REVIEW ARTICLE

MICROBALLOONS: A PROMISING APPROACH FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM AND THEIR ADVANTAGES, LIMITATIONS, RECENT ADVANCEMENT IN DRUG DELIVERY SYSTEM, PATENTS AND FUTURE ASPECTS

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ABSTRACT

The key objective of the present review was to collect the latest literature on technological advancements towards microballoons as novelistic buoyant drug delivery systems. Microballoons are hollow microspheres with a potential approach for gastric retention, offering controlled release of the drugs. It offers prominent targeting of drugs in the stomach. More significantly, it is an anticipated drug delivery system in the gastrointestinal tract's upper section. At a high pH environment, this drug delivery system improves the solubility of less soluble drugs. It is an innovative and authenticated drug delivery system, specifically for those drugs which are unable to tolerate the acidic pH. The microballoons are developed by several techniques like Solvent Evaporation, Solvent Diffusion-Evaporation, Solvent Diffusion and Spray Drying techniques, to develop the space of empty inner core. Moreover, this manuscript covers significance, limitations, applications, list of polymers used, characterization, formulation design and evaluation parameters of microballoons.

Keywords: Microballoons, gastroretentive drug delivery systems, preparation method, advantages limitations, recent advancement

INTRODUCTION

Microballoons are spherical hollow particles without any core. They release the medication into the digestive tract over time and continue to keep a sustained, optimum dose in the systemic circulation[1]. They are designed to smash the drawbacks of the traditional system of drug administration leading to improvement in bioavailability, enhancing the availability of the drug candidates which are less soluble in the high pH environment, increasing the duration of drug release, and reducing the drug waste[2]. One of the strong candidates for developing floating drug delivery systems is a drug with low bioavailability owing to site-specific absorption, particularly from the upper part of the gastrointestinal tract. This will increase the drug's absorption. Floating Drug Delivery Systems (FDDS) are the types of gastroretentive delivery that keep themselves buoyant in an environment of the stomach for an extended time period, and along with that, having lower bulk density in comparison to the various gastric fluids. This system floats on the gastric fluid while also resulting in the slow release of the drug at the desired rate.

The residues of the system leave the stomach, after the completion of the drug release from the system. This outcome provides effective control in the variation of the plasma drug concentration, and it also enhances the gastric retention time of the system[3]. Microballoons are developed on the basis of a non-effervescent approach. Microballoons ideal size range is < 200 µm, it is in the form of free-flowing powder along with the incorporation of various synthetic polymers and proteins[4]. They offer

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good-floating properties because of the empty space in the center.

Table I: Drug candidates suitable for floating drug delivery system

Sr. No.	Drugs	Dosage form	References
1.	Ranitidine HCl, repaglinide, famotidine, glipizide	Hollow microspheres	5-8
2.	Acetylsalicylic acid, acetaminophen, sotalol, cinnarazine,	Floating tablets	9-14
3.	Chlordiazepoxide HCl, diazepam, misoprostol, propranolol	Floating capsule	15-18
4.	Indomethacin, prednisolone	Floating granules	19-20
5.	Ibuprofen, tranilast, verapamil, ketoprofen, piroxicam	Floating microspheres	21-23
6.	Cinnarizine	Films	24
7.	Propranolol hydrochloride	Microballoons	25-26

Table II: Marketed preparations of floating drug delivery systems

Sr. no.	Drugs	Brand	Reference
1.	Levodopa and Benserzide	Madopar	27
2.	Diazepam	Valrelease	28
3.	Aluminum magnesium antacid	Topalkan	29
4.	Antacid	Almagate Flot-Coat	30
5.	Alginic acid and sodium bicarbonate	Liquid Gaviscon	31
6.	Pantoprazole sodium, misoprostol, propantheline	Tablet Micro balloons	
7.	Famotidine	Tablet and powder for suspension	

The drug release pattern depends upon various factors like the type of plasticizer, polymer and solvents used. This carrier system boosts the bioavailability of drugs that aren't easily soluble in environments with high pH, lengthens the time they are released from the body, decreases drug waste, and improves bioavailability overall. Gastroretentive dosage forms significantly improve GIT pharmacotherapy through local drug release and elevated levels at the gastric mucosa, and they are useful in the treatment of oesophagitis, duodenal and gastric ulcers, among other conditions. Numerous medications are helpful for floating drug delivery systems that are enlisted in Table I[5-26]. Several readily available marketable products are based on the research activity in floating drug delivery Table II[27-31].

Advantages of microballoons as drug carrier

These systems offer enhanced gastric retention time and also increase absorption as well as bioavailability (furosemide, riboflavin etc.). Effective drug use will boost bioavailability and lessen side effects' frequency or intensity. Despite the first pass effect, constant drug release will maintain a constant plasma drug concentration by halting changes in plasma drug concentration. Hollow microspheres are used to decrease material density, increase the period of gastric retention due to buoyancy, and promote medicine absorption that only dissolves in the stomach. They are superior to floating dosage forms for one unit because they distribute drugs consistently and with no chance of dose dumping. Gastric irritation can be avoided due to the sustained release effect. It is able to maintain plasma drug concentration and provides a superior therapeutic efficacy of drugs with short half-lives that can be achieved[32-34].

Floating microballoons can transport medicines with site-specific absorption windows, such as antiviral, antifungal, and potent antibiotics. Antifungal, antiviral, and antibiotic medications are only absorbed from a specific condition of the GI mucosa. When it comes to reducing the primary side effects of gastrointestinal discomfort, microballoons are incredibly effective. For example, indomethacin comes in the category of floating microballoons of nonsteroidal anti-inflammatory medications[35].

Limitations of microballoons

Food and the pace at which the drug travels through the gut can both affect how quickly the controlled release dosage form releases its active ingredient. Any deterioration of the release properties of the dosage

Table III: Ingredients used for microballoons development[49-50]

Drugs	Polymer	Solvent	Processing medium	Surfactants	Cross-linking agents	Hardening agents
Narrow therapeutic window in GI tract, absorbed from stomach and upper GIT, locally act in stomach, degrade in the colon, disturb normal colonic bacteria		Volatile	Hardens drug polymer emulsified droplets	Stabilizers		
Aspirin, salicylic acid, ethoxybenzamide, indomethacin, riboflavin, para amino benzoic acid, furosemide, calcium supplements, chlordiazepoxide, cinnarazine, riboflavin, levodopa, antacids, misoprostol, ranitidine HCL, metronidazole, amoxicillin trihydrate	Cellulose acetate, chitosan, Eudragit, Acrycoat, Methocel, polyacrylates, polyvinylacetate, Carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins	Ethanol, dichloromethane (DCM), aceto-nitrile, acetone, isopropyl alcohol (IPA), dimethyl formamide	Liquid paraffin, polyvinyl alcohol, water	Tween ® 80, Span ® 80, sodium lauryl sulphate	Form-aldehyde, glutar-aldehyde, tere-phthaloyl chloride	n-Hexane, petroleum ether

form could potentially become toxic because controlled release formulations frequently have a higher drug load. Such dosage forms should not be eaten or mashed because this leads to variations in the release rate from dose to dose[36-37].

Polymers used for the preparation of microballoons

Drug delivery methods based on microballoons are created using a variety of synthetic and natural polymers. In order to create floating microballoons both hydrophilic and hydrophobic polymers are typically used. In order to create hollow microspheres, polymers including Polycarbonate, Eudragit® S, and cellulose base polymers like Cellulose acetate are employed. Controlling the amount of polymer and the polymer-plasticizer ratio will minimize the amount of medication released[38].

FACTORS AFFECTING THE PHYSICOCHEMICAL PROPERTIES OF MICROBALLOONS

Plasticizers

It gives the material's wall flexibility and elasticity, preventing brittleness or rupture under pressure, thanks to the plasticizer addition. Additionally, it was demonstrated that the drug's rate of release significantly increased when the plasticizer concentration increased[39].

Emulsifier concentration

When the concentration of surfactant is lowered to 0.25 % from 1%, the particle size and distribution get larger. Emulsifiers are essential because they reduce the friction at the interface between dispersed droplets and the continuous phase and prevent droplet colliding and coalescing[40,41].

Stirring rate

The particle size of the microspheres depends on the stirring speed. The microspheres's size reduces due to higher stirring even though the increment is statistically insignificant. Within the parameters of the investigation, the vast majority of polymers are difficult to disperse into tiny droplets[42].

Temperature

Various temperatures, including 20, 30, 40, and 50^{0}C, are used to add the medicine and polymer solution to an aqueous solution of polyvinyl alcohol. The microspheres along with the highest surface porosity reach their maximum porosity at 20 or 30^{0}C. As temperature rises, the size of the particle gets smaller. The viscosity of the emulsion decreases when the power of mixing input increases, or when the temperature rises, making the emulsion much more easily de-stabilized[43].

Ratio of solvent

While using a large volume of liquid to bridge the gap, it inhibits the solidification of emulsion droplets, small-volume solvent are bridging results in the formation of irregularly shaped microspheres. Dichloromethane must be carefully regulated in volume. The morphology of the microspheres is dependent on the dichloromethane to ethanol ratio. To produce microspheres with a spherical shape, the ratio must be tuned. Round microspheres are produced when ethanol and dichloromethane are mixed in a 2:1 ratio[44,45].

Viscosity

At lower polymer concentrations, smaller microballoons are produced, and since they have a larger surface area, they will release medications more quickly[46].

Solvent's effect

Dichloromethane is chosen as the solvent for the creation of microballoons because it is effective at dissolving pharmaceuticals and polymers. Methanol is utilized to address the issue that occurs when dichloromethane is employed, as the microspheres' shape is not spherical. Although the shape is spherical when methanol is used, in order to fix the uneven texture, ethanol is used in place of methanol[47].

Mechanism of drug release from microballoons

The active drug portion is released at a set rate as they float above the gastric juice. With this approach, the alteration of plasma drug concentration is reduced while gastric retention time is increased. While in contact with gastric fluid, the microballoons turn into viscous gel form and the polymers create a colloidal barrier which initiates the permeation of the fluid into the system and hence the drug released. Further, when the gel's outer surface dissolves, then the layer is sustained through the hydration of the adjoining hydrocolloid layer. Microballoons float because the expanded polymer is less thick than stomach fluid when air is trapped inside of it Table III[48-50].

METHODS OF PREPARATION OF MICROBALLOONS[51-55]

Solvent evaporation method

Polymers are added to the bio actives and dissolved in the preferred solvents like dichloromethane, acetone or ethanol, either alone or in combination solvents, for gaining a homogeneous system. After that, enough liquid paraffin should be added to the mixed solution, and it is rotated at 1500 rpm to create the emulsion. The emulsion is then heated at 35°C for 3 h to create a stable emulsion in which the solvent had fully evaporated. The solidified microspheres are then filtered through the Whatman filter paper (Fig. 1).

Emulsion-Solvent diffusion method

The polymeric drug mixture is dissolved in dichloromethane solvent before being added drop by drop to a polyvinyl alcohol solution that has been stirred continuously for an hour at 1500 rpm at varied temperatures. This method shows a better affinity between therapeutics and organic solvents rather than aqueous vehicles and organic solvents. The active substance is dissolved in an organic solvent, and the resulting solution is then distributed over an aqueous media to form emulsion droplets. As a result, as the organic solvent steadily diffuses from the emulsion into nearby water phase, the aqueous phase starts diffusing into the droplets through which the medicine crystallizes (Fig. 2).

Solvent Diffusion-evaporation technique

In this procedure, polymers and 0.1% surfactants, such as PEG (polyethylene glycol), are combined with ethanol and dichloromethane in a 1:1 ratio at room temperature. Now, the combined solution is gradually added to 80 mL of polyvinyl alcohol (emulsifier), which is 0.46% w/w, while being continuously stirred for an hour to evaporate the organic solution, and then filtered. Based on the optimized outcome, the most effective formulation is selected.

Spray drying method

Here, polymer is liquefied in a selected volatile organic solvent (dichloromethane, acetone, etc.) and then sprayed into drying compartment as a slurry. The solute's concentration gradient inside the tiny droplet reaches its highest concentration at the droplet surface because the solution has a longer diffusion time than during droplet drying procedures. A cyclone separator is used to separate the developing solid-shelled microspheres, and any remaining solvent is drawn out during the vacuum drying procedure (Fig. 3).

CHARACTERIZATION OF MICROBALLOONS

Particle size

A calibrated ocular micrometre is used to quantify mean particle size after measuring 100–200 particles under an optical microscope, by screening in the mechanical stirrer with an ASTM nest of normal sieves and a 15-minute shaking time. Calculations are done to determine the distribution of various microsphere sizes within each batch[56]. This equation was used to determine the percentage in each range:

% in each range = {number of particles/200} x 100

Buoyancy percentage

A reasonable number of unfilled microspheres are introduced to 900 mL of 0.1N HCl. The resultant mixture is agitated at 100 rpm for 8 to 10 h in a dissolving unit. The layers of buoyant microspheres are separate using a pipette and a filter after 8 to 10 h. The sinking particulate layer's suspended particles are eliminated through filtration. In a desiccator, both varieties of particles (buoyant and settling microspheres) are dried until they reach a constant weight[57,58]. The formula below was used to get the microballoons' percentage buoyancy:

$$\% \text{ buoyancy} = \frac{\text{Weight of floating microballoons after drying} * 100}{\text{Weight of floating + settled microballoons after drying}}$$

Recovery

The recovery of microballoons containing a medicine was determined using polymers, monostearin, and the weight ratio of the dried microballoons to the drug loading amount[59].

Apparent particle density

The projective image count method was used to calculate apparent particle density. On a glass plate, tiny balloons were put. Using a system for analyzing and processing images, Heywood's diameter and the quantity of microballoons were measured (Q5001W, Leica, Japan)[60].

Drug release

The release rate of empty microspheres is calculated by utilizing a dissolution apparatus of the United States Pharmacopeia (USP) XXIII basket type. The dissolution rate equipment containing the dissolution medium and a weighed quantity of empty microspheres (stuffed with a capsule of hard gelatin) equal to the drug's dose are placed within the basket. Both the temperature of the dissolving fluid and the rotational speed are held constant at a consistent rpm of 37±1^{0}C. The drug release analysis is conducted under ideal sink conditions. To assess the concentration of microballoons in the dissolution media, a sample of a 5 mL is collected at each time point and put through liquid chromatography/mass spectrometry analysis. For each withdrawal, 5 mL of new dissolving fluid is added, preserving the dissolution fluid's original volume. There are three runs of each test[61,62].

Angle of repose

The microballoons were kept flowing through a funnel that was angled so that the bottom tip was 2 cm above the ground in order to calculate the angle of repose. The microballoons were transferred into the funnel when the surface of the microballoons pile's tip touched it. Calculating the $\tan^{-1}$ of the ratio between the pile height and base radius yields the angle of repose[63]. The formula below was used to calculate the angle of repose:

$$\theta = \tan^{-1} \frac{h}{r}$$

Swelling percentage

The molecular characteristics of swollen polymers are ascertained by tests that measure swelling. Dissolution apparatus, optical microscopy, and other specialized methods including light scattering imaging, cryogenic electron scanning microscopy, confocal laser scanning microscopy, ^{1}H NMR imaging, and dissolution apparatus (USP dissolution apparatus USP-24) Lab India dissolution 2000), are specifically being used for measuring the swelling[64]. Percentage swelling was determined in triplicate using the equation below:

$$\text{Percentage swelling} = \frac{\{Ws - Wd\}}{Wd} \times 100$$

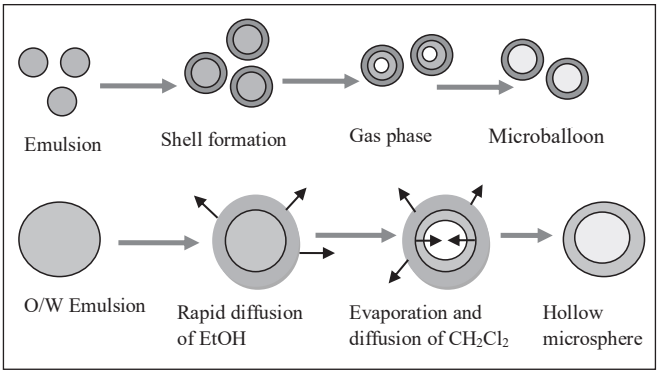

Fig. 1: Solvent evaporation method[109]

Percentage entrapment efficiency

To ascertain how much medicine is trapped, the microspheres are required to be smashed, and then extracted using aliquots of 0.1N HCl. The extract is required to be passed through 0.1N HCl to a volumetric 100 mL flask and made up the volume. The solution's absorbance in relation to a suitable blank is then calculated using a spectrophotometer[65]. The following equation is used to determine the percentage of drugs entrapped:

$$\% \text{ EE} = \frac{\{\text{calculated content of drug (x)}}{\text{theoretical content of drug}\}} \times 100$$

APPLICATION OF MICROBALLOONS

Due to their drastically varying densities, hollow and solid microspheres can be employed for a number of tasks. To lessen a material's density, hollow microspheres are widely utilized as additions. Depending on the material they are made of and the sizes they come in, solid microspheres have a wide range of uses. By concentrating drug concentrations at the gastric mucosa and localizing drug release, hollow microspheres can significantly improve stomach pharmacotherapy. This allows for the elimination of *Helicobacter pylori* from the submucosal tissue of the stomach and the treatment of stomach and duodenal ulcers, gastritis, and esophagitis.

These microsphere devices provide prolonged drug release properties and progressively release the medication. As a floatable, regulated medication delivery device, tranilast hollow microspheres are produced. Among the drugs lately found to be trapped in hollow microspheres are theophylline, ibuprofen, prednisolone, omeprazole, celecoxib, piroxicam, diltiazem hydrochloride, verapamil hydrochloride, riboflavin, aspirin, griseofulvin, and terfenadine. Floating microspheres can considerably improve the pharmacotherapy for the stomach by local medication release. Therefore, treating gastro-esophageal reflux illnesses, chronic gastritis, and peptic ulcers involves removing *H.pylori* from the sub-mucosal site of the stomach.

To treat *H. pylori* infection, floating bioadhesive microspheres containing acetohydroxamic acid have been produced. Hollow microspheres containing ranitidine hydrochloride are also produced for the treatment of stomach ulcers[66,67]. Floating microspheres are particularly useful for delivering insoluble and sparingly soluble medicines. As a medication's solubility increases, it is recognized that the overall time allowed for drug dissolution decreases, and as a result, transit time plays a crucial role in determining drug absorption. By restricting such medications to the stomach, hollow microspheres may avoid the danger that solubility will turn into the rate-limiting stage in release for weakly basic pharmaceuticals that are poorly soluble at an alkaline pH.

The sited gastric release is advantageous for medications that are efficiently absorbed through the stomach, such as verapamil hydrochloride. By changing the substance's absorption profile, the gastroretentive

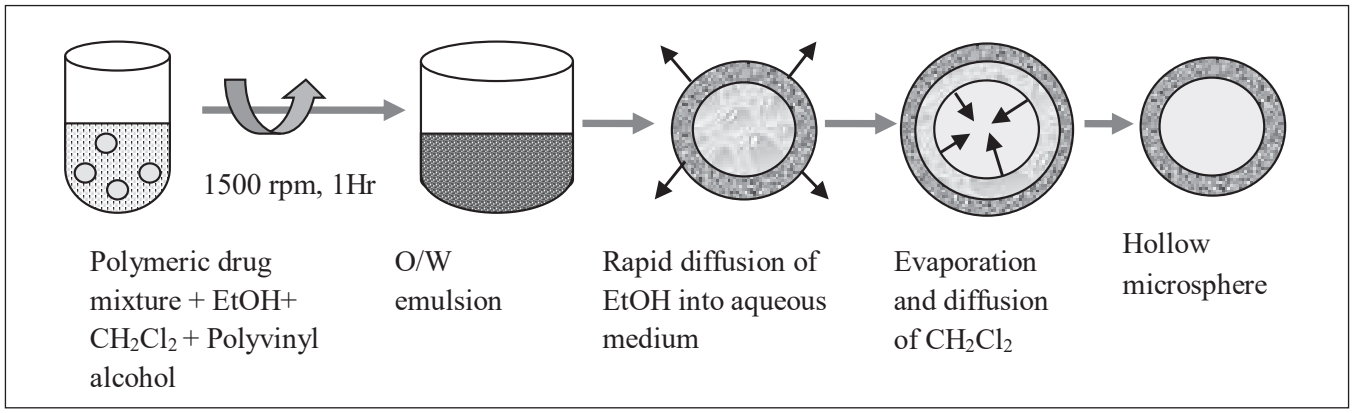

Fig. 2: Emulsion solvent diffusion method[110]

Table IV: Drug loaded microballoons prepared

Sl. No.	Name of Drug (Delivery system)	Ingredients (Polymer, Solvent, etc.)	Method of preparation	Result	Application	Reference
1.	Acebrophylline (Gastroretentive microballoons)	Hydroxypropyl methyl cellulose, Ethyl cellulose Ethanol: Di-chloromethane (1:1), Distilled water	Emulsion solvent diffusion	Controlled drug release for more than 12 h	Bronchial asthma treatment	69
2.	Pentoxifylline (Floating microballoons)	HPMC K4M, Ethyl cellulose, Ethanol: Di-chloromethane (1:1), Tween®80, Distilled Water	Solvent evaporation	Retarded drug release for 12 h	Peripheral arterial disease treatment	70
3.	Propranolol hydrochloride (Gastroretentive Floating microballoons)	Eudragit® S, Calcium Silicate, Polyvinyl Alcohol, Ethanol: Dichloromethane (2:1), Technetium-99 m	Solvent evaporation	Prolonged gastric residence time of over 6 h	Antihypertensive	71
4.	Domperidone (Floating microballoons)	Eudragit® RS100, HydroxyPropyl Methyl Cellulose, Ethanol: Dichloromethane (2:1), Polyvinyl Alcohol, Monostearin	Emulsion solvent diffusion	Sustained drug release over 12 h	Parkinson's disease treatment	72
5.	Domperidone (Floating microballoons)	Eudragit® RS100, Eudragit® RL100, Dichloromethane: Ethanol, Polyvinyl Alcohol	Emulsion solvent diffusion	Prolonged drug release for 12 h	Parkinson's disease treatment	73
6.	Riboflavin (Gastroretentive microballoons)	HPMC K4M, Ethyl Cellulose Ethanol: Dichloro-methane (1:1)	Emulsion solvent diffusion	Controlled drug release over 12 h	Ariboflavinosis treatment	74
7.	Theophylline (Multiple Unit Floating microballoons)	Ethyl Cellulose, Dibutylphthalate, Dichloromethane: Ethanol (3:7), Polyvinyl Alcohol, Sodium Chloride, Polysorbate® 80, Hydrochloric Acid	Emulsification-solvent diffusion	Microballoons floated on Simulated Gastric Fluid for more than 12 h	Asthma treatment	75
8.	Telmisartan (Gastroretentive microballoons)	Ethyl Cellulose, Polyvinyl Alcohol, Methanol: Dichloromethane (3:3), Tween®80	Emulsion solvent diffusion	Floating time of greater than 24 h	Antihypertensive	76
9.	Stavudine (Floating microballoons)	Eudragit® S100, Ethanol, Dichloromethane Heavy Liquid Paraffin	Emulsion solvent diffusion	Improved bioavailability, prolonged drug release for 24 h	HIV treatment	77

10.	Ketorolac trometamol (Floating microballoons)	HPMC K4M, Ethyl Cellulose, Dichloromethane, Sodium Lauryl Sulphate, Magnesium Stearate, Liquid Paraffin	Solvent evaporation	Microballoons floated on Simulated Gastric Fluid for more than 8 h	Anti- inflam-matory	78
11.	Nizatidine (Floating microballoons)	HydroxyPropyl Methyl Cellulose, Dichloromethane, Methanol, Polyvinyl Alcohol, Tween®20	Emulsion solvent diffusion	Sustained drug release over 12 h	Gastric Ulcer treatment	79
12.	Acetabulol hydrochloride (Floating microballoons)	Eudragit® RSPO, Dichloromethane: Ethanol (1:1)	Emulsion solvent diffusion evaporation	Sustained Drug delivery for 12 h	Asthma treatment	80
13.	Atenolol (Mucoadhesive microballoons)	Carbopol® 934P, Eudragit® RL100, Span® 80, Ethanol, Petroleum Ether, Olive Oil	Emulsion-solvent evaporation	Extended drug release for 12 h	Antihyper-tensive	81
14.	Glipizide (Mucoadhesive microspheres)	Sodium Alginate, Calcium Chloride, PEG 4000, HPMC K4M, Ethyl Cellulose, Petroleum Ether	Ionic Orifice Gelation	Controlled release pattern of drug up to 10 h	Antidiabetic	82
15.	Tolperisone hydrochloride (Floating microspheres)	Calcium Silicate, Ethyl Cellulose, Hydroxypropyl Methyl Cellulose, Methanol, Dichloromethane, Heavy Liquid Paraffin, Tween®80	Emulsion solvent diffusion	Controlled drug release for 12 h	Muscle Relaxant	83
16.	Orlistat (Gastroretentive microspheres)	Eudragit® RL100, Cellulose Acetate, Ethyl Cellulose, Polyvinyl Alcohol, Ethyl Acetate, Acetone, Ethanol	Solvent diffusion–evaporation	Prolonged drug release for 12 h	Obesity treatment	84
17.	Aceclofenac (microspheres)	Eudragit® S100, Eudragit® RL100, Eudragit® RS100, Sodium Lauryl Sulphate, Polyvinyl Alcohol, Chloroform, Methanol, Sodium Chloride, De-ionized Water	Solvent evaporation	Controlled drug release for 24 h	Anti-inflam-matory	85
18.	Esomeprazole (Floating Gastroretentive)	HPMC K4M, HPMA K15M, Ethyl Cellulose, Magnesium Stearate, Alcohol: Dichloromethane (1:1), Sodium Bicarbonate, Distilled Water, Liquid Paraffin, Span® 80, n-Hexane	Double emulsion solvent diffusion	Controlled drug release for 12 h	Antiulcer	86

19.	Rabiprazole sodium (Mucoadhesive microspheres)	Hydroxy Methyl Cellulose, Span® 80, Liquid Paraffin, Distilled Water, n-hexane,	Emulsification Solvent Evaporation	Sustained drug release for 12 h	Antiulcer	87
20.	Cimetidine (Floating microspheres)	Sodium Chloride, Dichloromethane, HydroxyPropyl Methyl Cellulose, Ethyl Cellulose, Tween®80, Water	Solvent Evaporation	Prolonged drug release (~8 h) and remained buoyant for > 10 h	Antiulcer	88
21.	Curcumin (Floating microspheres)	HydroxyPropyl Methyl Cellulose, Chitosan, Eudragit® S100, Ethanol: Dichloromethane (1:1), Tween®80, n-hexane	Emulsion-Solvent Diffusion Method	Sustained drug release for 24 h	Antidiabetic	89
22.	Famotidine (Mucoadhesive microspheres)	Sodium Carboxymethyl Cellulose, Sodium Alginate, Liquid Paraffin, Isopropyl Alcohol, Sodium Hydroxide, Acetone, Dichloromethane, Double Distilled Water	W/O Emulsification Solvent Evaporation Method	Prolonged drug release for more than 8 h	Antiulcer	90
23.	Captopril (Floating microspheres)	Ethyl Cellulose, HPMC K4M, Dichloromethane: Ethanol (1:1), Ethanol, Liquid Paraffin, Tween®80, Petroleum Ether	Non-aqueous solvent evaporation	Drug release for 12 h	Antihyper-tensive	91
24.	Ketoprofen (microspheres)	Ethyl Cellulose, Sodium Carboxymethyl Cellulose, Chloroform, Methanol, Dichloromethane,	Response surface methodology	Drug release for over a period of 12 h	Antiarthritic	92
25.	Diclofenac sodium (Hollow microspheres)	Eudragit® S100, Dichloromethane: Ethanol (1:1), Glyceryl Monostearate, Polyvinyl Alcohol, Water	Emulsion solvent diffusion	Controlled drug release over a period of 8 h	Anti-inflam-matory	93
26.	Indomethacin (Floating microballoons)	Eudragit® S100, Eudragit® RS100, Tween®80, Tween® 20, Polyvinyl Alcohol, Water	Emulsion solvent diffusion	Drug release for over a period of 24 h	Anti-inflam-matory	94

floating microspheres will increase the active agent's bioavailability. Polymer granules having interior voids produced by deacidification are buoyant and offer a regulated medication release of prednisolone when introduced to acidic and neutral environments. Floating hollow microcapsules with a gastroretentive controlled-release mechanism were used to administer melatonin. The medication is released from these microcapsules over a period of 1.75 to 6.7 h in the simulated stomach fluid.

The majority of mucoadhesive microcapsules, such as metoclopramide and glipizide-filled chitosan microspheres, stay in the stomach for more than 10 h[68]. These compounds, which can be administered via the floating microspheres, include antiviral, antifungal, and antibiotic drugs (sulphonamides, cephalosporins, penicillin, quinolones, aminoglycosides, and tetracyclines), which are only taken up from very specific locations of the GI mucosa. Non-steroidal anti-inflammatory agents, for

Table V: List of associated patents of microballoons in GRDDs[100-108]

S. No.	Name of the patent	Patent Number/Office	Assignee/Inventor	Reference
1.	Organic microballoon	United States US4582756A	Matsumoto Yushi Seiyaku Co Ltd	100
2.	Process for producing inorganic microspheres and glass microballoons	European Patent Office EP0801037B1	AGC Inc	101
3.	A gastroretentive pharmaceutical dosage form	European Patent Office EP2306983A1	University of the Witwatersrand, Johannesburg	102
4.	Cast explosive composition with microballoons	United States US5880399A	Dyno Nobel Inc	103
5.	Preparation method of titanium dioxide nano hollow microballoons in the presence of surfactant	China CN102786084A	Changzhou Expansion New Stuff Technology Co Ltd Changzhou University	104
6.	Apparatus for determining the filling pressure of a plurality of microballoons	United States US-4650328	Jorgensen, Betty S	105
7.	Preparation of carbon microballoons	United States US-4996009 A	Hasegawa Kazuhiro.	106
8.	A gastroretentive pharmaceutical dosage form	WIPO (PCT) WO2009153632A1	Viness Pillay, Yahya Choonara, Caragh Murphy, Sarashnee Moonisami	107
9.	Process for producing crystalline microballoons	Canada CA 2111141	Sunahara, Kazuo Sunahara, Kazuo.2006.	108

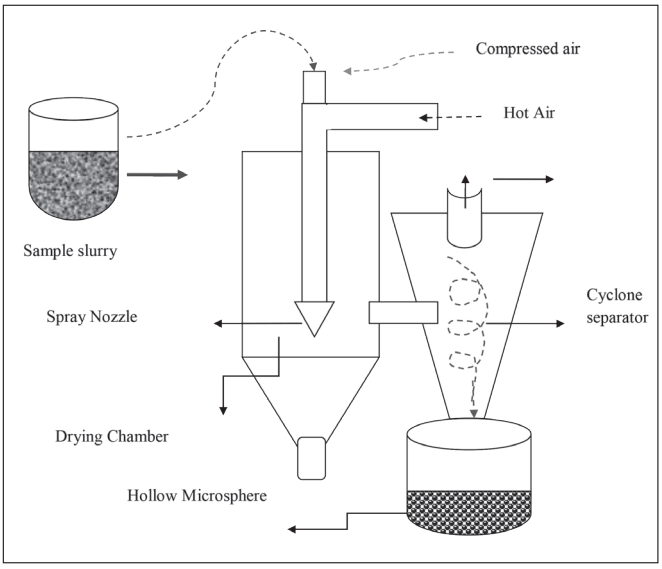

Fig. 3: Spray drying method[111]

example, floating indomethacin microspheres, are very useful for people with rheumatoid arthritis since they are highly effective for regulated release and also lessen the severe side effects of gastrointestinal discomfort Table IV[69-95].

RECENT ADVANCEMENT IN MICROBALLOONS

Recently, empty magnetite microspheres have been developed and used as drug transporters. Francisco Márquez *et al,* have discovered monodisperse hollow magnetite microspheres that were produced by a single hydrothermal stage without the need of a template[95]. By Yuning Huo *et al* a hollow CdS-TiO2 microsphere with enhanced visible light photocatalytic activity was created[96]. Kazuhiro S. *et al.* have used calcite microspheres as a precursor to make hollow carbonate apatite microspheres that can replace bone[97].

Recently, Changchun Wang *et al.* have discovered effective contrast agents for acoustic echo imaging in

homogeneous double-shell hollow microspheres, made utilizing a unique polymer backbone transition process[98]. Kapil Kumar and AK Rai revealed that recent technological advances have offered new avenues for the creation of empty curcumin microspheres as herbal medicine delivery vehicles[99]. Associated patents in the pharmaceutical field are shown in Table V[100-108].

FUTURE PERSPECTIVES

In future, patients may benefit from improved patient compliance and safety, thanks to the researchers' advanced and high-quality products that use drug delivery systems with gastroretentive. Each narrow GRT drug delivery system with gastric retention has been designed for a variety of clinical needs, such as dosage and disease state. The smallest cutoff size range above which dosage forms reside in the GIT for a long time is determined by comparing the efficacy of gastroretentive drug delivery systems in fed and fasted states. The growth of gastroretentive medication delivery devices may aid in the treatment of gastric and duodenal cancer. Many anti-reflux medications are being created using gastroretentive technologies, evaluating the efficacy of different medications in the fight against *H. pylori*. Design and development of gastroretentive drug delivery devices for Parkinson's disease therapy is offering a more detailed evaluation of the effects of various geometric shapes than past studies.

Novel mucoadhesive agents must be designed and synthesized in order to develop bioadhesive drug delivery systems for enhanced gastroretentive conditions, through the development of innovative mucoadhesive delivery methods that satisfy clinical and pharmaceutical needs using a variety of natural mucoadhesive agents. Additionally, it can considerably enhance pharmacotherapy of stomach by local drug release, which is utilized to most effectively remove *H. pylori* from submucosal tissue of the stomach and makes it helpful for treating the stomach as well as gastritis, duodenal ulcers, and esophagitis. Floating microballoons can be used to carry medications with narrow absorption windows. Additionally, these methods may enable the oral administration of peptide and protein-based drugs such as low molecular-weight heparin, insulin, and vasopressin. NSAIDs (non-steroidal anti-inflammatory drugs) can be controlled-released, and floating tiny balloons significantly lessen its principal adverse effect, stomach discomfort. In the near future, effective pharmaceutical treatments for a variety of disorders are projected to be made available in clinics in the form of floating tiny balloons.

CONCLUSION

This review concludes that microballoons offer the gastroretentive-based controlled release of the drugs. Due to their buoyancy, microballoons float above stomach contents for an extended period of time at a slow rate, reducing changes in plasma drug concentration.

It is an effective way to improve absorption as well as the bioavailability of the drug. It is innovative, and the most reliable drug delivery for especially those drugs that are enable to tolerate the stomach's acidic pH. The solvent diffusion method is used to prepare the microballoons, besides, solvent evaporation, solvent diffusion-evaporation, and spray drying methods to develop the empty inner center. The characterization of microballoons is done on the basis of percent drug loading yield, surface morphology, buoyancy, flow properties, *in vitro* release, FT-IR studies, and stability at gastric pH. Several drugs for various treatments have been formulated so far as microballoons, a potential gastro-retentive drug delivery platform.

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