide range of prolonged action formulations, which provide a continuous release of their active ingredients in a controlled and predetermined manner. One such approach is using polymeric microspheres as carriers for various therapeutic agents. Microspheres based drug delivery systems have received considerable attention in recent years. A microsphere is a homogenous or a monolithic structure made of one or more miscible polymers in which particulate drug is dispersed throughout the matrix at either the macroscopic (particulates) or molecular (dissolution) level [30]. Floating microspheres are multiple-unit dosage forms, and are considered that the majority of particles will remain above the stomach contents for an extended period of time. This approach reduces the inter subject variability in absorption, lowers the probability of dose dumping and bursting associated with the single-unit systems. It has also been described that multiple unit floating dosage forms, distribute more uniformly within the gastric content, resulting in long lasting effects [31]. Furthermore, floating microspheres have high loading capacity and enormous synthetic and natural polymers have been widely employed. Spherical polymeric microsponges, also referred to as "micro-balloons" have also been reported; moreover, microspheres have a characteristic internal hollow structure and showed an excellent *in vitro* floatability.

3. Approaches for development of floating microspheres

A variety of techniques for the development of floating controlled release microspheres have been developed by various scientific and technological investigators [32]. The selection of the technique depends on the nature of the polymer, the drug and their intended use. In preparation of floating controlled release microspheres, the choice of the optimal method has the greatest importance for the efficient entrapment of the active drug substance [33]. Different development techniques are used for the fabrication of floating microspheres such as solvent evaporation, ionotropic gelation method, phase separation, interfacial polymerization and spray drying technique etc. [34]. However, the solvent evaporation technique has been extensively used by a large number of researchers worldwide to explore the different vistas of floating microspheres.

Solvent evaporation technique

Development of floating microspheres by solvent evaporation method has been applied extensively in pharmaceutical industries for various purposes such as controlled drug delivery, masking the taste and odour of drugs, protection of drug degradation [35]. This method involves the emulsification of an organic solvent containing dissolved polymer and dissolved dispersed drug in an excess amount of continuous phase, with the help of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation [36]. In solvent evaporation technique, there are basically two systems which include single and multiple emulsion solvent evaporation technique [37].

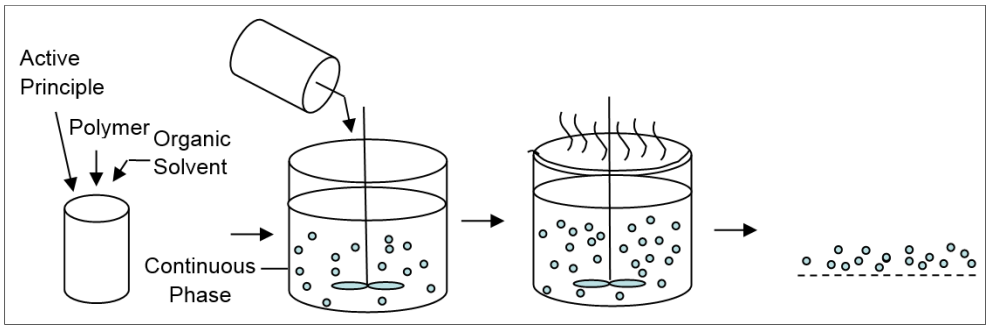

Fig. 1: Schematic overview over of principal process steps in microsphere preparation by solvent evaporation technique

Single emulsion solvent evaporation technique

In case of single emulsion solvent evaporation technique, there are also two systems such as oil-in-water (o/w) and water in oil (w/o). For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used [38]. This method is the simplest and effective method for the preparation of floating microspheres. In this method, the polymer is dissolved in organic solvents such as dichloromethane, chloroform or ethyl acetate, either alone or in combination as shown (figure 1), which had been used by various scientific investigators in their study. The drug is either dissolved or dispersed in polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a

stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavities in microspheres, thus making them hollow to impart the floating properties [39-42].

Oil-in-oil emulsification process is also sometimes referred as water-in-oil or non-aqueous emulsification solvent evaporation. In this process, either drug alone or drug and polymers are codissolved at room temperature into polar solvents such with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at specified revolutions per minute (rpm) and room temperature over a required period of time to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whatmann filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators.

Multiple emulsion technique

Multiple emulsion or double emulsion technique is appropriate for the efficient incorporation of water soluble peptides, proteins and other macromolecules. In this process the polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form an emulsion. The primary emulsion is reemulsified into an aqueous solution containing an emulsifier to produce multiple w/o/w dispersion. The organic phase acts as a barrier between the two aqueous phases, preventing the diffusion of the active material toward the external aqueous phase. Microspheres developed by w/o/w method exhibit various characteristics such as porous or nonporous external shell layer enclosing hollow, macroporous, or microporous internal structures depending on different parameters. These methods utilize high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. Afterwards, the solidified microparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants and finally, the product is lyophilized [43].

Microencapsulation by the solvent evaporation method is a complex process, which can be influenced by many process parameters, e.g., solvent type, solvent evaporation rate, temperature, solubility of polymer, drug and excipients in both emulsion phases, dispersion stirring rate, viscosity, solubility, volume and volume ratio between the inner and outer phases, the quantity of polymer and drug, and the physico-chemical properties and concentration of the stabilizer [44]. In this manuscript we have highlighted various significant research findings in the area of floating microspheres which represents variations in processes affecting parameters and operating conditions varied by various scientific investigators.

4. Research findings on solvent evaporation technique

Pandit *et al*., (2012) developed floating microspheres of metformin hydrochloride using ethyl cellulose polymer an emulsion solvent evaporation method. The objective of this study was to formulate floating microspheres in order to increase residence time at the site of absorption and thus improve its bioavailability; and to extend the duration of action along with possibilities of dose reduction. The pharmacokinetic and pharmacodynamic evaluation of selected formulation was carried out in male wistar diabetic rats. The data was statistically analyzed by unpaired t-test and in vivo studies has shown increased bioavailability and sustained action for more than 24 h with biological half life of 14 h [45]. Goswami *et al*., (2012) prepared and evaluated floating microspheres of valacyclovir HCl to localize the drug at the upper part of GIT for improved absorption. Microspheres were prepared by w/o emulsification solvent evaporation method using ethyl cellulose as a rate controlling polymer. Drug excipients compatibility studies and surface characterization were carried out using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and SEM respectively. *In vitro* and *in vivo* studies confirmed floating behaviour and concluded valacyclovir HCl loaded floating microspheres can be a suitable alternative to the conventional formulation, by localizing the drug at upper GIT [46].

Wasnik *et al*., (2012) prepared and characterized the floating drug delivery system of azithromycin as a model drug for eradication of *Helicobacter pylori* (H. pylori). Floating microspheres were prepared by solvent evaporation method using ethyl cellulose and hydroxyl propyl methyl cellulose polymer. Prepared microspheres were subjected to evaluation of particle size, incorporation efficiency, *in vitro* buoyancy and *in vitro* drug release characteristics. Attempts have been made to study the effects of stirring rate during preparation, polymer concentration, temperature on the size of microspheres and drug release characteristics. The results of this study indicated that the floating microspheres were formulated to provide site specific delivery of drugs with a view to provide an effective and safe therapy for eradication of *H. pylori* with a reduced dose and reduced duration of therapy [47]. Shah *et al*., (2012) fabricated floating microsphere of atorvastatin and sustained the drug release for a longer time in the upper GI tract to overcome the first pass metabolism of drug. Floating Microspheres with different in drug polymer ratio and revolutions per minute were formulated by non-aqueous solvent evaporation method with calcium carbonate acts as an effervescent agent. SEM and FTIR study of optimized has shown satisfactory result in terms of morphology and compatibility respectively. Model fitting analysis revealed the release pattern was following Higuchi model [48].

Al-Abadi *et al*., (2011) developed floating microspheres of gabapentin using polymers ethyl cellulose and cellulose acetate by the solvent evaporation method. The microspheres were characterized for their particle size, shape, percentage yield, drug entrapment, buoyancy ratio, drug- polymer interaction and *in-vitro* drug release kinetics. In addition, the effects of the polymer type, polymer: drug ratio, solvent system compositions and temperature on the microspheres characteristics were studied. And finally the mechanism of drug release from the most of the batches was mainly a fickian mechanism [49].

Saravanan *et al*., (2011) developed and evaluated ethyl cellulose floating microspheres loaded with ranitidine HCl by novel solvent evaporation-matrix erosion method. Scanning electron microscopy was used to characterize the surface morphology and revealed the presence of pores on the surface

of floating microspheres due to matrix erosion, which are responsible for floating ability. FTIR, DSC and X-ray diffraction (XRD) studies indicated intact and amorphous nature of the entrapped drug in the microspheres [50]. Josephine *et al*., (2011) prepared floating microspheres using eudragit RS 100 as a rate controlling polymer and stavudine as an antiretroviral drug. A reversed-phase liquid chromatographic (RP-HPLC) method was developed for the purpose of the research work. The floating microspheres were evaluated for micromeritics properties, particle size, % yield, *in vitro* buoyancy, incorporation efficiency and drug release. *In vitro* stavudine release data showed that all the prepared formulations released stavudine in a controlled manner for over 12 h [51].

Jelvehgari *et al*., (2010) designed sustained release floating microparticles of theophylline using two polymers of different permeability characteristics; Eudragit RL 100 and cellulose acetate butyrate by oil-in-oil emulsion solvent evaporation method. Encapsulation efficiency, the yield, particle size, floating capability, morphology of microspheres, XRD, and DSC were evaluated. Microspheres prepared with cellulose acetate butyrate showed the best floating ability in 0.1 M HCl more than 12 h. The XRD and DSC showed that theophylline in the drug loaded microspheres was stable and in crystalline form [52]. Vijaya *et al*., (2010) developed a floating multiparticulate unit system for metoprolol tartrate, using a porous carrier, with an outcome for delayed gastric emptying. Dried microparticles of metoprolol tartrate were prepared by solvent evaporation using eudragit RS-PO, polypropylene foam powder, and dichloromethane as release-rate modifying polymer, floating aids and solvent respectively. The developed microparticles showed suitable release properties, were free-flowing and exhibited good floating ability in rabbit stomach [53].

Kamila *et al*., (2009) prepared floating microspheres of rosiglitazone maleate by encapsulating the drug into Eudragit RS100 through nonaqueous emulsification solvent evaporation method. *In vitro* performances of microspheres were evaluated by percentage yield, particle size analysis, drug entrapment efficiency, *in vitro* floating behaviour, surface topography, drug–polymer compatibility, the crystallinity of the drug in the microspheres, and drug release studies. *In vitro* release was optimized by a {3, 3} simplex lattice mixture design to achieve predetermined target release. *In vivo* evaluation in albino rats suggested that floating microspheres of rosiglitazone could be a promising approach for better glycemic control [54]. Choudhary *et al*., (2010) formulated floating microspheres of carbidopa/levodopa to enhance their efficacy by increasing their gastric residence time, which is a major technique to improve efficacy of narrow absorption window drugs. The microspheres were prepared by the o/w emulsion-solvent diffusion method using polymers HPMC K15 M and ethyl cellulose. The effects of various formulation and process variables on the particle size, *in vitro* floating behaviour, percent drug entrapment, and *in vitro* drug release was studied. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression analysis demonstrated diffusion-controlled drug release from the microspheres [55].

Bhardwaj *et al*., (2010) prepared and evaluated floating microballoons of indomethacin as a model drug to increase its residence time in the stomach. The microballoons were prepared by the emulsion solvent diffusion technique using different ratio of acrylic polymers eudragit RS100 and eudragit S100 as carriers. SEM confirmed their spherical size, perforated smooth surface and a hollow cavity in them. Microballoons exhibited floating properties for more than 10 h. *In vitro* drug studies were performed in 0.1 M HCl with 0.1% sodium lauryl sulphate and phosphate buffer (pH 6.2). Different drug release kinetics models were applied for selected batches [56]. Senthilkumar *et al*., (2010) developed and evaluated floating microspheres of rabeprazole sodium as a model drug. Floating microspheres were prepared by solvent evaporation method using different polymers like hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose and chitosan. The average diameter and surface morphology of prepared microspheres were characterized by optical microscope and SEM respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using linear regression method. The microspheres were also investigated for buoyancy profile and incorporation efficiency [57].

Garg *et al*., (2010) prepared floating microspheres of silymarin by emulsion-solvent evaporation method using ethyl cellulose, HPMC and eudragit S100. Prepared microspheres were evaluated for flow properties based on parameters such as angle of repose and compressibility index, as well as for various other physicochemical properties including particle size, incorporation efficiency, *in vitro* floatability, *in vitro* drug release and surface morphology of the microspheres were characterised by SEM. The microspheres exhibited prolonged drug release for 12 h while still remained buoyant. Drug release kinetics, evaluated using the linear regression method, followed Higuchi kinetics and drug release mechanism was of the non-Fickian type [58]. Patil *et al*., (2009) prepare floating microspheres of acyclovir using different viscosities of ethyl cellulose to achieve an extended retention in the upper GIT which results in enhanced absorption and thereby improves bioavailability. The floating microspheres were prepared by emulsion solvent diffusion technique and triethyl citrate was used as a plasticizer. *In vitro* release study indicated that when the polymer concentration was increased and the drug loading was decreased, the release of drug from microspheres was decreased [59].

Rao *et al*., (2009) formulated and evaluated floating microspheres of rosiglitazone maleate for the prolongation of gastric residence time. Microspheres were prepared by the solvent diffusion evaporation method using ethyl cellulose and HPMC K100M. A 3^2 full factorial design was applied to optimize the formulations. Preliminary studies revealed that the polymer: drug ratio, concentration of polymer, and stirring speed significantly affected the characteristics of microspheres. The optimized batch exhibited a prolonged drug release and remained buoyant for more than 12 hours [60].

Garg *et al*., (2008) fabricated floating microspheres of acyclovir by emulsion solvent evaporation method using polymers HPMC, ethyl cellulose. SEM confirms the hollow nature of microspheres with pores on the surface of floating microspheres, which imparts floating properties to the prepared floating microspheres. The mean particle size increased and the drug release rate decreased at higher polymer concentration [61].

Mastiholimath *et al*., (2008) fabricated gastroretentive floating microparticulate system of an anti-ulcer drug, ranitidine HCl, through ethyl cellulose capable of floating on simulated gastric fluid for more than 12 h. Preparation of microparticles is done

by the solvent evaporation technique with modification by using an ethanol co-solvent system. *In vivo* bioavailability studies performed on rabbits and Tmax, Cmax, AUC were calculated and confirmed significant improvement in bioavailability [62].

Junyaprasert *et al*., (2008) developed and characterized floating properties and release characteristics of hollow microspheres of acyclovir. The hollow microspheres of acyclovir were prepared by the solvent evaporation diffusion method using eudragit S 100 as a controlled polymer. The hollow microspheres tended to float over 0.1 M HCl containing 0.02% tween 20 solutions for 24 h. The rate of acyclovir released from the microspheres was generally low in simulated gastric fluid without enzyme due to the low permeability of the polymer [63]. In another study Varshosaz *et al*., (2007) developed and characterized floating microballoons for oral delivery of cinnarizine by diffusion solvent evaporation technique to increase drug solubility and hence its bioavailability. The effect of process variables such as: Eudragit type, stirring rate and time of stirring after addition of the oily phase to the aqueous phase was evaluated on the yield, particle size, loading, release and floating behaviours of microspheres using a $2^{[3]}$ factorial design [64].

Wei *et al*., (2008) performed *in vitro* and *in vivo* evaluation on ranitidine HCl loaded hollow microspheres in rabbits. Hollow microspheres were prepared by novel solvent diffusion evaporation method using ethyl cellulose dissolved in a mixture of ethanol and ether. Pharmacokinetic analysis showed that the bioavailability from ranitidine HCl hollow microspheres alone was about three times that of common ranitidine hydrochloride gelatin capsules [65]. Nepal *et al*., (2007) developed floating microspheres with practical applications to fish farming. Each microsphere with a central hollow cavity was prepared using a solvent evaporation method with Eudragit E100 as polymer. Various manufacturing parameters were investigated by the single factor method. The macrolide antibiotic josamycin was selected as a model drug and loading efficiency of the drug in the microspheres was 64.7% [66]. Furthermore Tanwar *et al*., (2007) prepared and evaluated floating microspheres of verapamil HCl for improving the drug bioavailability by prolongation of gastric residence time. Cellulose acetate, acrycoat S100 and eudragit S100 loaded floating microspheres were prepared by the solvent diffusion evaporation method. Radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulphate floated on the gastric fluid for about 3.2 h and *in vitro* release studies demonstrated non-Fickian diffusion of the drug from the microspheres [67].

Kale *et al*., (2007) in another study developed multiple units floating drug delivery system of piroxicam using eudragit S polymer by the emulsification solvent evaporation method. Prepared microspheres remained buoyant continuously over the surface of acidic media for a period of 8-12 h [68]. Formulation and evaluation of floating microspheres of cimetidine have been done by Srivastava *et al*., (2005) to prolong the gastric residence time of the drug. The microspheres were prepared by the solvent evaporation method using polymers HPMC and ethyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method [69].

Similarly Patel *et al*., (2006) also reported *in vitro* evaluation and optimization of controlled release floating microspheres of metformin HCl. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique using ethyl cellulose as the rate controlling polymer. In this study, a two-step design was followed. In the first step, a central composite design was followed to study the effect of formulation variables on product characteristics. In the second step, a simplex lattice mixture design was followed to optimize the desired release profile using minimum number of experiments [70]. Jain *et al*., (2005) prepared and evaluated porous carrier based floating microspheres using calcium silicate as porous carrier, orlistat as an oral anti-obesity agent; and eudragit S as polymer by the solvent evaporation method. The gamma scintigraphy of the optimized formulation was performed in albino rabbits to monitor the transit of floating microspheres in the gastrointestinal tract. The enhanced elimination half-life observed after pharmacokinetic investigations [71].

In another study Jain *et al*., (2009) also designed floating microspheres by the emulsion solvent diffusion technique consisting of calcium silicate as a porous carrier; repaglinide, an oral hypoglycemic agent; and eudragit S as polymer by emulsion solvent diffusion technique consisting to increase its residence time [72]. Working on similar grounds Kouchak *et al*., (2007) prepared and evaluated multiple-unit oral floating system by emulsification-solvent diffusion method to prolong the gastric emptying time of theophylline using ethyl cellulose as polymer. Microballoons prepared at higher stirring rates released their drug content faster. Also, it is concluded that particle size and floating capability of microballoons could be adjusted by altering the stirring rate during microencapsulation [73]. In another research Deepa *et al*., (2009) developed floating microspheres of 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 by non-aqueous solvent evaporation method [74].

Sato *et al*., (2004) investigated the effect of physicochemical properties to determine the buoyancy of floating hollow microspheres prepared by the emulsion solvent diffusion method using eudragit S 100 polymer and riboflavin as a model drug. It was found that preparation temperature determined the formation of cavity inside the microsphere and the surface smoothness, determining the floatability and the drug release rate of the microsphere [75]. Streubel *et al*., (2006) developed low density foam-based, floating microparticles of diltiazem HCl and theophylline. Floating system was prepared by solvent evaporation method using a polypropylene microporous foam carrier, eudragit RS and polymethylmethacrylate polymers. The effects of various formulation and processing parameters on the resulting *in vitro* floating behaviour, internal and external particle morphology, drug loading, *in nitro* drug release and physical state of the incorporated drug were studied. The low density microparticles were compressed into rapidly disintegrating tablets in order to provide an administrable oral dosage form [76].

In addition floating-bioadhesive microballoons containing acetohydroxamic acid have been formulated by Umamahesvari *et al*., (2002) for clearance of *Helicobacter pylori*. Microballoons were prepared by a novel emulsion solvent diffusion method and characterized for size distribution, morphology, drug content, drug release, and *in vitro* floating property. The results suggested that acetohydoxamic acid

loaded floating microspheres are superior as potent urease inhibitors, whereas urease plays an important role in the colonization of *Helicobacter pylori* [77]. Lee *et al*., (1999) developed an oral drug delivery system with an internal hollow structure by a solvent diffusion and evaporation method. Floating microspheres were prepared using eudragit S100 as a rate controlling polymer with optimum rotation speed and temperature were 250 rpm and 25°C, respectively. Different drugs with various physico-chemical properties were used as model drugs for encapsulation and release tests. The release profiles were significantly different depending on the solubility of a drug in the release medium [78].

Another study has been developed by Stithit *et al*., (1998) and objective of this study was to prepare floating theophylline microspheres with zero order release profiles for use as buoyant reservoirs with increased retention time in the stomach. The microspheres were prepared by a modified emulsion-solvent evaporation method using a polymer mixture of cellulose acetate butyrate and Eudragit RL 100 (1:1). The resulting microspheres were characterized for size distribution, morphology, density, drug-polymer content, buoyant capacity and drug release behaviour. The microspheres were spherical with relatively smooth surfaces with round hollow cavities. The dissolution profiles of the floating microspheres showed near zero order kinetics and sustained release [79].

Various merits of the solvent evaporation technique are given in the following text:

Solvent evaporation is the oldest and most widely used method to encapsulate the variety of therapeutic agents.

- Technique of microencapsulation by solvent evaporation is widely applied in pharmaceutical industries to obtain the controlled release of the drug.
- Prolonged drug release dosage forms have outstanding clinical benefits, reducing dosing frequency, more convenience and acceptance for patients.
- Site specific drug delivery can be achieved.
- Floating microspheres are multiple unit dosage forms and release drug uniformly and there is no risk of dose dumping.
- Solvent evaporation method allows for the creation of microparticles which shows less inter and intra subject variability.
- A variety of film forming polymers can be used as coatings in this technique.
- Unlike other methods where the temperature sensitive compounds are degraded and control of particle size is difficult, solvent removal method is free from the disadvantages of phase separation inducing agents.
- Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

5. Conclusion

Floating drug delivery technology has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Floating microspheres developed by solvent evaporation technique are effective for release rate of target drug to a specific site and facilitates an enormous impact on health care. The properties of materials and the process engineering aspects strongly influence the properties of the microspheres and the resultant controlled release rate. Therefore the years to come should continue to yield innovative ideas including significant improvement of the physicochemical and toxicological properties of the actual formulations on the market. Thus, preparation technologies capable of producing larger amounts of microspheres in a safe, economical, robust and well-controlled manner are therefore required.

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