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A REVIEW ON FORMULATION AND EVALUATION OF GASTRORETENTIVE HYDROCHLOROTHIAZIDE FLOATING MICROSPHERES

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ABSTRACT

Hypertension or high blood pressure, is indeed a growing health concern globally, especially with factors like longer life expectancy and lifestyle choices contributing to the prevalence. Managing it is crucial for reducing the risk of related complications like heart disease and stroke. The present review is to study the formulation of gastro-retentive floating microspheres of hydrochlorothiazide and the effect of formulations variables like drug to polymer ratio and concentration of polymer dispersion. Hydrochlorothiazide work primarily by inhibiting the reabsorption of sodium and chloride ions in the distal convoluted tubules of the kidney, leading to increased excretion of sodium, chloride, and water, thus acting as a diuretic. The floating microsphere's purpose is to improve gastric retention time. Floating drug delivery systems are lower in bulk thickness than gastric juice and remind floating on gastric juice for a long period of time without impacting the gastric-emptying rate and increasing bioavailability.

Using the orifice ionic gelation technique to formulate hydrochlorothiazide floating microspheres is an interesting approach this technique involves the formation of microspheres by extruding a polymer solution containing the drug through a needle into a getting agent solution, where ionotropic gelatin occurs, this method can help control the release of the drug and potentially improve its bioavailability and therapeutic efficacy. These microspheres are formulated by using sodium alginate as sustained release polymer, sodium

bicarbonate as gas generating agent and calcium chloride as a cross linking agent. The rheological properties of the polymer dispersion were studied. The microspheres are formulated by different drug to polymer ratios at various concentrations of sodium alginate dispersion and also microspheres floating behavior, drug content, drug entrapment efficiency, micromeritic properties, swelling index, particle size, invitro drug release studies and release kinetics.

KEYWORDS: Hydrochlorothiazide, hypertension, gastro retentive drug delivery systems, floating microspheres, orifice-ionic gelation, sodium alginate.

INTRODUCTION

Hypertension is a significant public health concern given its widespread prevalence worldwide. It's associated with various serious health complications, including heart disease, stroke, and kidney failure. Early detection and management are crucial in mitigating its impact on global health.[1-4] Around 7.5 million deaths are 12.8% of the total of all annual deaths worldwide occur due to high blood pressure. Raised blood pressure is a major risk factor for chronic heart disease, coronary heart disease and stroke. Managing blood pressure levels effectively can significantly reduce the risk of these serious cardiovascular conditions and improve overall health outcomes. Regular monitoring and lifestyle modifications, along with appropriate medical intERV when necessary, are key in mitigating this risk. Elevated BP is positively correlated to the risk of coronary heart disease and stroke. Other than coronary heart disease and stroke, its complications include peripheral vascular disease, heart failure, peripheral, renal hemorrhage, retinal impairment, and visual impairment.[5]

The most popular method for the administration of medication is the oral root. The traditional delivery systems often require multiple doses throughout the day to maintain medicine concentrations with in the therapeutically active range. This is particularly true for medications with short half-lives or those that are rapidly metabolized are excreted by the body. Adherence to the prescribed dosage regimen in crucial to ensure optimal therapeutic outcomes and effectiveness of the treatment. The outcome indicates a major fluctuation in the amount of medication. Tactics to solve these traditional fluctuations contributed to the advancement of several NDDS. The aim of all drug delivery system is to provide the satisfying concentrations in the body with a therapeutic amount of medication at a particular location. Floating drug delivery is intended to hold the drug in the stomach and ideal for drugs with poor solubility and low intestinal fluid stability on the basis that FDDS makes the

dosage type less dense than gastric fluid to allow it swim on them. Without impacting the rate of gastric emptying. Drugs with shorter half-lives that are readily absorbed in GIT are highly removed from the circulation of the serum. To resolve these difficulties, the oral managed drug delivery mechanism has risen as they release the drug in to the GIT for longer periods of time and retain a steady concentration of medication in the serum. In the gastric area, gastro retentive dosage type may last for few hours and thus significantly increase the GRT to improve bioavailability, minimize drug waste and improve the solubility of drugs with low solubility. Floating microspheres are empty spherical particles without a center, in a strict sense. With free-flowing particles ranging in size from 1 to 1000μm.[6,7,8,9]

Hydrochlorothiazide is one of the best thiazide diuretic .It is taken orally and the dosage used for treatment of congestive heart failure and hypertension ranges from 25 to 50g daily. It can be taken alone or combination with other antihypertensive drugs up to 100mg if required. The half-life of hydrochlorothiazide is approximately 2.5 hours and its oral bioavailability is 70%.[10] It is only absorbed from the upper part of the duodenum and once it passes this absorption site, little or no absorption takes place.[11]

Thus, the main objective of the review was to study about the formulation and evaluation of gastro retentive drug delivery system (GRDDS), to understand the better absorption of drug in the stomach and also study the effect of polymer, polymer concentration and viscosity of polymer dispersion on drug release behavior and the buoyancy properties and micrometric properties of formulations.

Hypertension

Hypertension is the elevation of systolic BP, diastolic BP, or both above normal levels, is common in developed and developing countries and increases in prevalence with age increase. Although in recent years hypertension has been defined as a BP of 140/90 mmHg or more, the 2017 American College of Cardiology-American Heart Association (ACC-AHA) Hypertension Guideline adopted a lower threshold, in which hypertension is defined as a systolic BP of 130 mmHg or more or a diastolic BP of 80 mmHg or more.[12] Among adults in the United States, the overall prevalence of hypertension was 31.9% under the previous definition (blood pressure, ≥140/90 mmHg) and is 45.6% according to the 2017 ACC/AHA guideline definition (BP ≥ 130/80 mmHg).[13] Similarly, the rate of hypertension control was

61.0% among those receiving treatment at a target of less than 140/90 mmHg but only 46.6% at a target of less than 130/80 mmHg.

Worldwide, hypertension is the leading modifiable and major risk factor for CV events and mortality in adult.[14,15] Hypertension is present in 69% of adults with a first MI[15], in 77%of adults with a first stroke[15], in 74% of adults with HF[15], and in 60% of older adults with PAD.[16] Hypertension is also a major risk factor for development of SCD, a dissecting aortic aneurysm, angina pectoris, LVH, thoracic and abdominal aortic aneurysms, CKD, atrial fibrillation, DM, vascular dementia and ophthalmologic disease.[17] The increased risk associated with BP elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. A total of 69 drugs in 15 different classes, many of which are also available in single pill combinations, have been approved for the treatment of hypertension in the United States. Despite this treatment options, an estimated 10% to 15% of the general RH, is defined as uncontrolled BP on ≥3 antihypertensive drugs of different classes, in which one of them is diuretic, at optimal doses or requiring ≥4 drug to control blood pressure[18,19] and causes of RH are primarily hyperaldosteronism, Renovascular disease, Cushing syndrome and Pheochromocytoma. In addition, ≈0.5% of hypertension patients have refractory hypertension, defined as uncontrolled BP on ≥5 drugs.[20] Recent drug monitoring studies have revealed no adherence to BP lowering therapy in 25% to 65% of patients with apparent TRH.[21-24] In 24% to 34.5% of these individuals, who were prescribed 3-5 antihypertensive medications, no antihypertensive medication was detected in blood or urine samples.

A systemic review and Met analysis included 123 randomized studies of antihypertensive drug therapy in 613,815 individuals.[25] The review found that every 10 mm of Hg decrease in SBP significantly decreased major CV event by 20% CHD by 17%, stroke by 27%, and HF by 28%, which in all populations studied reduced all causes of mortality by 13%.[25] SPIRINT (systolic BP intervention trial) randomized 9361 adults to a systolic BP goal of <120 mm of Hg or <140 mm of Hg.[26] These patients have mean age of 67.9 years, systolic BP 130-180 mm of Hg and increased CV risk, no DM, history of stroke, or asymptomatic HF within the past 6 months, left ventricular ejection fraction <35%, and estimated glomerular filtration rate <20 ml/min/1.73m^2.[26] At 3.26 years follow up BP treatment reduced the primary composite outcome of MI, stroke, HF, or death from CV causes by 25%, all causes mortality by 27% HF by 38%, CV death by 43% and primary composite outcome or death by 22%.[26]

Gastro-retentive drug delivery system

Gastro-retentive drug delivery system (GRDDS) is one of the site-specific-delivery of the drugs at stomach. It is obtained by retaining dosage form in to stomach and drug is being released at sustained manner to specific site either in stomach or intestine.[27]

Table 1: Reasons for selecting gastro retentive drug delivery system over conventional drug delivery system.[28]

Conventional drug delivery System (CDDS)	Gastro-retentive drug delivery System (GRDDS)
➢ High risk of toxicity ➢ Less patient compliance ➢ Not suitable for delivery of drugs with narrow absorption window in small intestinal region ➢ Not much advantageous for drugs having rapid absorption through GIT, drugs which degrade in the colon, drugs acting locally in the stomach, drugs which are poorly soluble at an alkaline PH,	➢ Very low risk of toxicity ➢ Improves patient compliance ➢ Suitable for delivery of drugs with narrow absorption window in small intestinal region ➢ Very much advantageous for drugs acting locally in the stomach, drugs which degrade in the colon, drugs having rapid absorption through GIT.

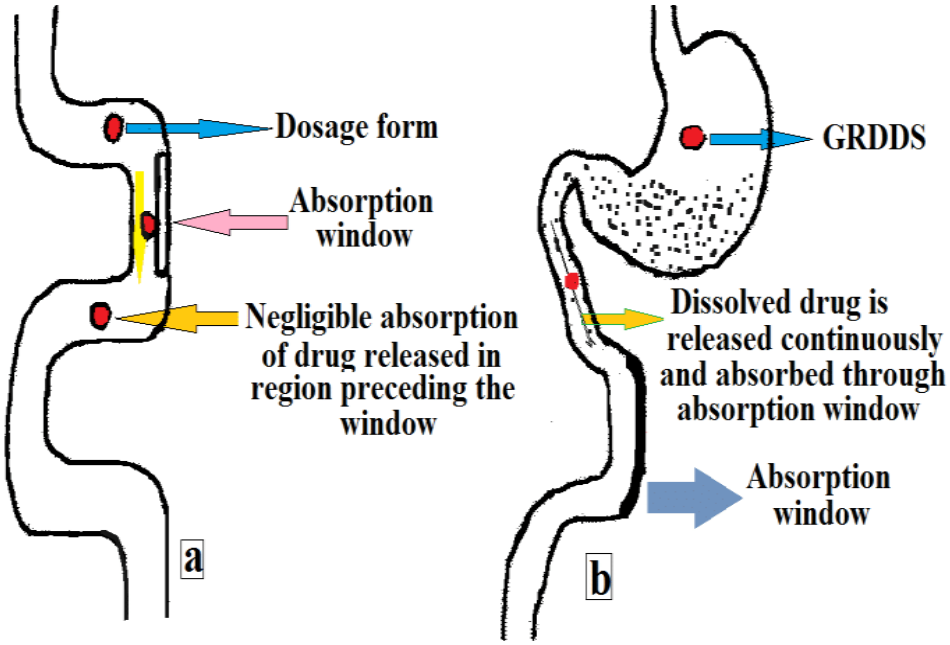

Figure 1: Mechanism of CDDS and GRDDS.[29]

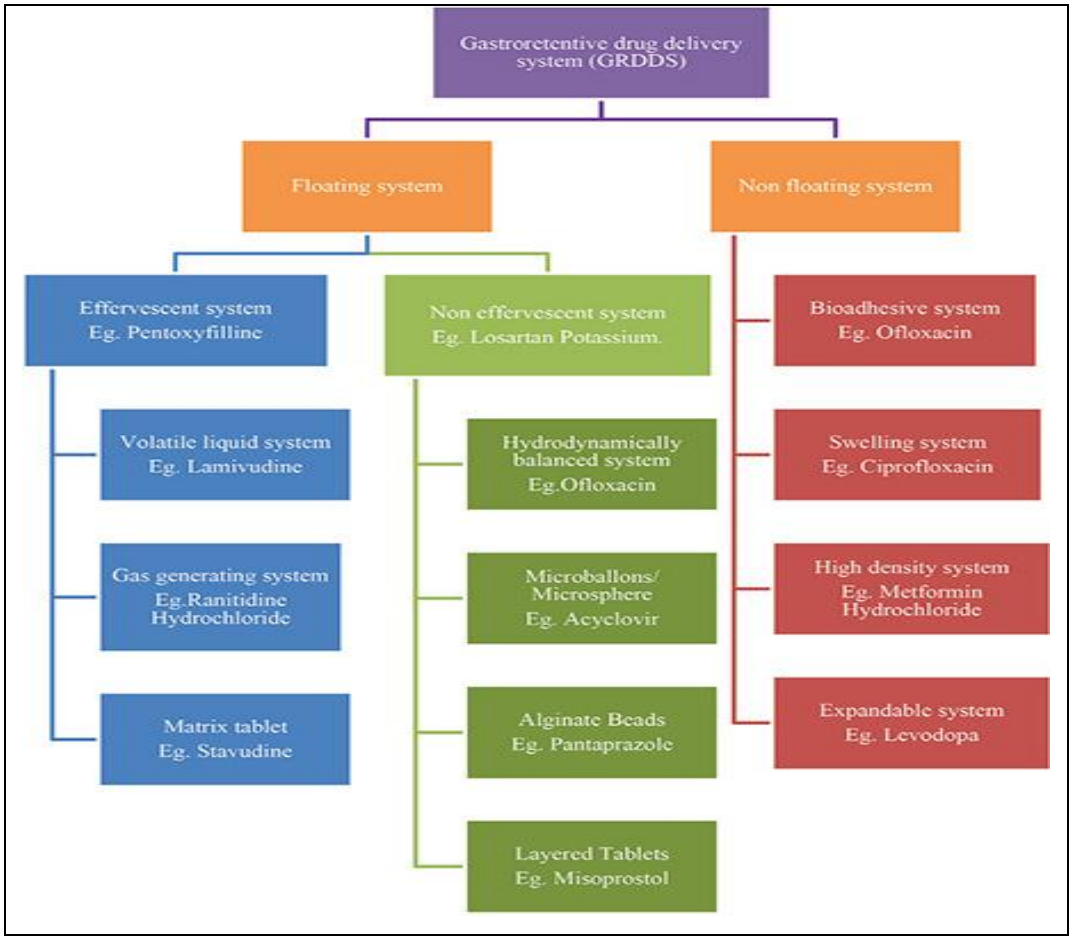

Figure 2: Classification of gastro-retentive drug delivery system.

Mechanism of floationg drug delivery system

They communicate with the acid in the stomach afer administration of the dosage type, since the outer layer of the floating microspheres includes polysaccharide, polymers, hydrates and forms a colloidal gel barrier that governs the movement of the drug and the gastric fluid in and out of the microspheres. The air molecules traps inside it because of this membrane, because it lowers its bulk density and lets it swim across the gastric fluid surface. For the flotation of the floating dosage type, a smaller amount of gastric fluid is requiredfor maximum cases. Mechanism of drug release form microspheres following methods.[30,31]

1. Erosion
2. Diffusion
3. Osmosis

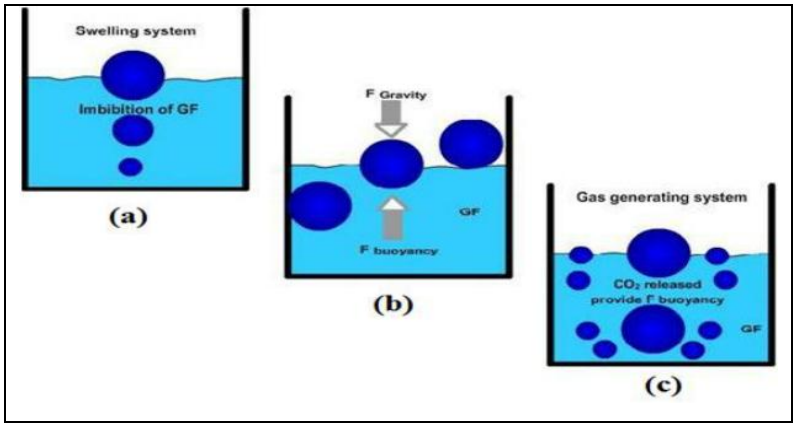

Figure 2: Mechanism of floating drug delivery system.

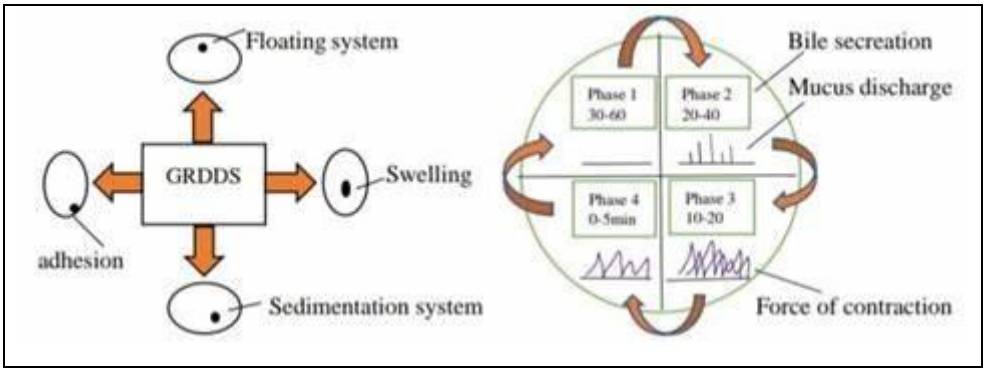

Figure 3: Approaches of gastro-retentive drug delivery system.

Advantages of gastro-retentive drug delivery system[32]

- Enhanced patient compliance by reducing the frequency of dosing.
- Enhanced therapeutic efficacy of drugs with a short half-life.
- Site-specific delivery of medications.
- Sustained and controlled release of drugs in the stomach.
- Improved residence time of drugs at the absorption site.
- Improved bioavailability from the gastrointestinal tract.
- Avoiding dose dumping of medicines.

Hydrochlorothiazide

FDA-Approved Indications

Hydrochlorothiazide is a medication approved by the U.S. Food and Drug Administration (FDA) to treat hypertension and peripheral edema. Hydrochlorothiazide works primarily by inhibiting the reabsorption of sodium and chloride ions in the distal convoluted tubules of the kidney, leading to increased excretion of sodium, chloride, and water, thus acting as a diuretic. For over 60 years, thiazides have been a reliable class of antihypertensive diuretics

that prevent sodium reabsorption and induce natriuresis and diuresis by directly inhibiting the sodium chloride cotransporter.[33]

Hydrochlorothiazide is FDA approved for treating essential hypertension either as a primary agent or an adjunct to other antihypertensive therapies.[34] Hydrochlorothiazide was initially approved for the treatment of hypertension in the 1960s.[35] According to some studies, thiazide-type diuretics and calcium channel blockers may lower blood pressure in black patients more effectively than the renin-angiotensin system (RAS) inhibitors or beta-blockers.[36]

Hydrochlorothiazide is also FDA-approved for the treatment of peripheral edema related to heart failure, corticosteroids, nephrotic syndromes, or estrogen therapy. Usually, loop diuretics are the preferred first-line treatment for peripheral edema, and hydrochlorothiazide is utilized as an adjunctive therapy.[37]

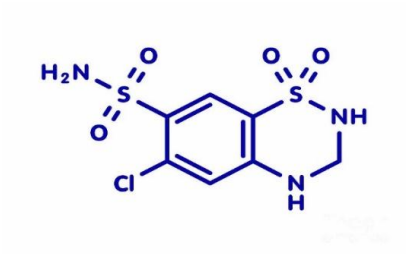

Figure 4: Chemical structure of Hydrochlorothiazide (HCTZ).

Mechanism of action

Hydrochlorothiazide directly inhibits the sodium chloride cotransporter located on the apical membrane of the distal convoluted tubules in the kidney. The distal convoluted tubule is responsible for reabsorbing approximately 5% to 10% of the sodium in the kidney.[38] This inhibition increases the concentration of sodium that moves to the collecting ducts by preventing sodium resorption in the distal convoluted tubules. Hydrochlorothiazide reduces the sodium-potassium ATPase pump's activity on the basolateral surface by preventing sodium from crossing the tubular lumen. This prevents the movement of sodium and water in to the interstitial space.

The elevated concentration of positively charged sodium ions moving through the distal convoluted tubule induces an ionic imbalance, further opening the voltage-gated channels. This transient receptor potential triggers an influx of calcium reabsorption from the tubular

lumen, facilitated across the basolateral surface through the calcium ATPase pump and sodium-calcium exchanger. Reabsorption of calcium in the distal convoluted tubules contributes to approximately 7% to 10% of filtered calcium retention.[39]

Aldosterone, the mineralocorticoid, is responsible for the modulation of sodium reabsorption and potassium excretion in the collecting ducts of the kidney. Elevated sodium concentration in the collecting duct prompts aldosterone to bind to the mineralocorticoid receptor, initiating the transcription of ion transport protein channels.[40] This leads to sodium reabsorption through the epithelial sodium channels in the principal cells and potassium excretion in the intercalated cells[41], resulting in natriuresis and diuresis effects.

In adults, the pharmacological effects of hydrochlorothiazide commence within 2 hours, peak after 4 hours, and persist for approximately 6 to 12 hours.[42] As the kidney is the primary excretory route for the medication, patients with renal impairment may exhibit a prolonged half-life and increased plasma concentration. Although no dosage adjustment is recommended for impaired renal function, the medication is unlikely to be effective in cases of several renal impairment with a creatinine clearance of less than 10.[43]

The initial diuresis and natriuresis effect mediated by the kidney causes an initial decrease in blood pressure through volume loss.[44] Over time, hydrochlorothiazide has demonstrated the ability to sustain blood pressure reduction by causing vasodilation and reducing peripheral vascular resistance.[45] Despite various proposed mechanisms, the exact mechanism by which hydrochlorothiazide causes peripheral vasodilation is not well understood.

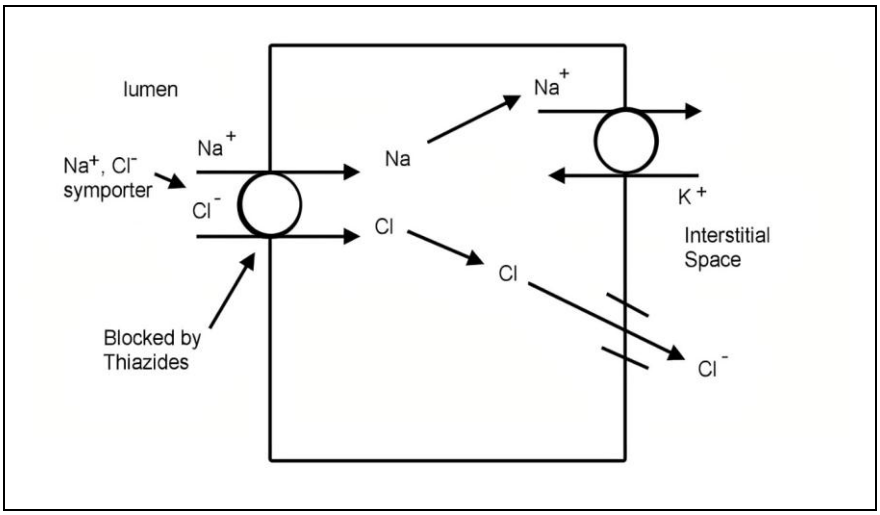

Figure 5: Mechanism of action of thiazide diuretics (Hydrochlorothiazide).

MATERIALS AND METHODS

Materials

Hydrochlorothiazide, sodium alginate, sodium bicarbonate, calcium chloride and glacial acetic acid.

Methods

Drug-excipient compatibility studies by FT-IR

The physio-chemical compatibility between the selected drug (Hydrochlorothiazide) and the excipients used in the research was tested by IR spectroscopy. The samples were scanned under diffuse reflectance using potassium bromate pellet technique. The spectra were recorded for pure drug, pure polymer and drug-polymer mixture using FT-IR. Samples were prepared in KBr desks (2mg sample in 200mg potassium bromate). The scanning range was 400-4000cm^{-1} and the resolution was 2cm^{-1}.

Preparation of microspheres

Orifice ionic gelation technique is used to formulate hydrochlorothiazide floating microspheres. Sodium alginate and gas forming agent sodium bi carbonate was dispersed in distilled water to form a uniform polymer mixture. The drug hydrochlorothiazide was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogenous dispersion. The gelation medium was prepared by dissolving calcium chloride in 1.5% glacial acetic acid solution. The homogenous alginate solution was extruded using 24G syringe needle into the gelation medium. The distance between the edge of the needle and surface of gelation medium was about 10 centimeters. The gel microspheres formed were left in the solution for 30minutes with gentle stirring room temperature to improve mechanical strength. After that the microsphere was collected and washed with distilled water twice, dried at 60℃ until get constant weight of microsphere.[46]

Studies on influence of sodium alginate dispersion viscosity

Accurately weighed quantity of sodium alginate and sodium bicarbonate was dissolved in distilled water to get 3, 3.5, 4.0, 4.5, and 5% w/v solutions. The viscosity of the prepared polymers was measured by using Brook field viscometer at shear rate of 0.13 to 0.66 and torque 10 to 50%. The viscosity of the polymer solution was noted as per Newtonian, Bingham and power law equations.

Newtonian equation:

$\sigma = \eta\gamma$

Where η = Viscosity in cps & γ = Shear rate in sec^{-1}.

Bingham equation:

$\sigma = \sigma_y + \eta_p\gamma$

Where η_p = Plastic viscosity & σ_y = Bingham yeild stress.

Power law:

$\sigma^n = \eta\gamma$

Where η = Viscosity coefficient and Exponent n= Index of pseudo plasticity.

Micromeritic properties of hydrochlorothiazide floating microspheres[47]

The flow properties of prepared microsphere were investigated by measuring the bulk density, taped density, Carr's index Hausner's ratio. The bulk and tapped densities were measured in a 10ml graduated measuring cylinder. The sample contained measuring cylinder was tapped mechanically by means of constant velocity rotating cam. The initial bulk volume and final tapped volume were noted from which their respective densities were calculated.

Drug content and entrapment efficacy of floating microspheres[48]

10mg of drug equivalent formulations was dissolved in 100ml of 0.1N HCL. The samples were assayed for drug content by UV-spectrophotometer by making suitable dilutions at 272nm and the drug content was calculated. The percentage entrapment efficiency was calculated by using following formula. **%Drug entrapment**= (calculated drug content /Theoretical drug content) ×100

In vitro drug release studies[49]

The drug release studies were carried out using dissolution apparatus USP type Ⅱ. A weight of floating microspheres corresponding to 25milligrams of drug was placed in basket. The dissolution medium used was 900ml of 0.1N hydrochloric acid at 37℃ and 100rpm. At specific time intervals, 5ml aliquots were withdrawn and analyzed by UV spectrophotometer at the respective λmax value 272nm after suitable dilution against suitable blank. The withdrawn volume was replaced with an equal volume of fresh 0.1N hydrochloric acid.

Invitro drug release kinetic studies

In order to study the exact mechanism of drug release from the alginate microspheres, drug release data was analyzed according to zero order, first order, Higuchi and Korsmeyer - Peppas equations. The order of drug release from alginate microspheres was described by

zero order kinetics or first order kinetics. The mechanism of drug release from matrix systems was analyzed by using Higuchi equation, and Korsmeyer drug release.

Floating behavior[50]

Three hundred milligrams of the microspheres were placed in 900ml of 0.1N hydrochloric acid. The mixture was stirred at 100rpm in a dissolution apparatus for 12h. After 12h, the layer of buoyant microspheres was pipetted and separated by filtration. Particles of both types were dried in a desiccator until constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was decided by the weight ratio of floating particles to the sum

$$\%\text{Buoyancy} = (Wf / Wf + Ws) \times 100$$

Where W_f and Ws are the weights of the floating and settled microspheres

Swelling index[51]

50mg of microspheres were weighed and transferred to a petri plate containing 10ml of 0.1N hydrochloric acid maintained at 37℃. The microspheres were withdrawn at 1hour intervals up to 4hrs. The swelling index was calculated by using the formula.

$$\text{Swelling index} = (W_t - W_o / W_t) \times 100$$

Where W_0 = Initial weight

W_t = weight of the microspheres at time t.

Particle size analysis[52]

The particles size of the drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model [SZX – 12] having resolution of 10xs was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 1/10mm [10µm]. In all measurements at least 100 particles in five different fields were studied. Each experiment was carried out in triplicate.

Scanning electron microscopy analysis [SEM][53]

The shape and surface characteristics were determined by scanning electron microscopy. A working distance of 20nm, a tilt of zero- degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within in a range of 50-100 magnifications.

Stability studies[54]

The optimized formulation was kept at room temperature for 3 months. Then the microspheres are evaluated for percent drug entrapment and dissolution study.

CONCLUSION

Floating microspheres indeed offer a competent strategy for enhancing the bioavailability and controlled release of beneficial agents. By remaining buoyant in the gastric fluid, they prolong the residence time in the stomach, leading to increased absorption of the drug or nutrient. This controlled release system helps optimize therapeutic outcomes while minimizing side effects. Major worldwide effects have been made to discover these systems, both in terms of therapeutic efficacy and compliance, which the release rate of target drug to a particular side and promote a vast effect on health care. In the working management of hypertension, the floating microspheres are expected to give clinical specialist with a new option of an affordable, healthy and extra bioavailable formulation. Hydrochlorothiazide is the diuretic of the benzothiadiazide group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. It is poorly water-soluble drug having plasma half-life 6 to 8 hours. So, the gastro retentive floating microspheres of hydrochlorothiazide helps in high serum concentration in a short period of time.

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