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Immediate Drug Release Dosage Form : An Update

Abdul Majid Abdul Mobeen and Prof. Dr. Avinash S. Jeddwar
NSPM College of Pharmacy, Darwha, Yavatmal, India

Abstract: *Among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self administration, compactness and easy manufacturing; sometimes immediate onset of action is required than conventional therapy in many cases. So that to overcome these drawbacks, immediate release dosage form has emerged as alternative oral dosage forms. Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. The basic approach used in development tablets is the use of superdis integrants like Cross linked Polyvinylpyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croscarmellose) etc. These superdisintegrants provide instantaneous disinteragation of tablet after administration in stomach. In this field immediate release liquid dosage forms and parenteral dosage form have also been introduced for treating patients. In liquid dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, AOT (dioctylsulfosuccinate) etc.*

Keywords: Polyvinylpyrrolidone

I. INTRODUCTION

In the present study and research novel drug delivery systems are developed for expanding markets/ indications, extending product life cycles and generating opportunities. Oral administration is the therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage fo rm technologies change in response to the unprecedented shifts in the drug discovery Such as genomics. The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide . The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quickonset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy. Most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance.

DEFINATION

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulation which are adapted to provide for modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug. Release term includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1 to 3, especially at, or about, pH=1. In one aspect of the invention a formulation as described herein with a compound of formula (I), or an acid addition salt thereof, in crystalline form releases drug under a range of pH conditions. In another aspect of the invention a formulation as described here in with a compound of formula or an acid addition salt thereof releases drug under pH conditions such as pH=1 to 3, especially at, or about, pH=1. Thus, formulations of the invention may release at least 70% (preferably 80%) of active ingredient within 4

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hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes), of administration, whether this be oral or parenteral.

PHARMACOKINATICS

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs

PHARMACODYNAMICS

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ. Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Decreased sensitivity of the CVS to adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics. Altered response to drug therapy elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed. Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive etc. For immediate release dosage forms. The combination choice depends on disease state of the patient. Problems with Existing Oral Dosage Form:Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an oesophagus may cause gastrointestinal ulceration Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia. Liquid medicaments are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult. Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications. Cost of products is main factor as parenteral formulations are most costly and discomfort. Desired Criteria for Immediate Release Drug Delivery system: Immediate release dosage form should-In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period. In the case of liquid dosage form it should be compatible with taste masking. Be portable without fragility concern. Have a pleasing mouth feel. It should not leave minimal or no residue in the mouth after oral administration.

MERITS

Merits of Immediate Release Drug Delivery System: Improved compliance/added convenience Improved stability, bioavailability. Suitable for controlled/sustained release actives Allows high drug loading. Ability to provide advantages of liquid medication in the form of solid preparation. Adaptable and amenable to existing processing and packaging machinery Cost- effective Improved solubility of the pharmaceutical composition; Decreased disintegration and dissolution times for immediate release oral dosage forms; Other Excipients: Excipients balance the properties of the actives in immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents. Bulking Materials: Bulking materials are significant in the formulation of fastmelting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolysates for higher aqueous solubility

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and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition .

EVALUATION OF TABLETS

These tests are as following:- 1. Appearance 2. Thickness 3. Hardness 4. Weight variation 5. Friability 6. Disintegration 7. Uniformity of dispersion 8. Wetting Time 9. Water absorption ratio 10. Drug content 11. In vitro Dissolution 12. Stability studies 1. Appearance: The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. 2. Thickness: The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm. 3. Hardness: The hardness of tablet is an indication of its strength against resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage. Measuring the force required to break the tablet across tests it. Hardness of 10 tablets (randomly) from whole tablet batch was determined by Monsanto hardness tester. Hardness measured in kg/cm2. 4. Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated 5. Friability test: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage of weight loss was calculated using the formula %f x 100 Here, %f = Percentage friability W0 = Initial weight (Before test) W1 = Final weight (After test) 6. Disintegration test: The USP device to rest disintegration was six glass tubes that are “3 long, open at the top, and held against 10 screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 20C, such that the tablets 8 | Page remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. 7. Uniformity of dispersion: Two tablets were kept in 100ml water and gently stirred for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered to pass the test if no residue remained on the screen. 8. Wetting Time: The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petridish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time. 9. Water Absorption Ratio: A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper. The wetted tablet was then weighed. Water absorption ratio, R was determined by using following formula R x 100 Here, R = Water absorption ratio Wb = Weight of tablet before water absorption Wa = Weight of tablet after water absorption 10. Drug content: 10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media buffer or 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed.

Spectrophotometrically and further calculation carried out to determine drug content in one tablet. 11. In vitro drug release studies: The immediate release tablets are subjected to in vitro drug release studies in pH 6.8 phosphate buffer or 0.1N HCl for 30 minutes to access the ability of formulation for providing immediate drug delivery. Drug release studies were carried out in dissolution test apparatus using specified volume 900ml of dissolution media maintained at 37±0.20C. The tablets are kept in the cylindrical basket or directly placed in medium with paddle then rotated at 100 rpm. 5ml of the sample from the dissolution medium are withdrawn at each time interval and 5ml of fresh medium was replaced each time. The samples were filtered and from the filtrate 1ml was taken and diluted to 10ml. These samples were analyzed spectrophotometrically and further calculation was carried out to get drug release. The drug released data were plotted and tested with zero order First order (Log % Remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants, correlation coefficient and dissolution efficiency were calculated. 12. Stability study: Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during

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storage, because of chemical alteration of the active ingredients or due to product instability ,lowering the concentration of the drug in the dosage form. Stability study of the dosage form must include a section for product characterization and another section to study the product stability during storage. Formulations are evaluated for their appearance, possible weight gain in drug content thickness, flatness, folding endurance, tensile strength, moisture content and moisture uptake, and invitro release study by keeping 9 | Page dosage form in different temperature and humidity condition after a specified time. The stability study indicates that the formulation is quite stable at different conditions of storage.

ORAL FORMULATIONS.

Oral formulations have earned a significant place among the various dosage forms developed so far for human administration. In most of the cases, the conventional oral delivery system show limited bioavailability because of fast gastricemptying time among many other reasons involved . However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest to this new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules, of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine. Solubility can also improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine. There are many drugs .that are prone to degradation in the colonic area. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustainedcontrolled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time. Apart from stemic action, GRDDS has proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried Helicobacter pylori from the submucosal tissue of the stomach. The history of GRDDS formulations dates back to almost three decades.

STOMACH PHYSIOLOGY

Success of GRDDS relies on the understanding of stomach physiology and related gastric emptying process. Structurally the human stomach is composed of three anatomical regions: fundus, body and antrum, as depicted in. After a meal, the average volume of a stomach is about 1.5 l, which varies from 250 to 500 ml during the innter-digestive phases. The part made of the fundus and the body acts as a reservoir of any undigested material, while the antrum performs as the principal site for the mixing action. Being the lower part, the antrum works as a pump for gastric emptying by a propelling action. Pylorus acts to separate the stomach from the duodenum and plays a major role in gastric residence time of the ingested materials. However, the pattern of the gastric motility is different for the fasting and fed state. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases. The motility pattern of the stomach is called migrating motor complex . 3. Approaches to fabricate gastro-retentive systems different approaches have been adopted by researchers to enhance gastric residence time with the prolonged drug release. The concept of high density formulation is one such approach. The developed dosage form was made heavy to withstand in vivo peristaltic movement and remained intact in spite of the GIT disturbance. Accordingly, the GI transit time was expected to prolong for an average of 5.8 h to 25h. Barium sulphate Iron powder, titanium oxide, and zinc oxide were incorporated in the formulation to increase the density of the dosage form. Increased dose size required to achieve that high density was one of themajor drawbacks of this kind of system, as reported by Chawla et al. Another novel idea was postulated to retain the dosage form within the 11 | Page stomach by the application of a magnetic field. The dosage form would contain magnetically active elements. One external magnet was required to position on the abdomen over the location of the stomach to retain the administered drug in place. Though innovative in design, lack of patient compliance was one of the major setbacks for in vivo design of this delivery system . With the introduction of swelling and expanding system, GRDDS managed to

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achieve significant success both in vitro and in vivo in order to retain the dosage form in the stomach. Bolton and Desai reported one such system that was designed to increase in size bigger than the diameter of pyloric sphincter and remain logged there. Alternatively, the system was named as 'plug type systems'due to their pyloric sphincter blocking attribute. Once the polymer came in contact with the gastric fluid, it absorbed waterand swelled. The selection of a suitable polymer (or combination of polymers) with appropriate molecular weight/viscosity grade and swelling properties enabled the dosage form to attain sustained release characteristic. Further advancement of such kind of dosage form has taken place with the introduction of novel polymers with super-porous nature, causing them to swell to an equilibrium size within a minute.

This characteristic rapid swelling property (swelling ratio is 1:100or more) of the polymer with an average pore size of more than 100 μm occurs due to capillary wetting through several interrelated open pores when the dosage form comes in contact with GI fluid. Another type of GRDDS has been designed utilizing buoyancy (floating) property of any dosage form experienced in GIfluid. The bulk density of the dosage form attains less than the density of gastric fluid (1.004 to 1.010 g/ml) after a certain lag time. This lag time depends on the rate of swelling of the polymer used in the formulation, which again depends on the type, viscosity grade, presence of wicking agent or swelling enhancers, etc. The said parameters of the formulation also determine the duration of floating as well as in vitro drug release rate. The efficacy of the floating behavior also depends on the physiological conditions of patients, like fed state or fasting state, amount of gastric fluid, etc. After the required drug release, the used dosage form is emptied out from the stomach. One additional attribute such as effervescence was incorporated within this swelling-based floating delivery system to improve the floating behavior. Various effervescent components (e.g. sodium bicarbonate,tartaric acid andcitric acid) were mixed within the dosage form. when these components come in contact with the gastric contents, carbon dioxide (CO2) is liberated as a result of a chemical reaction and it becomes trapped within the gellified hydrocolloid system. These combinations of effervescence and swelling help the dosage form achieve effective density less than the gastric fluid and result an upward motion onto a dosage form which maintains the buoyancy for a prolonged period of time. In addition to the single unit systems, the bi-layers and tri-layers design of this combination approach has also been considered to incorporate two different 12 | Page drugs with different release profiles.One of the drugs and excipients is individually formulated as sustained release layer containing the gas generating unit, whereas the outer layer includes the second drug for immediate release profile. Bioadhesive or muco-adhesive drug delivery systems were also tried as gastro-retentive systems. The dosage form was made to be attached inside the lumen of the stomach wall and survivethe gastrointestinal motility for a longer period . It was also beneficial as a site specific design to promote local drug absorption in an infected area of the stomach. Muco adhesive excipients like polycarbophil, lectins, carbopol, chitosan, carboxymethylcellulose, pectin and gliadin were reported as formulation compositions for this kind of design. The combination of macho adhesion and floating or swelling mechanism is being adopted as another novel approach for improved gastroretention attributes. In-situ gelling technique in combination with carbon dioxide bubble entrapment was also reported as another patient compliance design for gastroretention. This type of delivery system, initially as a solution form, contains sodium alginate as in situ gel forming polymer along with carbonates or bicarbonates as effervescent agents. When they come in contact with the gastric fluid, they swell and generate a viscous cohesive gel that contains entrapped carbon dioxide bubbles, causing the drug delivery systems to float. For gastroesophageal reflux treatment raft forming wereems are frequently used because of their tendency to produce a layer on the upper part of the gastric fluid 4. In vitro assessment of GRDDS In vitro evaluations of GRDDS are prerequisite to ensure the in vivo performance with respect to floating lag time and floating duration, as well as selection of right formulation composition. In case of tablet dosage form, the routine evaluation tests include general tabletting parameters like hardness, friability, general appearance, drug content, uniformity of content, weight variation, and in vitro drug release . For evaluation of floating behavior like floating lag time and the duration of floating for any GRDDS, deionized water and simulated gastric fluid have been used in the literature. These two media are used to observe possible differences in buoyancy capabilities of the dosage forms. Additionally, swelling property and the rate of swelling of the polymeric dosage forms placed in a dissolution medium (0.1N HCl) are tested for at least 8 h to ensure drug release and floating mechanism. This is done bymeasuring the size of the swollen tablet or the weight gain after collecting them at the end of the study . For in vitro drug release test, simulated gastric fluid is used as the test medium. Samples are withdrawn from the dissolution baskets with a predetermined time interval and are diluted appropriately to be analyzed for the drug

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content. Microscopic observation, preferably scanning electron microscopy, is used at different magnification powers for visualization of the surface morphology of the dosage form. For the gastro-retentive beads and microspheres, some other additional tests like drug loading, particle size analysis and drug entrapment efficiency are performed to optimize formulation composition and related processing parameters. Spectrophotometer, optical microscope and particle size analyzer are 13 | Page routinely used in these types of in vitro evaluation tests. In vivo gastric retention as a surrogate of pharmacokinetic study A well-designed in vivo study in appropriate animal model or healthy human subjects is required to prove the in vivo efficacy of any GRDDS. However, handling smaller animals like mice, rats, guinea pigs or rabbits for checking the gastric retention along with bioavailability study is difficult, especially for a big size tablet dosage form, That's why most of the literatures on formulation of GRDDS had shown the proof of in vivo gastric retention in relatively bigger sized animals like dog or human subjects, together with important importantly characterization studies such as dissolution study, estimation of floating lag time and floating duration. The extended in vivo gastric retention was hypothesized that the GRDDS was supposed to give improved therapeutic efficacy as compared to the conventional dosage form. Many sophisticated visualization techniques are helpful in this regard. Gamma scintigraphy is one such popular and elegant technique to provide appropriate assessment of gastro-retentivity in humans. A small amount of radioisotope with short half life is incorporated within the dosage form. The formulation is exposed to a neutron source that can cause it to release the characteristic gamma rays to be captured as an image after processing by a computer . formulated hollow calcium pectinate beads of diclofenac sodium for its chronopharmacological action. The floating beads were structurally hollow spheres with a bulk density of less than 1 g/ml and 34% porosity. An in vivo study was done on rabbits by gamma scintigraphy, which showed gastro-retention of beads up to 5 h. There are many other recent breports of success in vivo gastric retention of floating tablets and microspheres containing versatile drug molecules like ascaridole, calcium-disodium edentate, and repaglinide. Magnetic Resonance Imaging (MRI) is another technique to prove in vivo gastro-retention of a GRDDS. In vivo success of GRDDS in the background of pharmacokinetic attributes Based on a huge volume of literatures, it is quite established that oral gastro-retentive drug delivery system has been widely explored within the last three decades of research in drug delivery. However, only a handful of them have been evidenced with in vivo proofs. The following sections contain a glimpse of them arranged chronologically for animal and human subjects separately: developed a novel controlled release GRDDS of Levodopa by using unfolding polymeric membranes with extended dimensions and high rigidity. In vivo study was done with the beagle dogs pretreated with carbidopa. The developed formulation was administered and the location of the dosage form in the gastrointestinal tract was determined by X-ray. Also, serial blood samples were collected and examined for the active drug. It was found that the optimized controlled release GRDDS of Levodopa was able to maintain the therapeutic concentrations of Levodopa (>500 ng/ml) over 9 h. The mean absorption time was considerably prolonged compared to non-GR controlled release-particles and oral solution. jain et al. formulated floating microsphere of repaglinide (hypoglycemic agent) where calcium silicate was used as porous carrier and Eudragit as polymer. Sprague Dawley male rats were subjected to the organ distribution study and suspension of99mTc 14 | Page labeled floating microspheres were administered to albino rabbits orally with water. After the gastric residence time of 6 h as confirmed by gamma scintigraphy, the rats were sacrificed and organs were isolated organ distribution of the test compound was found to be uniform and the relative bioavailability was 3.17 times compared to marketed tablets. In vivo anti tumor study was carried out by Shishu and Aggarwal to check the therapeutic efficacy of floating calcium alginate beads of 5-flurouracil. It was found that the multiple unit floating system was able to reduce gastric tumor incidence by 74% in mice where the reduction of this incidence was found to be only 25% in the case of a conventional tablet dosage form. Pande et al. Prepared cefpodoxime proxetil microspheresas GRDDS. The solvent evaporation technique was used for the development of the drug loaded microspheres where ethyl cellulose and HPMC were used as the release retarded materials.

HUMAN STUDY

Chen et al. Developed a gastro-retentive tablets based on swelling/ effervescence mechanism with a combination of hydroxyethyl cellulose, sodium carboxymethyl cellulose, and sodium bicarbonate for administering antihypertensive drug losartan. Tablets were found to remain floating in vitro for more than 16 h with a swelling to 2 cm in diameter within 3 h. Additionally, the tablets showed pHdependent drug release with an extension for 24 h. When tested in

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healthy human volunteers, the optimized tablets achieved an enhanced bioavailability of approximately 164% relative to the immediate release market formulation named Cozaar®. As expected, the gastro-retentive floating tablets produced favorable pharmacokinetic parameters: maximum residence time (MRT) and Tmax values were greater and Cmax values were lower as compared to the commercial formulation.Bomma and Veerabrahma established efficacy of antibiotic treatment with gastro-retentive tablets of cefuroxime axetil over conventional tablets, Zocef®. Developed and optimized tablets were based on a combination of swelling (HPMC and Polyox WSR 303) and effervescence (citric acid, calcium carbonate) mechanism. In line with in vitro floating duration of more than 12 h with a floating lag time of less than 30 s, the 15 | Page optimized tablets could be retained 225 ± 30 min in human subjects as confirmed by in vivo radiographic studies. The same tablets were tested on eight healthy human volunteers. The developed floating tablets showed superior bioavailability than Zocef tablet. Based on in vivo performance, a significant difference was observed in Cmax, Tmax, t1/2, AUC0 − ∞, and mean residence time between test and reference ($P < 0.05$). As compared to the reference tablets, the floating tablets of cefuroxime axetil resulted in an increase of 1.61-fold relative bioavailability. In vivo efficacy of GRDDS containing a high load of nicotinamide (600mg) as an active drug was patented by Meijerink el al. Hypromellose was used as a swelling agent in that formulation. Eight healthy adult volunteers were used to explore their pharmacokinetic profiles. Blood samples as well as urine were collected at a predetermined time intervals. 8.HUMAN STUDY The developed dosage form was capable of maintaining as increased nicotinamide plasma levels in vivo for a period of at least 8 hafter ingestion by the volunteers. Ranade et al. Studied ellagic acid and aloe vera gel powder as a bilayer floating tablet prepared with HPMC K15Mand sodium bicarbonate to treat stomach ulcer. The researchers reported 75% ulcer inhibition in comparison to 57 % ulcer inhibition with ellagic acid alone. This efficacy was resulted from the tablets that showed in vitro floating duration of only 4 h with a cumulative 92% drug release. In another study , efficacy of gastro-retentive emulsion gel calcium pectinate beads contacting cinnarizine prepared by the ionotropic gelation method was established by Abouelatta et al. The researchers reported improved in vivo efficacy with a mean AUC0 − 24 and AUC0 − ∞ enhancement of 1.79 and 3.80 times, respectively, compared to a conventional tablet in healthy human volunteers. Interestingly, the beads composed of pectin glyceryl monooleate and labrafac lipophile WL 1349 has instant in vitro floating capacity. Although many GRDDS with various novel fabrication options have been reported for their in vitro success, their commercialization success is not significant. A glimpse of a few new candidates together with the old once. 7. Challenges ahead with GRDDS The retention time of the dosage forms in the GIT is one of the determinants of the bioavailability of oral drug delivery systems. In case of GRDDS, it is rather specific to the stomach only.Therefore, for developing a GRDDS, the main challenge is retaining the delivery system in the stomach or the upper part of thesmall intestine for a long time until all the drugs have been released at a predetermined rate. The process of gastric emptying time is highly variable. Among many other factors, it mainly depends on the dosage form as well as fed or fasted state of the stomach.The gastric retention time is extended in the fed state, whereas shortened by the fasting state. Other physiological barriers and factors like the type of food, caloric content, gender and age play significant roles in the variation of gastric emptying time. Because of high caloric content, high fat meal strongly prolongs the process of gastric emptying. Indigestible polymers or fatty acid salts also modify the motility pattern of the stomach under fed state and help in reducing gastric emptying rate. Additionally, patients have variable GRT depending on gender and age, 16 | Page as reported by Mojaverian et al. [83]. The pylorus limitation plays an important role in gastric retention of any GRDDS.The pylorus size is about 2 to 3 mm during the digestion and the diameter becomes 12.8 ± 7.0 mm during the inter-digestive phase. Thus, all particles must have a diameter lower than 5 mm so that they can pass through the pylorus into the duodenum [84].Another factor to consider here is the variation in pylorus size and its peristaltic movement of the animal (e.g. dog, rabbit model) from that of the human . So, in vivo efficacy results need to be concluded carefully. Size and shape of the dosage form, individual's disease state, and body mass index are some other factors on which gastric residence time is dependent and related to the efficacy of the dosage form [84]. However, it has been reported that sometimes multiple-unit GRDDS shows an improved and predictable drug release compared to a singleunit GRDDS. Due to a combination of the lag time and the gastric emptying process, a single unit gastro-retentive dosage form (GRDF) may ultimately exit the stomach before the dosage form becomes functional.Hence, to develop an optimum GRDDS, the main challenges are to overcome the problems associated with the gastric emptying rate of the stomach together with maintaining an appropriate drug release rate for an extended period of time before it gets metabolized in the system.

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II. CONCLUSION

According to the review of different published literature and detailed investigations on commercial products, it can be concluded that no single gastroretentive system could be marked as the best suited for any drug candidate. However, several advantages of GRDDS for patients have been evidenced in the majority of them. Individual drug candidate or a combination of the drugs needs to be assessed case by case regarding the necessary dose and the ease of manufacturing process. Polymer selection remains a critical factor for the formulations that contain high dose. This selection is essential for the compressibility needed to exploit the high doses of the APIs. However, the criteria of ideal polymer should be based on its amount in the dosage form; a minimum quantity that provides a substantial gastric retention should be preferred [5]. Although several approaches like floating, bio-adhesion, effervescence, sinking, magnetic, swelling, etc. Have been proposed over the years, reports on their in vivo success have not been captured significantly. 17 | Page Formulation wise, the major trend has been shifted toward the use of swelling polymer matrix together with effervescence in the design of floating delivery systems. Commercially it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. In terms of delivering drugs to the systemic circulation along with enhanced effectiveness, it is expected that GRDDS will become more popular in the near future. However, it is necessary to establish their efficacy by properly designed in vivo studies for a specific drug because of the complexity in pharmacokinetic and pharmacodynamic parameters.

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