Comprehensive review on characterizations and application of gastro-retentive floating drug delivery system

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Abstract

Current pharmaceutical situation focuses on the preparation of gastro-retentive floating drug delivery system (GRFDDS). This systems has gained noteworthy interest in the past decades. These are the low density systems that float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. GRFDDS is used to delay the residence time of delivery in stomach. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents that delaying gastric emptying. This results in targeting of release of drug at a specific site for the systemic or local effects. GRDDS is used to overcome challenges associated with conventional oral dosage forms and to release the drug at a specific absorption site to improve bioavailability of particular drug substance. Some floating drug delivery systems have shown the capability to accommodate these variations without affecting drug release. This review mainly focuses characterizations and application of gastro-retentive floating drug delivery systems.

Keywords: Gastro-retentive; Gastric residence time; Characterizations; Application

1. Introduction

The oral drugs delivery with a narrow absorption window in the gastrointestinal tract is frequently restricted by poor bioavailability with formulations due to incomplete drug release and small dwelling time [1]. There are many drug delivery system such emulsion, suspension, mucoadhesive tablets, nasal delivery system, etc available for various drugs [2-10]. Gastro-retentive floating drug delivery system (GRFDDS) is one of the drug delivery system which is used to delay the residence time of delivery in stomach. GRFDDS are the low density systems that float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate [11]. Oral drug delivery accounts for largest proportion of administered formulations due to the easy administration, patient acquiescence, and flexibility in formulation [12]. This review mainly focuses various physicochemical characterizations of GRFDDS and highlights application thereof.

2. Approaches to GRFDDS

2.1. Practical approaches

The idea of FDDS was 1st delineate within the literature as early as 1968, once Davis (1968) disclosed a way to beat the issue practiced by some persons of gagging or choking when swallowing healthful pills. The author recommended that...
such problem may well be overcome by providing pill having a density of but one.0g/cm3, in order that pill can float on water surface. Since then many approaches are wont to develop a perfect floating drug delivery system [13].

2.2. Style Single and Multiple Unit

indefinite quantity kind the following approaches are used for the planning of floating indefinite quantity types of single and multiple unit systems [14].

2.3. Single unit indefinite quantity forms

2.3.1. Floating lag time

It’s the time taken by the pill to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.

2.3.2. In-vitro drug hardness and length of floating

This can be determined by victimization USP II equipment (paddle) stirring at a speed of fifty or one hundred revolutions per minute at thirty seven ± zero.2°C in simulated internal organ fluid (pH one.2 while not pepsin). Aliquots of the samples are collected and analyzed for the drug content. The time (hrs.) that the tablets stay buoyant on the surface of the dissolution medium is that the length of floating and is visually determined.

2.3.3. In-vivo analysis for gastro-retention

This can be administrated by suggests that of X-ray or Gamma scintigraphic watching of the indefinite quantity kind transition within the bum. The tablets are evaluated for hardness, weight variation, etc. In denseness approaches, the orbicular shells apparently having lower density than that of internal organ fluid are often used as a carrier like popcorn, pop rice, polystrol for the drug for its controlled unharness [15]. The chemical compound of selection are often either alkyl polysaccharide or HPMC. Counting on sort of unharness desired. Finally the merchandise floats on the internal organ fluid whereas emotional the drug bit by bit over a protracted length.

Fluid stuffed floating chamber sort of indefinite quantity forms includes incorporation of a gas stuffed floatation chamber in to a small porous element that homes as a reservoir having apertures gift at high and bottom walls through that the alimentary canal fluid enters to dissolve the drug.

2.4. Hydro dynamically balanced system

These systems square measure designed to prolong the keep of the indefinite quantity forms within the viscus tract and aid in enhancing the absorption. Medication having a more robust solubility in acidic surroundings and conjointly having specific web site of absorption within the higher a part of intestine is achieved by these HBS systems. To retain in abdomen for a chronic amount of your time the indefinite quantity type should have bulk density of but ‘1’ and needs to maintain its structural integrity and unleash drug perpetually from the indefinite quantity type. Among all the benefits single-unit formulations square measure related to some limitations/problems like projecting along or being deadlocked within the bum which can result in potential danger of manufacturing irritation [16].

2.5. Multiple Unit indefinite quantity Forms

Apart from the In-vitro unleash, period of floating and in vivo gastro-retention tests, the multiple unit indefinite quantity forms also are evaluated.

2.5.1. Morphological analysis

Morphological and dimensional analysis with the help of scanning microscopy (SEM). The scale can even be measured mistreatment associate degree optical magnifier.

2.5.2. In-vitro floating ability (Buoyancy %)

A far-famed amount of microspheres square measure adjoin the surface of a USP (Type II) dissolution equipment stuffed with 900 milliliter of zero.1 N HCl containing zero.002% v/v Tween eighty and agitated at a hundred rate for twelve hours. After twelve hours, the floating and settled layers square measure separated, dried during a desiccator and weighed. The buoyancy is calculated from the subsequent formula.

\[
\text{Buoyancy (\%)} = \frac{W_f}{(W_f + W_s)} \times 100
\]
Where, Wf - square measure the weights of floating; Ws- Square measure the weights of settled microspheres.

2.5.3. Drug-excipients (DE) interactions

This is often done mistreatment FTIR. Look of a brand new peak, and/or disappearance of original drug or excipient peak indicates the DE interaction. Except the higher than mentioned analysis parameters, granules also are evaluated for the impact of ageing with the assistance of Differential Scanning measuring system or hot stage polarizing research. Multiparticulate indefinite quantity forms square measure gaining abundant favor over single-unit indefinite quantity forms. The potential advantages embody inflated bioavailability; inevitable, consistent and usually short viscus duration, no risk of dose dumping; reduced risk of native irritation, and therefore the flexibility to mix pellets with totally different compositions or unleash patterns [17].

However, potential drug loading of a multiparticulate system is lower thanks to the proportionately higher would like for excipients (e.g., sugar cores). Most multiparticulate pulsatile delivery systems square measure reservoir devices coated with a respectable compound layer. Upon water ingress, drug is free from the core once rupturing of the encompassing compound layer, because of pressure build-up at intervals the system. The pressure necessary to rupture the coating may be achieved with swelling agents, gas manufacturing effervescent excipients or inflated pressure level.

Water permeation and mechanical resistance of the outer membrane square measure major factors poignant the lag time. Water soluble medication square measure principally free by diffusion; whereas for water insoluble drug, the discharge depends on dissolution of drug [18].

3. Evaluation of GRFDDS

There are a unit totally different studies set out within the literature indicate that pharmaceutical dose forms exhibiting stomachic residence in vitro floating etiquette show prolonged stomachic residence in vivo. However, it’s to be grasp that sensible in vitro floating bearing alone isn't comfortable proof for economical stomachic retention in vivo. The consequences of the coincidental presence of food and of the complicated motility of the abdomen area unit tough to estimate. Obviously, solely in vivo studies will give definite proof that prolonged stomachic residence is obtained. In-vitro analysis of floating tablets evaluation was performed to assess the chemistry properties and unleash characteristics of the developed formulations.

3.1. Pre-compression parameters

3.1.1. Angle of Repose

The resistance forces during a loose powder or granules may be measured by angle of repose. This can be the utmost angle doable between the surface of a pile of powder or granules and therefore the horizontal plane. The granules were permit to flow between the funnel mounted to a stand at conclusive height (h). The angle of repose was then calculated by measure the peak and radius of the heap of granules fashioned [19] (Table 1).

\[
\tan \theta = \frac{h}{r}
\]

Where, \( \theta = \tan^{-1} \left( \frac{h}{r} \right) \); \( \theta \) = angle of repose; \( h \) = height of the heap; \( r \) = radius of the heap.

<table>
<thead>
<tr>
<th>Angle of repose</th>
<th>Powder flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>Excellent</td>
</tr>
<tr>
<td>25-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-40</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

3.1.2. Compressibility index

The flow ability of powder may be evaluated by scrutiny the majority density (\( \rho_0 \)) and tapped density (\( \rho_t \)) of powder and therefore the rate at that it packed down. Softness index was calculated by –

\[
\text{Compressibility index (\%)} = \frac{\rho_t - \rho_0}{\rho_0} \times 100
\]

Where, \( \rho_0 = \) Bulk density g/ml002E; \( \rho_t = \) tapped density g/ml.
3.2. Post-compression parameters

3.2.1. Shape of tablet
Compressed pills were examined underneath the magnifying lens for the form of the tablet. Thickness and diameter were measured employing a graduated varnir caliper. 3 tablets of every formulation were picked willy-nilly and thickness was measured on an individual basis.

3.2.2. Hardness
Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined [20].

3.2.3. Friability test
The friability of tablets was set on by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were at first weighed (W initial) and shifted into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by-

\[
\% \text{Friability} = 100 \left(1 - \frac{W_0}{W_f}\right)
\]

% Friability of tablets less than 1% was considered bearable.

3.2.4. Tablet density
Tablet density was a principal parameter for floating tablets. The tablet would levitate only when its density was less than that of gastric fluid (1.004). The density was set on using following association [21].

\[ V = \pi r^2 h \quad d = \frac{m}{V} \]

Where,
\( V \) = volume of tablet (cc);
\( r \) = radius of tablet (cm);
\( h \) = crown thickness of tablet (g/cc);
\( m \) = mass of tablet.

3.2.5. Weight variation test
Ten tablets were pick randomly from each batch and weighed independently to check for weight variation. A little variation was permit in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed show in Table 2.

Table 2 Percentage deviation in weight variation.

<table>
<thead>
<tr>
<th>Average weight of tablet</th>
<th>Percentage deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 mg or less</td>
<td>10</td>
</tr>
<tr>
<td>&gt;130 mg and &lt; 324 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>324 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

4. Characterization parameter

4.1. Size and shape evaluation
The particle size and form plays a significant role in deciding solubility rate of the medicine and therefore doubtless its bioavailability. The particle size of the formulation determined exploitation Sieve analysis, Air elutriation analysis, picture analysis, Optical magnifier, Electro résistance numération ways (Coulter counter), geological phenomenon techniques, optical maser optical phenomenon ways, ultrasound attenuation spectrographic analysis, pollution Emissions Measurements etc [22].
4.2. Surface topography
The surface topography and structures were determined exploitation scanning microscope (SEM, JEOL JSM – 6701 F, Japan) operated with AN acceleration voltage of 10k.v, Contact angle meter, Atomic force research (AFM), Contact profilimeter [23].

4.3. Determination of moisture content
The water content intrinsically is rarely of interest. Rather, it appear whether or not a result presume for trade and production has normal properties like-

- Storability
- Agglomeration within the case of powders
- Microbiological stability
- Flow properties, viscosity
- Dry substance content
- Concentration or purity
- business grade (compliance with quality agreements)

Thus wetness content of the ready formulations determined by Karl fisher volumetric analysis, vacuum drying, Thermo gravimetric ways, Air kitchen appliance methodology, wetness Meters, Freeze drying additionally as by physical ways [24].

4.4. Swelling studies
Swelling studies were bring about to calculate molecular variable of swollen polymers. Swelling studies determined by exploitation Dissolution equipment, optical research and alternative subtle techniques that embody H1NMRimaging, Confocal optical maser scanning research (CLSM), refrigerant scanning microscopy (Cryo-SEM), light-weight scattering imaging (LSI) etc. The swelling studies by exploitation Dissolution equipment (USP dissolution equipment (usp-24) lab India disso 2000) was calculated as per the subsequent formula [25].

\[
\text{Swelling magnitude relation} = \frac{\text{Weight of wet formulation}}{\text{Weight of formulations}}
\]

4.5. Drug content
Percentage drug content provides what quantity of the drug that was gift within the formulation. It shouldn't exceed the bounds non-inheritable by the quality monographs. Drug content determined by exploitation HPLC, HPTLC ways, close to infrared spectrographic analysis (NIRS), Micro titrimetric ways, Inductively Coupled Plasma Atomic Emission spectroscope (ICPAES) and conjointly by exploitation spectrographic analysis techniques [26-52].

4.6. Percentage entrapment efficiency
Percentage defense potency was reliable for quantifying the part distribution of drug within the ready formulations. Defense potency determined by exploitation 3 ways like small qualitative analysis methodology, immoderate activity and pressure immoderate filtration [53].

4.7. Floating time and dissolution
The take a look at for floating time measure is sometimes performed in stirred stomachic fluid or zero.1 mole/ lit HCl maintained at 37°C. It's determined by exploitation USP dissolution equipment containing 900 milliliter of zero.1 mole/lit HCl because the dissolution medium at 37°C. The time taken by the dose type to float is termed as floating lag time and therefore the time that the dose type floats is termed because the floating or flotation time [54]. An additional relevant in-vitro dissolution methodology pro-posed to gauge a floating drug delivery system (for pill dose form) [55].

A one hundred milliliter glass beaker was changed by adding a firearm at the lowest of the beaker in order that the beaker will hold seventy milliliter of zero.1 mol/lit HCl dissolution medium and permit assortment of samples. A burette was mounted higher than the beaker to deliver the dissolution medium at a rate of two ml/min to mimic stomachic acid secretion rate. The performance of the changed dissolution equipment was compared with USP dissolution equipment a pair of (Paddle). The matter of adherence of the pill to the shaft of the paddle was determined with the USP dissolution
equipment. The pill failed to follow the agitative device within the planned dissolution methodology. The drug unleashed followed zero-order dynamics within the planned methodology.

Similarity of dissolution curves was determined between the USP methodology and therefore the proposed methodology at 100 percent distinction level (f2=57). The planned take a look at might show sensible in vitro-in vivo correlation since an effort is created to mimic the in vivo conditions like stomachic volume, stomachic evacuation, and stomachic acid secretion rate.

4.8. Drug release
Dissolution tests area unit performed exploitation the dissolution equipment. Samples area unit withdrawn sporadically from the dissolution medium with replacement so analyzed for his or her drug content when associate applicable dilution [56].

4.9. Powder X-ray diffraction
X-ray powder optical phenomenon (Philips analytical, model-pw1710) is that the predominant tool for the study of crystalline materials and is eminently fitted to the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between a pair of °C and sixty °C. The voltage and current used were 30KV and 30mA severally [57].

4.10. Fourier transformed infrared analysis
Fourier-transformed infrared qualitative analysis (FTIR, Shimadzu, Model-RT-IR-8300) may be a technique principally accustomed determine organic, polymeric and a few inorganic materials in addition as for purposeful cluster determination. Fourier Transformed Infrared Analysis (FT-IR) measurements of pure drug, compound and drug loaded compound formulations were obtained on FTIR. The pellets were ready on KBr-press beneath hydraulic pressure of 150kg/cm² the spectra were scanned over the frequency vary of 3600 to four hundred cm⁻¹ at the close temperature [58].

4.11. Differential Scanning calorimetry (DSC)
DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) area unit accustomed characterize water of association of prescribed drugs. Thermo grams of developed preparations were obtained exploitation DSC instrument equipped with associate intercooler. Indium/Zinc standards were accustomed calibrate the DSC temperature and Η scale. The sample preparations were hermitically sealed in associate atomic number 13 pans and heated at a continuing rate of 10°C/min; over a temperature vary of 25°C -65°C. Inert atmosphere was maintained by purging N gas at the flow of 50ml/min [59].

5. Application of GRFDDS
5.1. Enhanced Bioavailability
The bioavailability of vitamin B2 metal-GRDF is considerably increased compared to the administration of non-GRDF CR chemical compound formulations. There are a unit many totally different processes, associated with absorption and transit of the drug within the digestive tube, that act concomitantly to influence the magnitude of drug absorption [60].

5.2. Sustained drug delivery
Oral metal formulations area unit encountered with issues like internal organ duration within the stinker. These issues will be overcome with the HBS systems which might stay within the abdomen for long periods and have a bulk density <1 as results of that they will float on the internal organ contents. These systems area unit comparatively larger in size and spending from the orifice gap is prohibited [61].

5.3. Site specific drug delivery systems
These systems area unit significantly advantageous for medicine that area unit specifically absorbed from the abdomen or the proximal a part of the little viscous . The controlled, slow delivery of drug to the abdomen provides ample native therapeutic levels and limits the general exposure to the drug. This reduces aspect effects that area unit caused by the drug within the blood circulation. Additionally, the prolonged internal organ convenience from a web site directed delivery system may additionally cut back the dosing frequency. Eg: Lasix and vitamin B2 [62].
5.4. Absorption enhancement
Drugs that area unit having poor bioavailability attributable to web site specific absorption from the higher a part of the stinker area unit potential candidates to be developed as floating drug delivery systems, there by maximizing their absorption [63].

5.5. Decreased adverse activity at the colon
Retention of the drug within the HBS systems at the abdomen minimizes the number of drug that reaches the colon. Thus, undesirable activities of the drug in colon is also prevented. This Pharmacodynamics facet provides the principle for GRDF formulation for beta lactum antibiotics that area unit absorbed solely from the little viscous, and whose presence within the colon ends up in the development of microorganism’s resistance.

5.6. Reduced fluctuations of drug concentration
Continuous input of the drug following CRGRDF administration produces blood drug concentrations. Among a narrower vary compared to the immediate unleash indefinite quantity forms. Thus, fluctuations in drug effects area unit decreased and concentration dependent adverse effects that area unit related to peak concentrations will be prevented. This feature is of special importance for medicine with a slim therapeutic index [64].

5.7. Future perspective of GRFDDS
The GRFDDS of the normal amount kind is one in all the foremost challenges at intervals the pharmaceutical business, significantly for drugs that unit absorbed from the upper a district of the organ. Developing GRDDS will facilitate to beat the drawbacks associated with commonplace amount kind, although a lot of work is needed on its shortcomings. To date, many studies are performed on GRDDS utilizing the sole system approach like floating, expandable, and mucoadhesive systems. Though varied GRDDS technologies are extensively explored to realize roaring gastroretentive systems, most have their own limitations. The variation in GRT, particularly within the fed and fasted states, continues to be one in every of the most challenges moon-faced by several formulation scientists. No single approach can be the simplest for partitioning the issues. It’s fascinating to explore appropriate GRDDS that may overcome the constraints of one approach. Therefore, future works on GRDDS ought to be centered on mixtures of various mechanisms so as to prolong viscus retention of dose forms even within the fasted state.

6. Conclusion
GRFDDS can provide many advantages for drugs with low bioavailability. These systems restrict the absorption of the drug in the upper gastrointestinal tract and they can be delivered capably thereby improving their absorption and intensifying absolute bioavailability. The in vivo studies are important to create the optional dosage form for a specific drug because of complexity of pharmacokinetics and pharmacodynamics parameters. Gastro-retentive drug delivery has great significance to increase the therapeutic efficacy of drugs those having a narrow absorption window, high solubility at acidic pH (in Stomach), and low solubility or instability at alkaline pH (intestine). But understanding the anatomy and physiology of the stomach, the effect of formulation and process variables on the quality of dosage form is necessary for successful GRDDS design. Even though numerous GRDDS have been reported in the literature such as low or high density, bio or mucoadhesive, and magnetic systems, but their effectiveness or clinical significance is necessary to be studied. To understand, the influence of formulation and process variables of the dosage form performance QbD approach can be used.

Compliance with ethical standards

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The author declares no conflict of interest.
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