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Review

A Floating System for Drug Delivery using Microballoons

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ABSTRACT: Gastro-retentive floating microspheres were developed as a result of the recent advancements in floating delivery systems for drugs (FDDS), which included the uniform dispersion of multiparticulate dosage forms along the GIT. This could lead to more consistent drug absorption and a lower risk of local irritation. Microballoons (MB), a multi-unit extended release with a sphere-shaped cavity encased in a tough polymer shell, have been developed as a dosage form with exceptional buoyancy in the stomach. This preparation for constrained intestinal absorption is made to float on top of gastric acid, that has a relative density lower than 1. By using enteric acrylic polymers and the emulsion solvent diffusion method, microballoons are prepared and filled to drug in one's outer polymer casings. Enteric acrylic plastics are used to generate microballoons that are drug-loaded in one's external polymer casings and dissipate in a solution of dichloromethane and ethanol. Cavity development in microparticles seems to be particularly correlated with dichloromethane evaporation. Microballoons with a drug distributed or dispersed all through the particle-matrix have the potential for a controlled drug release and float continuously for more than 12 hours in vitro out over the surface of an acidified dissolution medium with surfactant. The drug is released slowly and at the desired rate as the microballoons glide over the components of the stomach, increasing gastro-retention time and lowering fluctuations in plasma concentration.

KEYWORDS: Gastro retentive drug delivery systems; non-effervescent systems; floating drug delivery systems; microballoons; CRDDS

1. Introduction

Traditional oral dosage forms, like capsules and tablets deliver a specific concentration of the medication in the blood circulation that does not release over time at a constant rate. By attempting to regulate its own release into the body with smaller and less frequent doses, a buccal drug delivery offers drug release at a pre-controlled, suitable frequency, either systematically or locally, for the intended duration of time. This system maximizes a drug's therapeutic effect.¹

1.1. Floating drug delivery system

Davis described a floating system for delivering drugs (1968). These are low-density structures with enough buoyant force to hover over stomach contents. The drug is released slowly at a constant rate from the system whereas the structure is floating on the stomach contents. The residual system is expelled from the stomach after the drug is released. This improves bioavailability by lowering drug fluctuations, raising GRT, and increasing GRT. There have been many developed floating system which is based on grains, particles, caplets, tablet devices, sheeting films, beads, and empty microcapsules.^{2,3}

It could be divided into two different systems:^{4,5}



1.1.1. Effervescent System

Systems containing volatile liquids (Intragastric floating GRDDS)

Devices for gas production (Intra gastric single layer and bilayered floating tablets, Multiple unit type floating pills)

1.1.2. Non-Effervescent Systems

Barrier systems based on hydrocolloid gel

System of micro porous compartments

Beads of alginate and pectin

Microspheres that are hollow (Microballoons)

2. Hollow Microspheres / Microballoons:

Microballoons seem to be non-effervescent gastro-retentive drug-delivery structures. Microballoons (Hollow microspheres) are, strictly speaking, blank spherical particles without any core. These microspheres were indeed typically free-flowing powders composed of proteins or synthetic materials, with a size of less than 200 micrometres.⁶

Microballoons are one of the most beneficial buoyant systems because of the core hollow space within the microsphere, which has the special advantages of multi - input frameworks and better-floating properties. Among the novel methods used in their preparation are the simple solvent removal method, the emulsification diffusion method, the single emulsification technique, the twofold emulsification technique, the phase separation coacervation technique, the polymerization technique, the spray drying and spray congealing method, and the hot melt encapsulation method. The type of polymer, plasticizer, and solvents used during preparation have a significant impact on the floating properties and rate of drug release. In the preparation of hollow microspheres, polymers like polylactic acid, Eudragit® S, as well as hydroxy propyl methyl cellulose cellulose acetate are used, and drug release can be modulated by optimising encapsulation efficiency and the polymer-plasticizer ratio.⁷

To develop a hollow internal structure in hollow microspheres/microballoons filled with drug in their outer polymeric matrix, innovative techniques including such evaporation of the solvent or solvent diffusion/evaporation are used. The drug and an enteric acrylic polymer mixture are dispersed in ethanol/dichloromethane solution and poured into an agitated Poly Vinyl Alcohol (PVA) solution that is thermally controlled at 40°C. The organic solvent is evaporated from the emulsion after it has formed a stable emulsion through raising the temperature under stress or by vigorous stirring.⁸ The vapour phase is created in the hollow inner cavity of a polymer microsphere with drug by both the vaporisation of dichloromethane with in droplet of dispersed polymer. For more than 12 hours, the Microballoon floats continuously upon that exterior of just an acidified dissolution media containing surfactant.^{9,10}

3. Microballoons and Hollow Microspheres Flotation Mechanisms:

A gel constitutes once stomach acid and floating microcapsules or microballoons are brought into contact, moisturizing polymeric materials to create a colloidal gel barrier that controls the rate of fluid permeability into the device and, consequently, release of the drug. The gel layer is maintained as the outer surface of the dosage form dissolves by the moisture of the adjacent hydrocolloid layer. The trapped air in the swollen polymer lowers the density of the microspheres and gives them buoyancy. But even so, a negligible gastric content is needed to achieve appropriate buoyancy.¹¹

Table 1: Components needed to prepare Micro balloons ¹²

Components and goal	Examples
Polymers - control the drugs release rate	Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocel, Polyacrylates, Polyvinyl Acetate, Carbopol, Agar,

	Polyethylene oxide, Polycarbonates, Acrylic resins and Polyethylene etc.
Solvents - should have high volatile characteristics, allowing them to quickly separate from the emulsion, having left hollow microspheres.	Ethanol, Dichloromethane (DCM), Acetonitrile, Acetone, Isopropyl alcohol (IPA), Dimethylformamide (DMF)
Processing Medium - When the drug liquid solution is began pouring into it, it is used to harden the drug polymer dispersed droplets and must not interact with both the former.	Liquid paraffin, Polyvinyl alcohol and Water
Surfactant - they seem to be stabilisers or dispersants that also serve to toughen the microspheres.	Tween 80, Span 80 and SLS.
Cross-linking agent - used it to cross-link microspheres chemically	Formaldehyde, Glutaraldehyde or by using Di acid chlorides such as Terephthaloyl chloride
Hardening agent - aids inside the hardening of microspheres constructed inside the processing medium	n-hexane, Petroleum ether (in case the processing medium is liquid paraffin)

4. Hollow microsphere/micro balloon preparatory techniques:

Various scientific and technological researchers have developed a different methods for both the advancement of controlled-release microspheres that float. The technique chosen is determined by the characteristics of a polymer, the drug, and the intended use.¹³ Several methods, including evaporation of the solvent, ionotropic gel formation, emulsification, inter-facial polycondensation, and spray drying, are used to create floating microparticles.¹⁴ But even so, a lot of researchers from all over the world have used the solvent removal method to look into the various vistas of floating microspheres. There are two types of solvent evaporation techniques: mono and numerous emulsion solvent evaporation techniques.¹⁵

4.1. Solvent evaporation method:

Polymers used for the advancement of these mechanisms include Eudragit, HPMC KM4, and ethyl cellulose, among others. Polymers are combined with drugs and then dissolved in ethanol, acetone, or dichloromethane solutions, alone or in combination, to produce a homogeneous polymer solution. The solution is then continued to pour in to the 100 mL of liquid paraffin and rotated at 1500 rpm. The emulsion is formed and heated for 3 hours at 350°C. The acetone or dichloromethane is entirely disappeared just after formation of a stable emulsion, and the resulting solidified microspheres are filtered using Filtered through whatmann filter paper. The floating and sustained characteristics are provided by the hollow microspheres.¹⁶ (Fig 1).

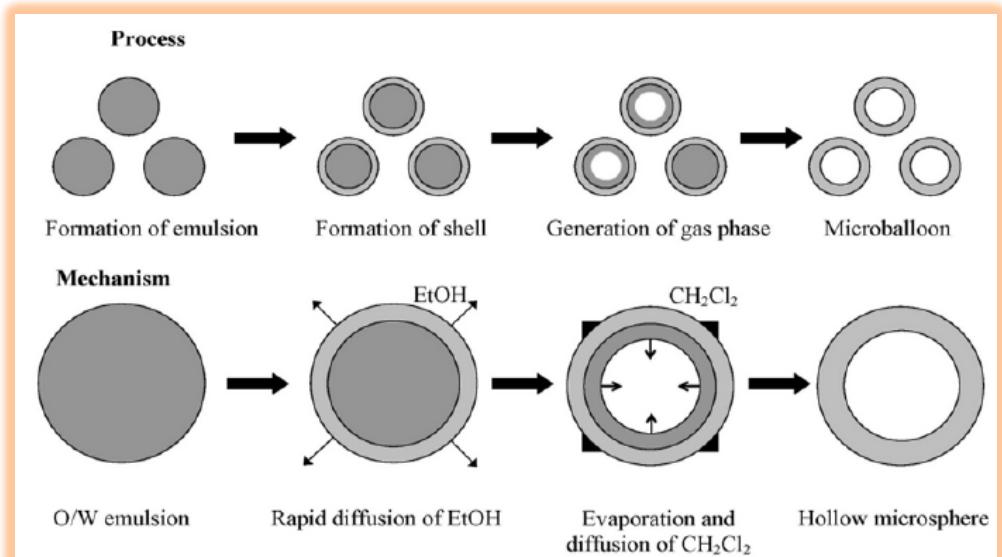


Fig 1: Solvent evaporation method.

4.2. Emulsion-based solvent diffusion method:

Drop by drop, the ethanol: dichloromethane solution that contains the drug-polymer mixture is added to the polyvinyl alcohol solution. The aforementioned mixture is blended at various temperatures for an hour at 1500 rpm.¹⁷

The attraction between both the drug and the solvent is stronger inside the diffusion of emulsion solvents method than between the organic solvent and the aqueous solvent. Despite the fact that the organic solvent is miscible, the drug is dissolved within it and the solution is dispersed in the appropriate solvent, resulting in emulsion droplets. The organic solvent gradually diffuses out of the dispersed phase into the surrounding aqueous phase, and the aqueous phase diffuses into the droplets, causing the drug to crystallize.¹⁸ (Fig 2).

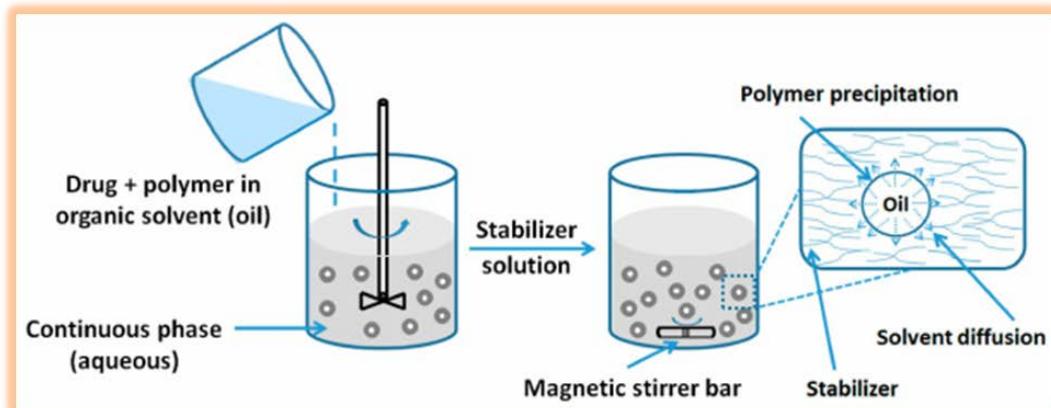


Fig 2: Emulsion solvent diffusion method

4.3. Solvent diffusion evaporation technique:

Both the emulsion solvent diffusion technique and the emulsion solvent diffusion technique have been slightly modified in this technique. At room temperature, the drug, polymers, and 0.1% emulsifier such as PEG are mixed in an ethanol: dichloromethane (1:1) solution. This solution is gradually added to 80 ml of 0.46% w/w polyvinyl alcohol as an emulsifier. This is stirred for 1 hour with a propeller agitator to allow the organic solution to evaporate before being filtered. The best formulation is chosen based on the optimised results of various processing parameters including such polymer ratio, drug:polymer ratio, stirring speed, and emulsifier concentration as shown in (Fig3).¹⁹

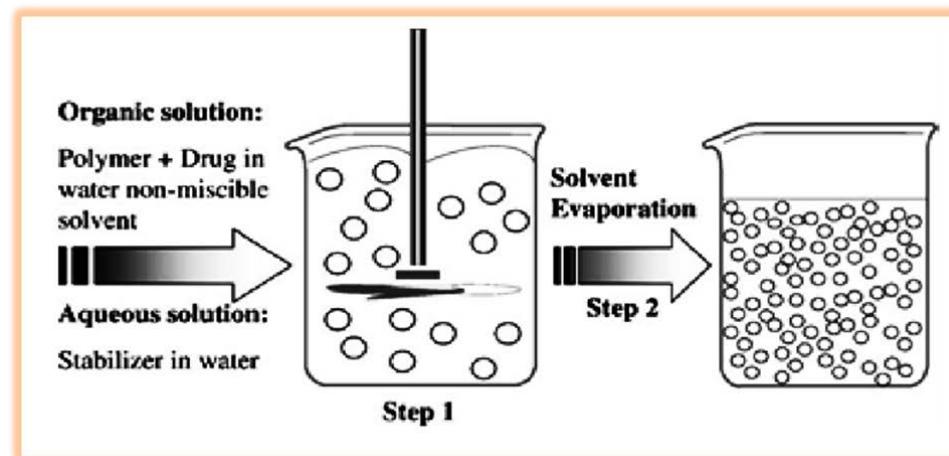


Fig 3: Solvent diffusion evaporation technique.

4.4. Sprayed Drying:

Spray drying is by far the most widely employed particulate forming and drying method. It is an ideal process because it can achieve the desired distribution of particle size, bulk density, and particle shape in a single step.²⁰

To begin, a slurry of polymer is formed inside an appropriate organic volatile solvent such like dichloromethane, acetone, etc. After spraying the mixture into the drying chamber, a gradient of concentration of the solute forms within the small droplet, with both the greatest concentration at the droplet surface. This is because the time it takes for the solute to diffuse is longer than the time it takes for the solvent in the drops to evaporate even during drying process. Following that, a solid shell forms, which leads to the formation of microspheres. The solid products are usually separated from the gases using a cyclone separator, whereas the trace amounts of solvent have been eliminated by evaporation of the solvent and the product lines are stored for later use.²¹ (Fig 4).

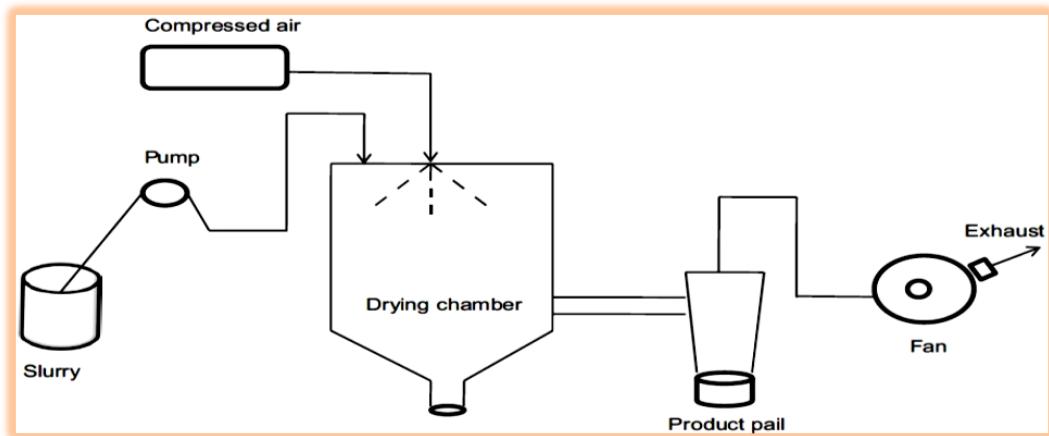


Fig 4: Sprayed drying technique.

5. Physical and chemical characteristics of Hollow Microspheres/Micro balloons:

The solvent removal technique of microcapsules is a complicated task that may be impacted by the succeeding process variables.²²

5.1. Stirring rate:

The microparticles - size of the nanoparticles is affected by the agitation speed. The size of microparticles reduces as stirring speed increases. It is possible that increasing the stirring speed the polymer's main body is broken up into smaller particles²³.

5.2. Preparation's Temperature:

It has an impact on the permeability and morphologies of microspheres. Lower-temperature microspheres (20 or 30°C) produce highly permeable microspheres with larger porosity and an irregular surface. Hollow microspheres prepared at 40°C have a higher roundness and smoother surfaces than empty microparticles prepared at lower temperatures. Because there is no cavity in empty microparticles prepared at higher temperatures (50°C), they have an elevated evident particulate density and low buoyancy. At 40 degrees Celsius, the drug and polymers combined to form a shell that was created by the instantaneous evaporation of dichloromethane and the diffusion of ethanol into the aqueous phase²⁴. The particle size decreases as that of the preparatory temperature rises. At extreme temps, the emulsification becomes less thick and much easier to break into smaller particles with the force of mixing input.²⁵ Microspheres made at high temperatures have a homogeneous porous structure distribution.

After their initial drug release, microparticles constituted at extremely high temperatures have very slow release rates. Faster solvent evaporation results in a plain surface, round shape, and lesser encapsulation.

5.3. Admixtures:

It will make the microsphere material's external surface extra resilient and flexible, preventing from becoming brittle or rupturing under pressure. The drug release from microparticles significantly increases as the plasticizer concentration was increased²⁶.

5.4. Volume of aqueous phase (Continuous phase):

The particle size is reduced as the capacity of the aqueous medium rises, so the buoyancy rises. The possible advantage of just using high quantities of the aqueous environment is that the necessary stirring times are reduced. Dichloromethane is 1% w/v miscible in aqueous, and in higher quantities (400 to 500 milliliters), dispersion into the aqueous solution and particle solidification took place faster than in smaller volumes (200 milliliters) of the outer aqueous phase²⁷.

5.5. Ratio of solvents:

The connecting liquid is essential in the creation of microspheres. Whenever a good solvent disperses into a poor solvent, causing the drug and polymer to precipitate, a bridging liquid has to be present to keep the microsphere's spherical shape. Too little connecting liquid can result in irregularly shaped microsparticles, while too much connecting liquid can protect emulsified particles from cementing. As a result, the quantity of dichloromethane must be carefully monitored²⁸. The proportion of dichloromethane to ethanol affects the morphology of the microspheres, so the ratio was optimised to achieve the best circular morphology. The best results with perfectly circular shape are obtained when the ethanol to dichloromethane ratio is 2:1²⁷.

5.6. Viscosity and polymer content:

Relatively small microparticles will then constituted as lesser polymer concentrations as well as it will have a greater external area exposed to the solubilization medium, resulting in higher drug release²⁹. The rheology of the medium increases as polymer concentration increases, resulting in increased surface tension. Snipping efficiency decreases with increasing viscosity, leading to the formation of bigger particles. The yield of hollow microspheres decreases as viscosity increases, while mean radius and dosage of a drug load increase. Solubility and dissolution profiles could be slowed by raising the amount of polymer in preparations, and particle diameter, external characteristics of microparticles, and solubilization can be altered by varying the drug-to-polymer ratio.³⁰.

5.7. Effect of solvent:

Because it is a good solvent for most polymers and drugs, dichloromethane is used as the polar inner organic denatured alcohol for the manufacture of microparticles. However, it is discovered that now the microparticles produced by it are not spherical in nature. To address this issue, methanol is combined with dichloromethane in the process of making microparticles. The resulting microparticles are oval in appearance but doesn't have a plain surface. To overcome this issue, scientists skeptically screen various solvents based on boiling points, including dichloromethane (39.75 °C), acetone (56.5 °C), methanol (64.7 °C), and ethanol (78.4 °C). Because of boiling point increased from DCM to ethanol, ethanol should be used in place of DCM/methanol for the best results. The majority of water-soluble drugs as well as water-insoluble polymeric materials are dissolved in ethanol which is non-toxic and regarded as a good solvent. Because ethanol has a higher boiling point than other solvents such as dichloromethane, acetone, and methanol, it prevents

immediate polymer precipitation, and the resulting microspheres are completely round with a plain surface³¹.

5.8. Concentration of emulsifying agent:

In addition to preventing drops from crashing into one another and forming agglomerates, the emulsifying agent (surfactant) lowers the surface tension between the continuous and dispersed phases. Drops are more probable to collide and fuse to form larger globules at lower emulsifier concentrations because there is insufficient emulsifier to protect the whole particle surface. The encapsulation efficiency decreases as the emulsifying agent concentration increased. As a result, the optimal emulsifier concentration should be determined.³².

6. Characterization of Microballoons:³³

6.1. Micromeritic properties:

Micromeritic characteristics including such particle diameter, flow properties (Angle of Repose, Hausner's Ratio), and density distinguish floating microspheres. The fixed funnel method is used to calculate the angle of repose, and the compressibility index is calculated by observing the change in volume with a bulk density apparatus.

6.2. Interactions between drugs and excipients:

This is accomplished through the use of Fourier-transform infrared spectroscopy (FTIR). The DE connection is indicated by the emergence of the newest peak and/or the vanishing of the existing drug or inactive ingredients peak.

6.3. Scanning electron microscopy (SEM):

A scanning electron microscope is used to examine the texture and inner structure of the floating multi particulates morphologically (SEM).

6.4. The use of differential scanning colorimetry and X-ray diffraction:

It's indeed crucial to know the physiological state of a drug in multiple unit structures. As during process, the crystallisation of the drug could alter, and such changes will affect the release of drug characteristics. The crystalline phase of a drug can be investigated using the X-ray powder diffraction (XRD) technique and differential scanning colorimetry (DSC).

6.5. Floating Behavior:

It's indeed crucial to know the physical state of a drug in multiparticulate structures. As during process, the crystallisation of the drug could alter, and other such changes will affect the release of drug characteristics. The crystalline phase of a drug could be investigated using the X-ray powder diffraction (XRD) method as well as differential scanning colorimetry (DSC).

$$\text{Buoyancy (\%)} = (\text{W}_f / (\text{W}_f + \text{W}_s)) \times 100$$

Where the weights of the settled and floating microspheres, respectively, are W_f and W_s.

6.6. % of drug-related entrapment:

The ability to produce floating microparticles is thoroughly mixed, then suspended in a small amount of solvent. The suspension was then filtered to completely separate rock fragments. The drug components were examined, and the following equation was used to determine the percentage of drug entrapment.

$$\text{% Drug Entrapment} = (\text{Actual drug content} / \text{Theoretical drug content}) \times 100$$

6.7. Tests for *in vitro* dissolution:

A USP apparatus and a paddle are typically used for *in vitro* dissolution tests. With 900 ml simulated gastrointestinal fluid (PH 1.2, no enzymes) as the dissolution medium and a rotation speed of 50–100 rpm, the drug's *in vitro* release from microspheres is investigated at 37°C predetermined time intervals, an aliquot of 5 ml of solution was withdrawn and replaced with 5 ml of fresh dissolution medium. Any appropriate analysis technique, such as UV spectroscopy or HPLC, was used to analyse samples at highest wave length.

7. Conclusion:

Micro-balloons seem to be innovative drug delivery systems that are made to float for an extended period of time over the stomach contents. Floating micro-balloons have the benefit of remaining buoyant and uniformly dispersed over the gastric fluid, avoiding variations in gastric acid secretion and allowing the drug to be released for extended periods of time. Microballoons precisely control the rate of target drug release to a particular site as gastric retaining pharmaceutical formulations. Floating micro-balloons are especially promising for the development of a gastro-retentive drug delivery system with therapeutic properties.

References:

1. Kumar R and Philip A. Gastro retentive dosage forms for prolonging gastric residence time. *Int J Pharm Med.* 2007; 21(2): 157-171.
2. Yang L, Fassihi R. Zero order release kinetics from self-correcting floatable configuration drug delivery system. *J. Pharm. Sci.* 1996; 85: 170-173.
3. Chickering DE, Jacob JS, Mathowitz E. Bioadhesive microspheres II: Characterization and evaluation of bioadhesion involving hard, erodible polymers and soft tissue. *Reactive polymers.* 1995; 25: 189-206.
4. Dhole AR, Gaikwad PD, Bankar VH, Pawar SP, A Review on Floating Multiparticulate Drug Delivery System. A Novel Approach to Gastric Retention, *IJPSRR.* 2011; 6(2): 205-211.
5. Somwanshi SB, Dolas RT, Nikam VK, Gaware VM, Kotade KB, Dhamak KB and Khadse AN, Floating Multiparticulate Oral Sustained Release Drug Delivery System. *J.Chem. Pharm. Res.* 2011; 3(1): 536-547.
6. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier System, New Delhi: CBS Publishers and Distributors; 2002, 417-54.
7. Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J. Pharm. Sci.* 1992; 81: 135-140.
8. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powdering. *J. Pharm.* 2002; 241(2): 279-292.
9. Pujara ND, Patel NV, Thacker AP, Raval BK, Doshi SM, Parmar RB. Floating microspheres: A novel approach for gastro retention. *World journal of pharmacy and pharmaceutical sciences.* 2012; 1(3): 872-89.
10. Garg R, Gupta GD. Progress in controlled gastro retentive delivery systems. *Trop. J. Pharm. Res.* 2008; 7(3): 1055-1066.
11. Gayathridevi M, Adlin JNJ, Tamizh MT. Floating microsphere: a review. *International Journal of Research in Pharmacy and Chemistry* 2016; 6(3): 501-510.
12. Ritesh K, Surbhi K, Amrish C, Pawan K, Gautam, Vijay KS. Microballoons: an advance avenue for gastro retentive drug delivery system-a review. *UK Journal of Pharmaceutical and Biosciences* 2016; 4(4): 29-40.
13. Lassalle V, Ferreira ML. PLA Nano-and microparticles for drug delivery: An overview of the methods of preparation. *Macromolecular Bioscience* 2007; 7(6):767-783.
14. Watts PJ, Davis MC, Melia CD. Microencapsulation using emulsification/solvent evaporation: An overview of techniques and applications. *Critical Reviews in Therapeutics Drug Carrier Systems.* 1990; 7(3):235-258.
15. Soppimath V, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug delivery systems to increase gastric retention of drugs. *Drug Metabolism Reviews.* 2001; 33(2):149-160.
16. Joshi VK, Jaimini M. Microballoons drug delivery system: A review. *AJPRD.* 2013; 1(1): 7-17.
17. Patel DM, Patel MJ, Patel CN. Multi Particulate System: A Novel Approach in Gastroretentive Drug Delivery. *IJAPR.* 2011; 2(4): 96-106.
18. G Saneshan V, Krishna Kanth VSVSP. Preparation and *in vitro* evaluation of microballoon drug delivery system of Telmisartan. *Int. J. Pharm. Sci. and Drug Res.* 2013; 5(4): 141-145.
19. Sharma Megha, Kohli Seema, Dinda Agnimitra. *In vitro* and *in vivo* evaluation of Repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer. *Saudi Pharm. J.* 2015; 23: 675-682.

20. G Saneshan V, Krishna Kanth VSVSP. Preparation and *in vitro* evaluation of microballoon drug delivery system of Telmisartan. *Int. J. Pharm. Sci. and Drug Res.* 2013; 5(4): 141-145.
21. Sharma Megha, Kohli Seema, Dinda Agnimitra. In vitro and in vivo evaluation of Repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer. *Saudi Pharm. J.* 2015; 23: 675-682.
22. Behera AL, Patil SV, Sahoo SK. Formulation and characteristics of 5flourouracil microspheres by solvent evaporation method. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2011; 3(1):32-35.
23. Srivastava AK.; Ridhurkar DN.; Wadhwa S. Floating microspheres of cimetidine: Formulation, characterization and in vitro evaluation. *Acta Pharm* 2005; 55:277-285.
24. Kothawade, S. N., & Pacharne, V. M. (2018). Formulation And Evaluation of Liquid And Solid Self Micro Emulsifying Drug Delivery System of Eprosartan Mesylate. *International Journal of Pharmaceutical Sciences and Research*, 9(12), 5333-5338.
25. Sato, Y, Kawashima Y, Takeuchi H, Yamamoto H. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. *Eur. J. Pharm. Biopharm* 2003; 55: 297-304.
26. Kothawade, S. N., Kadam, N. R., Aragade, P. D., & Baheti, D. G. (2010). Formulation and characterization of telmisatan solid dispersions. *International Journal of PharmTech Research*, 2(1), 341-347.
27. Reddy KVR, Chowdary PS, Naik Factors affecting microspheres formation. *Amt J Pharm Tech Res* 2015; 5(2).
28. Bagmar Ujwala, R., Redasani, V. K., & Kothawade Sachin, N. (2013). Preparation and in-vitro evaluation of loperamide hydrochloride spherical crystals by emulsion solvent diffusion technique. *Int J Pharm Pharm Sci*, 5(2), 409-13.
29. Patil MP, Patil HS, Bharat WT, Vinod MT, Patil VR. Formulation and in-vitro evaluation of floating microspheres of acyclovir. *Arch Pharm Sci Res.* 2009; 1: 194-198.
30. Kothawade, S. N., & Chaudhari, P. D. (2021). Development of Biodegradable Porous Starch Foam for Improving Oral Delivery of Eprosartan Mesylate. *Journal of Advanced Scientific Research*, 12(03 Suppl 1), 120-126.
31. Jain SK, Awasthi AM, Jain NK, Agarwal GP. Calcium silicate based microspheres of Repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization. *J. Control. Release.* 2005; 107: 3000-3009.
32. Pingale, P. L., Shinkar, D. M., & Kothawade, S. N. Formulation of Linseed Hydrogel-Based Floating Drug Delivery System for Gatifloxacin. *European Journal of Molecular & Clinical Medicine*, 7(05), 2020.
33. Hu R, Zhu J, Cheng G, Sun Y, Mel K, Li S. Preparation of sustained-release Simvastatin microspheres by the spherical crystallization technique. *Asian J. Pharm. Sci.* 2006; 1: 47-52.
34. Arane, P. M., Ghanwat, D. A., Boyane, V., Kothawade, S. N., & Doshi, P. (2011). Preparation and in Vitro Characterization of Eprosartan Mesylate Solid Dispersions using Skimmed Milk Powder as Carrier. *International Journal of Advances in Pharmaceutical Research*, 2(12), 658-665.
35. Gattani Y.S, Kawtikwar PS, Sakarkar DM. Formulation and evaluation of gastro retentive multiparticulate drug delivery system of aceclofenac. *Int J Chem Tech Res.* 2009; 1:1-10.
36. Baykara T, Kiliçarslan M. The effect of the drug/ polymer ratio on the properties of the verapamil HCl loaded microspheres. *Int J Pharm.* 2003; 52:99-109.
37. SN Kothawade, AS Lunkad, UR Bagmar. Formulation and Physical Characterization of Microcrystals for Dissolution Rate Enhancement of Telmisartan. *BioMedRx.* 2013; 1 (2): 188-194
38. Bornare PN, Avachat AM, Avachat MK, Patel KB. Jain KS. Development and characterization of sustained release microspheres of Ropinirole HCl: study of various process parameters. *AAPS*, 2009. T3219.
39. Nilkumhang N, Basit AW. The robustness and flexibility of an emulsion solvent evaporation method to prepare pH-responsive microparticles. *Int J Pharm.* 2009; 377:135-141.
40. Mukund JY, Kantilal BR, Sudhakar RN. Floating microspheres: A review. *Brazilian Journal of Pharmaceutical Sciences.* 2012; 48(1):1-7.