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Review on Gastroretentive Drug Delivery System

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Abstract

The oral delivery in English way was the very popular method, due to the ready taking of medicine and administration process. After oral administration of a drug, the process of its bioavailability being influenced by its stay in stomach are imperative. Lately, gastroretentive drug delivery systems (GRDDS) have been extensively used for drugs with a narrow absorption window, an inability to formulate the dose at high pH due to decreased stability and increasing solubility at low pH level Such drugs are the part of the design of medicine system that keeps for a while in the stomach and upon release of its active components causes the desired effect in the stomach. Achieving the desired result of gastric retention of drugs may be done through the use of agents of effervescence, mucoadhesive polymers, magnetic matter, bouncy enhancing carriers, along with a method which is effective in forming plug-like substances that are resistant to emptying of the stomach. Such conclusion records a concise viewpoint about the essential attributes of the latest individually addressed procedures on GRDDS.

Key words: Bioavailability, bio/mucoadhesivesystem, therapeuticwindow, gastricemptying

Introduction

Oral administration is still the most administrated approach notwithstanding continuous improvement in drug delivery approaches since patients still find it easy to use and comfortable with this method. The point release drug delivery systems, by the way, are meant to be as an oral medication.[1] Those delivery systems deliver the medications in one after another, pre-determined, predictable and controlled dose. Such drugs do not make a good oral candidate having its challenges on stability and absorption. This drawback of the drug can be solved by the use of modern technologies, which facilitate these drugs to stay in the stomach for a longer period at -3 time. The drug delivery system example of which has got the name of gastroretentive drug delivery (GRDDS) ranks high among the drug delivery methods. GRDDS are proper for those pharmaceuticals, such as albuterol:[2] which are absorbed in the stomach; are unstable in an alkaline environment (e.g. ranitidine and metformin);[3] are poorly soluble in an alkaline environment (e.g. furosemide and diazepam) [4]; and have conditions within an absorption zone (e.g. riboflavin) [5]

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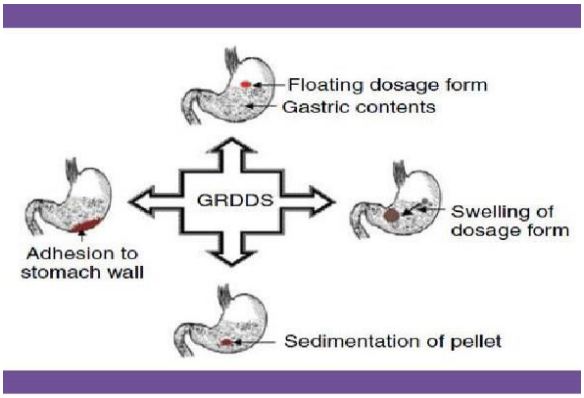
Some of the common advantages associated with use of GRDDS include improved patient compliance by reducing the frequency of dosing; improved therapeutic efficacy of drugs with a short half-life; site-specific delivery of medications; sustained and controlled release of drugs in the stomach; enhanced residence time of drugs at the absorption site; improved bioavailability from the gastrointestinal tract; avoiding dose dumping of medicines.[6]

To develop GRDDS, different materials like ion-exchange resins, mucoadhesives, high-density materials, raft forming substances, magnetic substances, and superporous hydrogels are used.[7,8] Thisreviewprovidesaconciseaccountofvariousattributesof recentlydeveloped approaches forGRDDS

Anatomyandphysiologyofthestomach

Comprehending the structure and operation of the stomach is crucial to the development of effective gastroretentive dosage forms. Anatomically, the stomach is composed of three parts: the fundus, which is located closest to the esophagus and serves as a storage area for food that has been swallowed; the body; and the antrum, which is the last portion and connects the body to the small intestine. Antrum aids in stomach emptying and churning.9. During a fast, the stomach and intestine go through a cycle of contractions known as the migrating myoelectric cycle every 120 to 180 minutes. It is separated into four additional phases. The term "digestive motility pattern" refers to the pattern of contraction alterations in a fed state.10 Phase 1 (basal phase) and Phase 2 make up this pattern.



PhysicochemicalpropertiesofGRDDS

Physicochemical properties of GRDDS include density, size, and shape of the dosage form,which play major roles in the formulation of GRDDS. The dosage forms having a density lowerthanthegastriccontentscanfloattothesurface, while high-densitysystemssinktothebottomofthestomach.Foran idealformulation,thedensityshouldbeintherangeof1.0 -2.5 g/cm^3.Dosageformshavingadiameterofmorethan7. 5mm showbettergastricresidencetime(GRT).Circular,spherical ortetrahedron-shapeddevicesshowexcellentgastroprotective properties.[12]

PhysiologicalfactorsaffectingretentionofGRDDSinthe stomach

The fed or unfed state, the type of meal, the calorie content, and the frequency of feeding are the main variables influencing the gastric retention time of dosage forms. Because of the increased GI motility during fasting, there is a reduction in gastric retention time. Peristalsis is the cause of the emptying of the stomach contents. The gastric residence is brief if the onset of peristalsis aligns with the administration of the dosage form. Peristalsis, on the other hand, is delayed after meals and could contribute to the formulation's longer gastric residence. A meal rich in calories that includes proteins, fats, and fibrous materials prolongs the period of gastric retention. Because peristalsis is persistently inhibited when there are multiple meals, the gastric retention is greater thanthat of a single meal. Additionally, a few other elements, like age and sex. [13- 15]

Gastoretentive dosage form approaches

Continuous research and advancements in various approaches to gastroretentive dosage forms over the last few years are aspresentedinFigure2.TheseapproachestoGRDDS helpin deliver in the medicament in a sustained and restrained way through the gastrointestinal tract.

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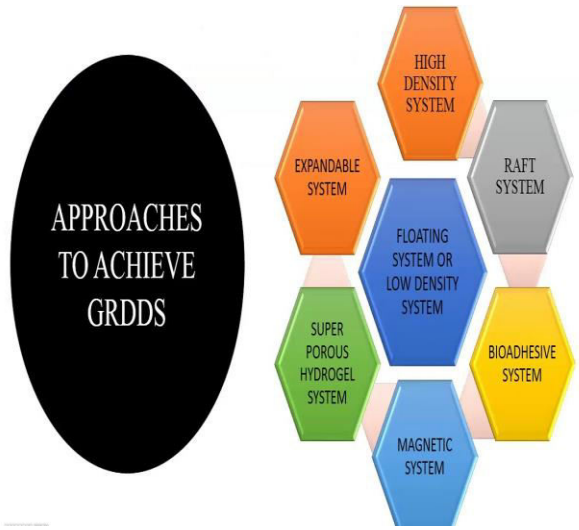
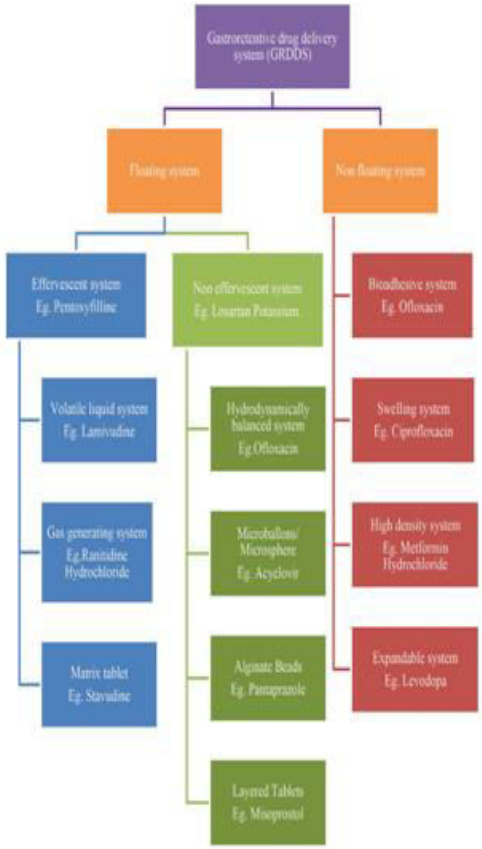


Figure 2: Approaches of gastroretentive drug delivery system

Classification of GRDDS



ClassificationofGRDDS

GRDDSareclassifiedintomainlytwotypes:floatingandnon-floatingsystems.Floatingsystemsarefurtherclassifiedinto effervescent system and non-effervescent systems basedon the mechanism of floating, while non-floating systems classifiedintofourdifferentclassesbasedonthemechanism usedforgastroretention.Figure3depictstheclassificationof the GRDDS.

I- **High-densitysystem**

The densityof dosage form plays an important factorinthe formulation of the GRDDS. A high-density system uses its weight as a retention mechanism. To enhance the gastric residence of a drug inthe stomach, its densitymust exceed thenormalstomachcontent(1.004g/mL).[16]Figure4A depicts theprincipleofahigh-densitysystem.Clarkeetal.[17]compared gastrointestinal transit of placebo pellet systems of varying densitiesusinggammascintigraphy.Theyreportedth atGRT ofsuchaformulationcanbeextendedfromanaverageof 5.8 hto25h,dependingmoreondensitythanonthediameter of the pellets.

II- **Floatingorlow-densitysystem**

Anotherapproachtoincreasegastricresidenceistolowerthe densityofdosageformthanthenormalgastriccontent.These systems remain buoyant due to lower density and provide continuous drug release. In this way, they increase GRT of thedrugandimproveitsbioavailability.[18]Figure4Bdepictsthe principle offloating or low-density systems.

(A) **Effervescentsystem**

This system uses carbonates (*e.g.* sodium bicarbonate) to generate*insitu*carbondioxide(CO_2).[19,20]Organicacids(*e.g.* citricandtartaricacids)areaddedtospeedupthereaction,thus reducingthedensityofdosageformandremainingbuoyantin thestomach.[20]Itiscategorizedintotwoclasses:

a) Volatileliquid/vacuumtype:Thesearefurtherclassifiedin to threetypes.

i) Inflatablesystem

Itconsistsofapulloutsystemhavingaspacefilledwithvolatile liquidsthatevaporateatbodytemperature.Thus,whenthese systemsareintroducedintothestomach,thechamberinflates, and the system floats. The inflatable chamber comprises a bioerodiblepolymerfilamentthatismadefrompolymerslike polyvinylalcoholand polyethylene.Whentheinflatablechamber floats in the gastrointestinal fluid semipermeable membrane alongwithpolyethyleneglycol6,000toincreaseflexibility and controlthemembranepermeability.Thepreparedsystemis reportedtostayinthestomachforaperiodof21.72hrather than12.48hofthereferencetabletanddeliversthedrugin an approximatelyzero-ordermannerfor24h.

*b) Matrixtablets:*Theyareoftwotypes,*i.e.*single-layerand bilayer matrix tablets. The single-layer matrix tablets are preparedusingadrugandahydrocolloidforminggel, while thebilayermatrixtabletcontainsoneimmediate-releaselayer andanothersustainedreleaselayer.Saisivametal.[25]developed single-layer floating matrix tablets of losartan potassium usingdifferentproportionsofHPMC-K4Mandkarayagumas retardingpolymerandsodiumbicarbonateasanefferve scent agent by direct compression method. Results of an *in vivo* study ofoptimizedformulationdisplayedthefloatabilityoftabletin gastriccontentandprolongedtheGRTtoapproximately12h. X-rayimagingstudyinalbinorabbitsindicatedtheresidenceof tabletinthestomachevenafteraperiodof12h.

c) Gas generating systems: Gas-generating systems are preparedusingeffervescentcompoundsalongwithhydrophilic polymers.

i) Floatingcapsules

These dosage forms involve encapsulation of drugs in hydrophilicpolymerslikeethylcelluloseandeudragit RS-100 witheffervescentagentssuchassodiumbicarbonate,calcium carbonate,*etc.*Moursyetal.[26]developedahydrodynamically balanced capsule containing a mixture of nicardipine hydrochloride and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolves with subsequent swelling, forming a gelatinous barrier, which remains buoyant in the gastric juice for an extended period.

ii) **Floatingpills**

Multiple unit types of oral floating dosage forms have been developedusingahydrophilicpolymerintheouterlayerandan effervescentagentintheinnerlayer.Whenitcomesincontact with the gastric fluid, the outer layer of hydrophilic polymer startstoswellandthensinks,butastheeffervescentagent meetsgastriccontent,itreleasesCO_2,andthesystemstarts to float.[27,28]Mekaetal.[29] preparedmultiple-unitminitabofcaptopril basedon a gasformationtechniqueto prolongthe GRTandto increasethe overall bioavailabilityofthe drug. Theydeveloped drug-containing core units using the direct compression process,whichwerecoatedwiththreesuccessivelayers ofan innerseal coat, effervescent layer(sodium bicarbonate), and an outer gas-entrapped polymeric membrane of polymethacrylates (eudragit RL30D, RS30D, and combinations of them). They found thatincreasingthecoatinglevelofgas-entrappedpolymeric membranedecreasedthedrugrelease.

iii) **Floatingsystemswithionexchangeresins**

Thesefloatingsystemsaremainlydevelopedtoprolongtheir GRT ofdosageformsusingionexchangeresin.Theyconsistofdrug resin complex beads loaded with bicarbonate ions, andtheyare coatedwithhydrophilicpolymers.[30]Itresultsinthegeneration ofCO_2gaswhenitcomesincontactwiththegastricfluidand causesthebeadstofloat.Atyabietal.[31]developedafloating systembasedonanionexchangeresin,whichconsistsofresin

beads,loadedwithbicarbonateandanegativelycharge ddrug that was boundtothe resin. Two resins, *i.e.*Amberlite IRA-400 andDowex2x10,wereinvestigatedandbothexhibited*invit ro* floatingtimesofover24husingastandardizedprocedure .The coateddosageformremainedforover3hinthestomach with thenon-coatedsystemanddemonstratedamarkedincreasein retentionoverconventionalformulation.

(B) **Non-effervescentsystems**

In non-effervescent floating systems, the drug comes in contactwithgastricfluidanditswells.Itmaintainsitss hape, anditsdensityremainslessthanone,henceitfloatsingas tric juice.[32]Matrixformingpolymer,gel-forming,orswellabletype hydrocolloids are used for these types of floating systems. They are further classified as follows:

i. **Hydrodynamicallybalancedsystems(HBS)**

These systems mainly consist of a mixture of drugs and hydrocolloidsthatformsagelatinousbarrier,whenitco mesin contactwithgastricfluidduetoswellingofthecombinat ion.It remainsbuoyantinthestomachforanextendedperiod asits bulkdensityislessthanoneingastricfluid.NayakandMal akar[33]developed gastroretentive theophylline HBS capsules using HPMC, polyethylene oxide, polyvinylpyrrolidone, ethylcellulose, liquid paraffin, and lactoseto controlthe deliveryoftheophylline fora longerperiod inthe stomach with a minimum floatingtime of 6 h.

ii. **Microballoons**

Microballoonsaredescribedbythegradualadditionof drug- containing emulsion into a volatile solvent. On evaporation of the solvent,gasisgeneratedinadispersedpolymerdroplet,w hich resultsintheformationofaninteriororificeinthemicrosp here of the drug with polymer. It is also called emulsion solvent diffusionmethod.[22]Thefloatingtimeofmicrospheres depends uponthetypeandamountofpolymerusedintheformula tion. Gupta et al.[34]developed pantoprazole sodium-loaded microspheres using eudragitL100 by adopting an emulsion solvent diffusion method with a non-effervescent approach. Theresultsof*invitro*and*invivo*studiesexhibitedasuita ble drug-releasepatternintermsofincreasedbioavailabilityan d efficientulcerhealingeffect.Figure6depictsthestepsinv olved inthepreparationofmicroballoonsbysolventdiffusion method.

iii. **Alginatebeads**

Thesesystemsarepreparedusingahydrocolloidgel-forming agentandsodiumalginateastheinterlockingagents.In the presenceofgastricfluid,thehydrocolloidabsorbswat erand formsabarrierthatresultsinentrapmentofairinthepoly mer, whichcausesswellingofthepolymer,andhencethedo sage form starts to float, and results in releasing the drug for a prolongedperiod.GhareebandRadhi[35] developedtrimetazidine calciumalginatefloatingbeadsusingsodiumalginates olution (2, 3, and 4% w/v), HPMC, and peppermint oil (15, 20, and 25%v/v)usingemulsiongelationmethod.Theyfoundt hatoil entrappedfloatingbeadsgavepromisingresultsforsust aining thereleaseofthedrugover10h.

iv. **Layeredtablets**

Layered tablets are more popular due to ease of their preparation,lowcost,andhighstability.

Single-layered floating tablets: These tablets were developed bymixingdrugandgasgeneratingagentswithinthema trix tablet.Theseformulationshavelowerbulkdensitythang astric fluid,andthustheyremainbuoyantinthestomachbyincreas ing GRT.[36]Kimetal.[37]developednon-effervescentgastroretentive tablets of pregabalin once a day using wet granulation and compaction. They found that the amounts of HPMC and crospovidonewerefoundbecriticalfactorsaffecting*i nvitro* dissolution and floating properties of the prepared tablets.

Figure7depictsaschematicofsingle-layeredfloatingtablets.

a. Double-layeredfloatingtablets: It comprises of two formulationsseparatedbylayering,oneontopoftheother, having two different release profiles.[3,38]Kuldeep et al.[39]developed a bilayer floating tablet of metoprolol succinate (sustained-releaselayer)androsuvastatincalcium(immediate-release layer) by direct compression method. HPMC K100, K4M,andK15Mwereusedasgel-formingagents,whilecross carmellose sodium, sodium starch glycolate, and crospovidone wereusedassuperdisintegrant.Sodiumbicarbonateis used asaneffervescentagent.Fromthe*invitro*buoyancystudy, it was observedthat asthe concentration of gas-generating agentsincreases,floatinglagtimedecreases.Also,thepolymer gasgeneratingagentratiowasfoundtoinfluencethefloating lagtimeandthetotaldurationoffloating.

***III-* Mucoadhesiveandbioadhesivesystems**

A mucoadhesive and bioadhesive system uses its adhesive propertiestotargetadrugtoaspecificregionofthebody for anextendedperiod.Figure4Ddisplaysamucoadhesivesystem ofGRDDS.Forthis,bioadhesiveormucoadhesivepolymers.

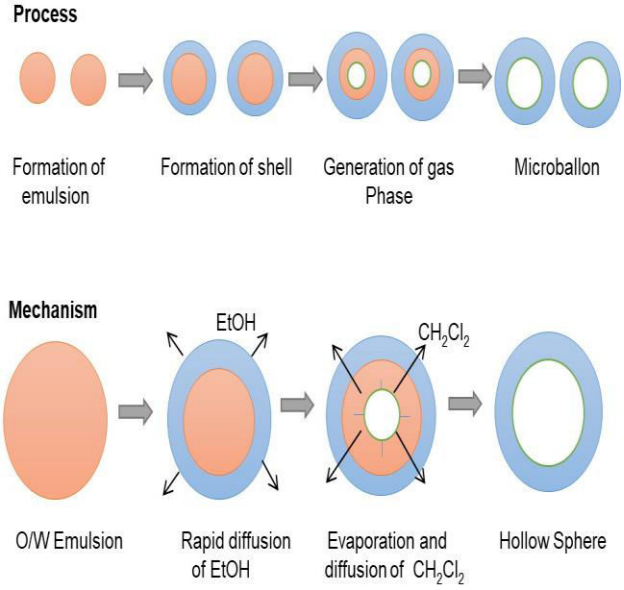


Figure6.Preparationtechniqueandmechanismofmicroballoonsformation

aremainlyused.[40]Naturalpolymerssuchassodiumalginate, gelatin,guargum,*etc.*,andsemisyntheticpolymerssuchas HPMC,lectins,carbopol,andsodiumcarboxymethylcellulose arewidelyusedformucoadhesion.Theadhesionismediated byhydration,bonding,orreceptorinteractions.[41,42] Madgulkar et al.[43]developed sustained-release tablets of itraconazole usingmucoadhesivepolymercarbopol934PandHPMCK4M. Theyconfirmedsustaineddrugreleaseandgastricretention for six hours in albino rats. Figure 8 depicts the principle of mucoadhesive drug delivery systems.

***IV-* Swellingsystem**

Thesesystems,whencomeincontactwithgastricfluid,their size increases significantlythan that of the pyloric sphincter andthus,afterswelling,remainloggedinthestomach.These arealsocalleda"plugtypesystem".[44]Controlledandsustained drugreleaseisachievedusinganappropriateexcipient.The swellingabilityofpolymermainlydependsuponthedegreeof cross-linkingofhydrophilicpolymernetwork.Thehighdegree ofcross-linkingmaintainstheintegrityofthesystem,whilealowdegreeofcross-linkingcausesextensiveswellingresulting in rapid dissolution ofthe polymer.[45]

***V-* Superporoushydrogels**

Superporous hydrogels are a three-dimensional network of hydrophilic polymers that have numerous super-size pores inside them. The swelling of superporous hydrogels occurs bythemechanismofcapillarywettingthroughinterconnected open pores. To develop superporous hydrogels, certain ingredientslikeinitiatorsandcross-linkersareusedtoinitiate the cross-linking.[46]Other ingredients were foam stabilizers, foaming aids, and foaming agents. Desu et al.[47]developeda superporous hydrogel system using *N'*, *N'*-methylene bisacrylamide as the cross-linking

operator and polyvinyl alcoholasacompositespecialist,ammoniumpersulfateand *N*,*N*-tetramethylenediamineasaninitiatorpairandSpan80asasurfactant.Theyareusedasafrothstabilizertomakea permeablestructureusingthegas-formingmethod.

VI- **Magneticsystem**

Inthissystem,byusingastrongmagnetwithapowerfulmagnetic fieldontothebodysurface,themovementofgastroretentive formulationwithasmallinternalmagnetiscontrolled.Several reportstell aboutthe positive results ofthis system, butthe success of this system depends upon the selection of the magnet position with very high precision.[48]Gröninget al.[49]developed peroral acyclovir depot tablets with an internal magnet.Anextracorporealmagnetwasusedtoprolongthe GRT ofthedosageformandtoinfluencethedurationofabsorption ofacyclovir.Theyperformedan*invivo*studywithfivehealthy malesubjectsanddeterminedtheplasmaconcentration-time profilesofacyclovir.Computersimulationswerecarriedoutto displaytheinfluence of GRT of acyclovirdepot preparations on theplasmaconcentration-timeprofilesofacyclovir.Figure4E displays a magnetic system of GRDDS.

Invitroassessment

ForGRDDS, *invitro*assessment isveryessentialto predict gastrictransitbehavior.Followingaretheparameters, which should be considered for designing novel gastroretentive formulations.

i. **Buoyancylagtime**

Itisthetimetakenforgastroretentiveformulationstomove ontothesurfaceofthedissolutionmedium.Itisdetermined usingaUSPdissolutionapparatuscontaining900mLof0.1N HClsolutionasatestingmediummaintainedat37°C.Thetime requiredtofloatdifferentdosageformsnotedasfloatinglag time.[50]

ii. **Floatingtime**

Thisdeterminesthebuoyancyofdosageform.Inthistest,a specific dissolution apparatus is used depending uponthetype of dosage form with 900 mL of dissolution medium kept at 37°C.Thefloatingtimeorfloatingdurationofthedosageform is determined byvisual observation.[51,52]

iii. **Specificgravity/density**

Specific gravity estimates are essential for both low-density andhigh-densityGRDDS.Specificgravityisdeterminedusing the displacement method.[53]

iv. **Swellingindex**

Swellingindexisdeterminedbyimmersingthetablets in0.1 NHClat37°Candtheirperiodicremovalatregularintervals.[54]

v. **Wateruptake**

Inthisstudy,thedosageformisremovedfromthedissolution medium after the regular interval and a weight change is determined.[55]

$$\text{Wateruptake(WU)}=(W_t-W_o)*100/W_o$$

where W_t= weight ofthe dosage form attimet, W_o= initial weight of the dosage form

vi. **Weightvariation**

Variousofficialmethodsarerecommendedbypharmacopeias to calculatethe weightvariation. Usually,the individual and averageweightof20tabletsarerecorded.Fromthesedata, averageweightandweightvariationiscalculated.[56,57]

iii.Hardnessand friability

HardnessorcrushingstrengthisdeterminedusingaMonsanto tester,Strongcobbtester,Pfizertester,*etc.*Friability(strength) oftabletsisdeterminedusingaRochefriabilator.[58,59]

viii. **Invitrodissolutiontests**

Thistestisperformedto determine drug release from GRDDS in gastricfluidandintestinalfluidmaintainedat37°Catadefinite timeusingUSPdissolutiontypeIIapparatus(paddle).[59,60]

Here,after*invitro*assesment,Table1representstherecent

trendsinGRDDS,whileTable2representsthenameso fdrug candidates for GRDDS.

Evaluationofmicrosphereandbeads

Anopticalmicroscopewasusedtomeasuretheparticle size of beads and microspheres. Surface morphology and cross-sectionalmorphologyareevaluatedwiththehelpofascanning electron microscope.

Invivoassessment

a. Radiology

This technique is mainly used to determine the position of gastroretentivedosageformfilledwithbariumsulfate (radio-opaquemarker)insidethebodysystemconcerningtime using X-ray.X-raypicturesaretakenatdifferentintervalstorecord thecorrectpositionofthedosageform.[61,62]

b. **Scintigraphy**

Similarto radiology, it is used to determine *invivo*floating behavioroftheGastroretentivedosageform.Inscintigraphy, 99mTcpertechnetateisusedasanemittingmaterialinsteadof anX-raytoengulftheformulationtorecordtheimage.[63,64]

c. **Gastroscopy**

Gastroscopy is widely used for visual examinations of gastroretentivedosageforms.Inthistechnique,anilluminate optical,tubular,andslenderinstrumentcalled"endoscope"is usedtolookdeepinsidethebodypartssuchasthestomach, esophagus, and small intestine.[65,66]

d. **Ultrasonography**

It is a diagnostic imagingtechnique, in which ultrasound is used forimaginginternalbodystructures.Themaindisadvantageof thistestisnon-detectabilityatentrails.[1,66,67]

e. **^{13}Coctanoicacidbreathtest**

Radioactive ^{13}C octanoic acid is usedto assessthe extent of absorptionofdrugsfromGRDDS.

f.Magneticmarkermonitoring

Compared with radiology and scintigraphy, this method is radiation-less, and thus is non-

Table1.Showingsomerecenttrendsin GRDDS

Drug	Requirementsfordevelopment	Dosageforms	References
Diltiazem HCl	a)Lowsolubility b)Shorthalf-life c)Lowbioavailability(40-50%)	Osmotictablet (pump)	63
Theophylline	a)Shorthalf-life b)Lowbioavailability	Floatingcapsule	64
Metformin HCl	a)Shorthalf-life b)Lowbioavailability	Beads	65
Ciprofloxacin hydrochloride	Lowbioavailability Shorteliminationhalf-life	CRfloatingtablet	66
Acyclovir	Shorthalf-life b) Oralbioavailabilityispoor(15-30%)duetopoorwatersolubility DegradeathighpH	SRfloatingmicrosphere	67
Ranitidine HCl	Shorthalf-life Absorptionwindowinapartof GIT Poorbioavailability	Floating(pulsatile) DDS	68
Ciprofloxacin HCl	Shorteliminationhalf-life(about4h) b) Narrowabsorptionwindowandabsorbedinproximal SI Freelysolubleinwater	Floatingtablet(matrix)	69
Ziduvudine	Dosedependantsolubility Shortbiologicalhalf-life Poorbioavailability	Tablet	72
Cephalexin	Acidicdrug Shorthalf-life Poorbioavailability	Floatingtablet	73
GRDDS:Gastroretentivedrugdeliverysystems			

hazardous.[67,68] It involves real-time tracking of the dosage form in the gastrointestinal tract.[69,70] This technique is mainly used for the determination of the gastrointestinal motility and dissolution behavior of pharmaceuticals. In this technique, the dosage form is labeled as a magnetic dipole by incorporating a trace of ferromagnetic particles and recording the magnetic dipole field by an apparatus responsive to bio-magnetic measurement.[71-73]

Conclusion

GRDDS are unique systems and have become important in the last three decades. It offers various advantages, *viz.*, site-specific, slow, and controlled release of drugs from different types of gastroretentive dosage forms, thus improving patient compliance and reducing the side effects by minimizing dosing frequency. Therefore, it is expected that in the future, various pharmaceutical companies will come forward to initialize gastroretentive drug delivery technology to create excellent advantages, prolonging patents, and a better outcome for their marketed formulations.

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