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Peer Review Article: Combined novel approach to enhance the solubility and Intestinal absorption: A recent review.

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Abstract

For oral pharmaceutical products to achieve high bioavailability and minimal variability, the API must dissolve and be stable in the GI media as well as sufficiently absorb at pertinent sites in the large intestine and small intestine. The possibility for API absorption from any dosage form is determined by an important biopharmaceutical parameter known as regional intestine effective permeability. For effective estimation of the manufacturing potential of a dosage form, it is especially crucial to understand the quantity of drug absorption from the human large intestine. Drug development is difficult because enhancing a drug's solubility, dissolution, and bioavailability is challenging. Among the four classes of the biopharmaceutical classification system (BCS) major work has been done on the low soluble drugs. In recent years poor solubility has been a major challenge for pharmaceutical scientists and a lot of experimental works are ongoing. Changing polymorphic forms by different new approaches and increase in the surface area is a widely used and comparatively simple method for increasing solubility and making the drug more bioavailable. For achieving the desired effects, permeability (intestinal absorption) is also playing an important role like solubility, but the focus of scientists is less on the permeability enhancement of low permeable drugs in respect of solubility. Sometimes it has been tried but with very limited success. The objective of this paper to provide a comprehensive review on improving solubility, release and intestinal absorption of low soluble and low permeable drugs with a combined novel approach of solubility and absorption enhancement. The ability to produce high soluble and high permeable drugs will grow significantly in the coming years and this will help to grow the revenue of the innovators as well as generic pharmaceutical companies.

Keywords

Absorption, Bioavailability, Dissolution, Duodenum, Gastrointestinal tract, Gastrointestinal transit time, Gastroretention, Milling, Permeability, Poor water-soluble drug(s), Polymer(s), Solvent evaporation, Spray drying

Introduction

Most drugs are administered orally in solid dosage forms. In such dosage forms, the delivery of the active ingredients to systemic circulation requires initial transport through the GI membrane. Solubility characteristics play a key role in this initial process. Hydrophilicity favours drug dissolution in aqueous media of the GI lumen, while lipophilicity favours subsequent penetration into the lipoidal membrane. For efficient absorption, a proper balance between these two opposing properties is required[1]. Because of the limited fluid volume within the GI lumen, the efficiency of absorption is also affected by the size of dose. If the drug dose is low and falls in the low soluble class it may absorb completely. On the other hand if the dose is high and belongs to the low soluble class then absorption is affected and drug

absorption is reduced. Numerous variables, including the drug's poor water solubility and poor membrane permeability, can impede drug absorption from the gastrointestinal system [2]. Any drug substance that is administered orally first needs to dissolve in the stomach or intestines before it can be absorbed by the GI tract's membranes and enter the body's circulatory system. Consequently, there are two disciplines of pharmaceutical research that should focus on increasing the bioavailability of active agents:

(i) Enhancing the solubility of low water-soluble drugs to increase dissolution rate
(ii) Increase the permeability (intestinal absorption) of poorly absorbed drugs.

Bioavailability

The amount of an oral medicine that reaches the systemic circulation in an unchanged molecular state is measured by the bioavailability, a crucial pharmacokinetic parameter.

$F = Fabs \times (1 - EG) \times (1 - EH)$

Where F is the bioavailability, and EG - amount extracted in the gut wall and EH are the amount extracted in the liver.

The active pharmacological ingredient's solubility, luminal stability (chemical and enzymatic), intestinal permeability, and intestinal transit time play a substantial impact in determining the amount of the dose that is absorbed (Fabs) and its absorption rate (API). Most drug products are required to provide an optimal plasma concentration-time profile that delivers the required pharmacodynamic response and minimum side effects in order to attain high bioavailability.[3]

Methods for enhancement of bioavailability- There are three main approaches for resolving the bioavailability issues:

A) Pharmaceutical approach: Design and development of the drug's formulation, manufacturing techniques, or physiochemical characteristics.

B) Pharmacokinetic approach: A drug's response can be changed by changing its chemical composition.

C) Biological approach: The way a medicine is administered may change, for example, from oral to parenteral. Aqueous solubility is a very important factors in the third approach[4].

Our aim in this article to explore the pharmaceutical approach i.e, solubility and intestinal permeability enhancement and applied in the same formulation. From our literature search, there is no research or review article available to date that focusses on the *ex/in vivo* performance of solubility enhanced gastro-retention techniques. In this respect, the goal of this review is to compile the *ex/in-vivo* studies of GRDDS (gastro-retentive drug delivery system) in terms of pharmacodynamic, pharmacokinetic characteristics, gastro-retention methods, and inherent difficulties or limitations for *ex/in-vivo* evaluations as reported by numerous researchers.

Solubility

If a drug molecule is absolutely soluble at the highest single therapeutic dose in 250 ml or less of aqueous media with a pH range of 1.2-6.8 at 37°C, it is said to be highly soluble. Therapeutic effectiveness of drugs totally depends on absorption and solubility of drug molecules. One essential factor for achieving the desired drug concentration in the systemic circulation and demonstrating a pharmacological response is solubility. Approximately half of newly discovered APIs entering in a drug development stream have failed because of inadequate biopharmaceutical characteristics[5]**.**

Intestinal absorption

The integrity of the tight connections in the intestinal epithelial wall is compromised, allowing material from the lumen to translocate into the blood circulation, other organs and adipose tissue[6].

Factors affecting the intestinal absorption

Gastric emptying time

When a medicament is best absorbed from the distal region of the small intestine, fast gastric emptying, the process by which food exits the stomach and enters the duodenum, is required. But when drugs are absorbed from the proximal part of the small intestine then prolonged drug availability for more absorption is desired. To allow this to occur a delayed gastric emptying formulation is required.[7].

Intestinal transit time

The majority of medications are primarily absorbed in the intestine, hence prolonged intestine transit time is ideal for complete drug absorption [8].
Prolonged intestinal time is desirable for-

1. A formulation that dissolves slowly from its dosage form (low soluble).
2. Enteric coated formulations, that dissolve only in the intestine.
3. Most part of drugs that absorb in the specific site of the intestine.

Table 1. Transit times in the intestinal regions

Intestinal region	**Transit time**
Duodenum	5 Minutes
Jejunum	2 Hours
Ileum	3 to 6 Hours
Caecum	0.1 to 1 Hour
Colon	6-12 hrs

Food, diseases, and drugs can all affect how quickly food travels through the digestive tract.

Combined approach

This is a mixed approach in which we thought to work on two problems of the same formulation. In the first phase of the review we focus on solubility enhancement employing suitable methods, both physical and chemical. Subsequently we explored gastroretention techniques to be applied on the same formulation to increase intestinal absorption[9]

1. Solubility enhancement

Solubility enhancement techniques:

Chemical modification, physical modification and some other techniques can increase drug solubility[10]**.**

A. Physical Modifications: Different methods of particle size reduction such as micronization and nano-suspension, modification of the crystal habit such as polymorphs, amorphous form and co-crystallization exemplify physical modification. Some other techniques include drug dispersion in carriers/solvents like eutectic mixtures, solid dispersions and cryogenic techniques.

B. Chemical Modifications: These include salt formation, buffer usage, derivatization, complexation, and pH change.

C. Miscellaneous Methods: these include use of adjuvants such as surfactants, supercritical fluid process, solubilizers, hydrotropy co-solvency, and novel excipients. We will focus some important solubility enhancement methods in this article.

1. Particle size reduction

This is very popular and the most applied method of solubility enhancement. The size of the drug particle determines how soluble it is; as a particle gets smaller, its surface area increases. Greater contact with the solvent is made possible by the greater surface area, increasing solubility. Traditional particle size reduction techniques, like milling and spray drying, depend on mechanical stress to break down the active ingredient.[11].

2. Complexation

A. Physical mixture: In this method of complexation, active drug and excipient/polymers are used in different ratios and mixed with a mortar and pestle for approximately an hour with constant trituration. The mixture is passed through desired fine sieves and collected in a desiccator.

B. Kneading method: In this important method active drug and excipient/polymers in different ratios are added to the mortar and pestle and triturated with a small quantity of solvents to prepare a slurry. Slowly the drug is transferred into the slurry with continuous trituration. The prepared slurry is then air dried at room temperature for the desired time. The resultant product is passed through a suitable fine sieve and collected in a desiccator.

C. Co-precipitate method: In this method the active drug is dissolved in solvents and a suitable polymer is dissolved in aqueous media. Liquid form of API and polymers are mixed respectively in different ratios. The mixture is stirred at room temperature for an hour and then the solvent is evaporated. The dried mass is passed through a suitable fine sieve and collected in a desiccator[12].

3. Hydrotropy

A solubilization phenomena known as hydrotropy occurs when a considerable amount of a second solute is incorporated, increasing the solubility of the first solute. Numerous drugs with poor water solubility have been seen to become more soluble in concentrated aqueous hydrotropic solutions/buffer solutions and urea.[13,14].

4. Solid dispersion techniques

A. The fusion (melt) method: A hot plate with calculated proportions of carriers is placed inside, and the mixture is continuously stirred as it melts at a temperature of approximately 60 °C. To ensure homogeneity, the active medication is properly weighed and added to the melted carriers whilst being stirred. To obtain a transparent, homogenous melt, the mixture is heated. After being taken off the hot plate, the pan is set aside to cool at normal room temperature.

B. The solvent method: In a round-bottom flask, a calculated weighed quantity of the API and the carriers are dissolved in the bare minimum amount of chloroform. A rotating flask evaporator is used to evaporate the solvent. The resulting solid semisolid mass is poured into an aluminium container and left to air dry.

C. Dropping method: A pipette is used to dispense a melting dispersed drug-carrier mixture, which is then put on a plate and solidifies into rounded particles. The pipette size and melt viscosity, among other things, have an impact on the size and shape of the particles. Because viscosity is very temperature sensitive, it is crucial to regulate the temperature so that the melt solidifies into a spherical shape when it is dropped on the plate.[15,16,17].

5. Spray drying techniques

A. Micro particles by spray drying: By dissolving the drug or drug-polymer mixture in an ethanol/water solution, spray-dried particles consisting of the active drug alone or the drug with a suitable polymer in varying proportions are generated. By using a spray dryer, the solution dried. The created microparticles are collected, sorted using a cyclone splitter, and kept in a desiccator at normal room temperature until needed.

B. Micro particles by spray chilling: Created by melting appropriate ratios of the drug or drug and appropriate polymer mixture at 85-90°C. The melted mixture is maintained at 85-90°C and atomized into air controlled at 20°C using a pneumatic nozzle that has been specially built. A desiccator is used to gather the particles using a cyclone separator. [18]

6. Supercritical fluid technologies

A. Anti-solvent precipitation: This comprises of a precipitator that operates in a continuous co-current mode and continuously discharges from the bottom, with the anti-solvent and liquid solution fed separately to the upper part of the chamber. A high-pressure piston pump moves the liquid solution into the chamber. A high-pressure piston pump is used to distribute the anti-solvent. The precipitator is a

cylinder with an inner capacity of 500cm3. Through a steel nozzle, the liquid solution is introduced into the chamber. Before entering the precipitator in a tube portion, the supercritical carbon dioxide is heated by an electric cord that is regulated by a controller. Two electric thin band heaters that are coupled to a temperature controller heat the precipitator. At the bottom of the container is a sintered steel filter with sufficient porosity to catch the generated particles. From a second vessel, the solvents are separated and collected[14].

B. Gas anti-solvent recrystallisation: By adding the anti-solvent gas to a solution with dissolved solute, it is possible to accelerate crystallisation. The super critical fluid anti-solvent and carrier solvent need to be at least partially miscible with one another as one of the fundamental requirements for this method.

C. **Solution-enhanced dispersion by supercritical fluids:** Using a coaxial nozzle configuration, the supercritical fluid and drug solution are transferred concurrently into the particle formation vessel, causing the drug solution solvent to be dispersed, mixed, and extracted by the supercritical fluid, resulting in extremely high super-saturation ratios. Uniform conditions for particle formation are provided by temperature, pressure, and precise metering of drug solution and supercritical fluid flow rates through a nozzle. By selecting a suitable solvent, it is possible to adjust the required particle shape, which aids in controlling product particle size [19].

7. Preparation methods of nano-suspensions

A. Media milling: High-shear media mills are used in the formulation of the nano-suspensions. The milling chamber, which is filled with water, drug, milling media, and stabiliser, is rotated for a minimum of 2–7 days at a very high shear rate under controlled temperature. Due to the application of high energy shear pressures, the effect of the milling media with the drug causes the drug's microparticulate form to break down into nanoparticulate form.[13,11.]

B. Nanojet technology: Utilizing a chamber in which a circulation of suspension is split into two-three components that collide under intense pressure. Particle size reduction occurs as a result of the process's high shear force creation. This procedure is known as nanojet technology or opposite stream.

8. Amorphous systems

Drugs are around 10–1600 times more soluble in amorphous form than in crystalline form. The enhanced drug wetting, deagglomeration, and micellisation with hydrophilic polymers, as well as the drug's high energy amorphous form, are responsible for the improvement in amorphous system dissolution, Adding pharmaceutically acceptable polymers to an amorphous system is one of the most common ways to stabilize it[20].

2. Intestinal absorption enhancement

Gastro retention drug delivery system - Advanced and challenging approach

One of the most significant innovative drug delivery systems is the gastro-retentive drug delivery system (GRDDS), which has a number of benefits and great promise for developing dosage forms for a variety of chronic conditions. Due to quick gastric emptying time and specific drug absorption sites, most oral administration techniques only have limited bioavailability[21]. GRDDS is a revolutionary method that greatly increases patient compliance by lengthening the duration of medication release and increasing attributes like stomach retention time. Many pharmacological compounds, such as metformin HCl and baclofen, have a low bioavailability due to fast stomach emptying and conventional oral dosage forms. The stomach or the proximal section of the small intestine is the primary location of medication absorption, while the distal region of the intestine has an absorption problem. Even if medications are less soluble in an environment with a raised pH in the intestine, absorption can also be improved by extending the time they are retained in the stomach. There are numerous medications that are vulnerable to degradation in the colonic area, including Captopril, Metronidazole, and Ranitidine HCl. T Drugs having short half-lives must be dosed frequently to obtain the desired therapeutic effect since they tend to leave the systemic circulation fast. By gradually releasing the medication in the stomach and keeping an effective drug concentration in the systemic circulation for the necessary amount of time, solubility enhanced delayed release formulations with added gastric retention properties can get around these limitations.[22].

Stomach physiology

Understanding stomach physiology is essential for developing GRDDS and the associated gastric emptying process. As shown in Fig. 1, the human stomach is divided into three anatomical regions: the fundus, the body, and the antrum (pylorus). After a meal, the typical stomach volume is 1.5L, ranging from 250 to 500 ml during the digestive process. The pylorus serves as the primary site for the mixing activity, while the body and fundus serve as a reserve for any undigested material. The pylorus, which is located lower, uses a pushing motion to expel gastric contents. [23]

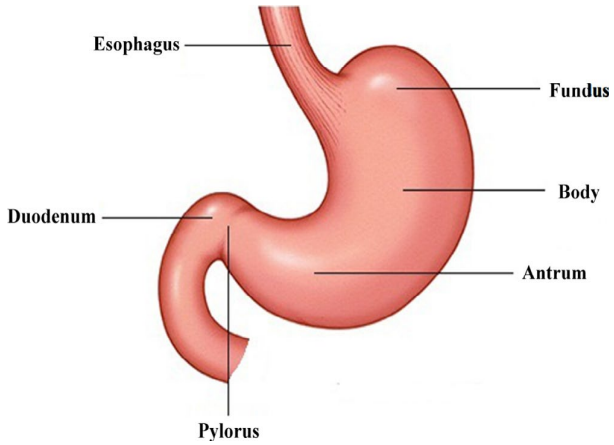

Fig.1 Human stomach

The antrum serves as a barrier between the stomach and duodenum and is crucial to the amount of time that ingested substances spend in the stomach. However, the stomach motility pattern varies between the fed and fasted states. Cycles of activity and relaxation are systematized in the stomach motility pattern. Each cycle lasts between 90 and 120 minutes and features four segments. The term "migrating motor complex" refers to the stomach's pattern of movement (MMC).

Gastroretention techniques- Novel approach of enhancing absorption

Research scientists have applied different approaches to increase gastric retention times with the extended drug release. The concept of dense formulation is an example of a new approach (Fig. 2). This method involves making the dose form hefty (density: 2.5 to 3.5 g/ml) so that it could survive in vivo peristaltic movement and endure the GIT disturbance without breaking down. As a result, it was anticipated that the GI transit time would increase by an average of 5.8 to 25 hours.[8].

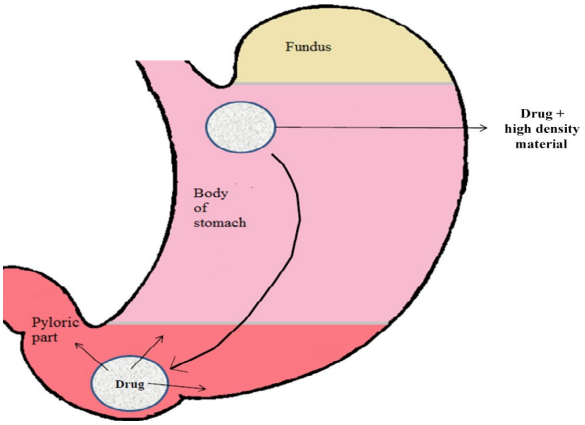

Fig. 2 – GRDDS based on high density

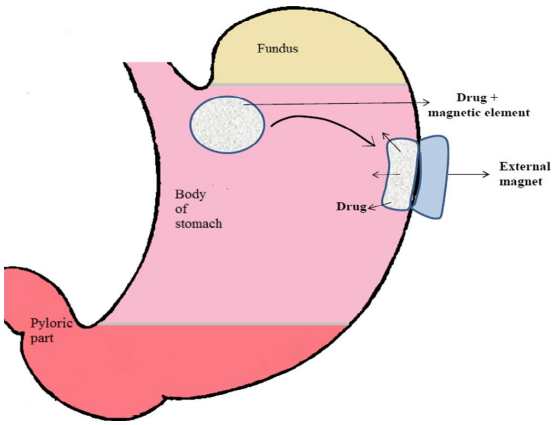

Fig. 3 – GRDDS based on magnetic force

Several high density excipients, including titanium oxide, dibasic calcium phosphate, microcrystalline cellulose, and zinc oxide, were included in the formulation to enhance density.
Applying a magnetic field is a novel approach proposed to hold the dosage form in the stomach. One of the key downsides of high dose formulations is the increased dose size/weight required to attain that density. The medication's include magnetically active ingredients. To hold the supplied medication in place, one external magnet must be placed on above the location of the stomach. [2,24](Fig. 3).

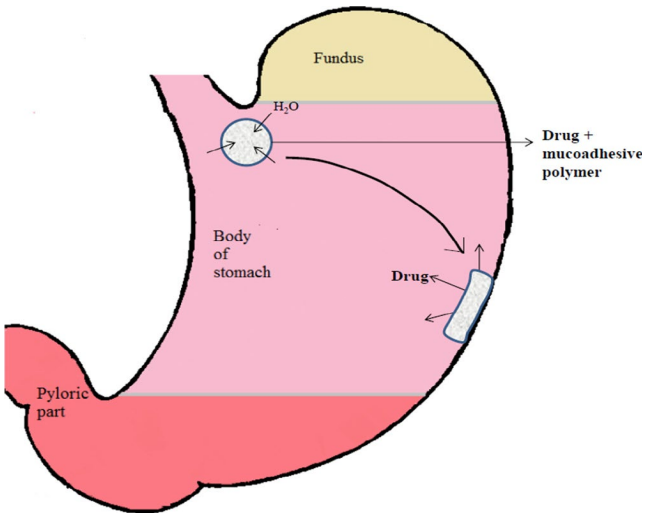

Fig.4 – GRDDS based on muco-adhesion.

Gastro-retentive methods include bioadhesive or muco-adhesive drug delivery devices. The dosage forms are designed to adhere inside the stomach wall's lumen and endure gastrointestinal motility for a longer time (Fig. 4). It is also advantageous as a target-specific design to encourage local medicine absorption in a stomach infection. For this type of design, formulations contain bioadhesive excipients. Another unique strategy for improved gastro-retention is the combination of adhesion and swelling or floating mechanisms.

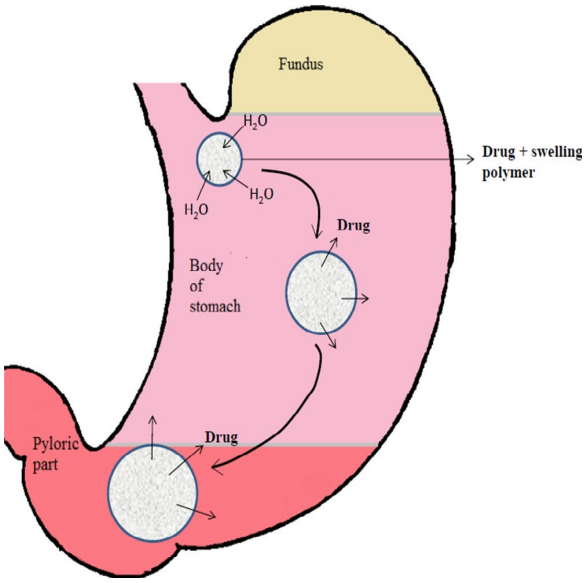

Fig. 5 –GRDDS based on polymer swelling.

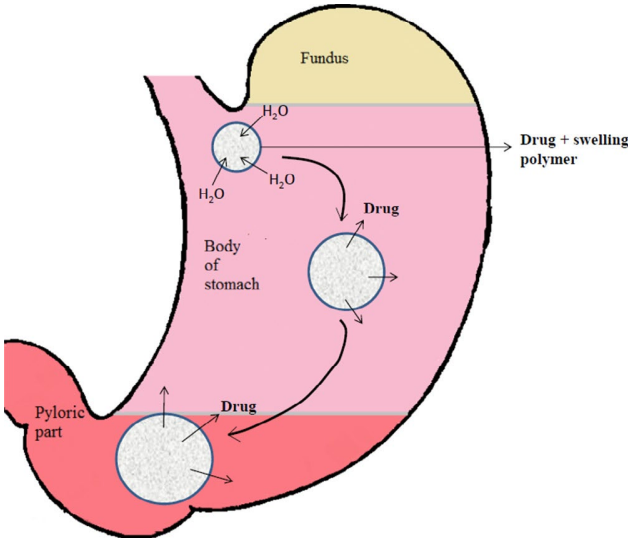

Fig. 6 –GRDDS based on combination of polymer swelling and effervescence.

To keep the formulation in the stomach, GRDDS was successful in both vitro and in vivo after adding a swelling mechanism (Fig. 5). One such system was described by research scientists as being intended to grow to a size greater than the diameter of the pyloric sphincter and able to lodge there (Fig. 5). Due to this system's ability to block the pyloric sphincter, it was given the moniker "plug type systems". The polymer absorbed water and became larger after coming in touch with the gastric fluid. The dosage form was able to achieve a delayed-release characteristic by choosing a suitable polymer with the desired molecular weight, viscosity, and swelling qualities.

Another sort of GRDDS has been developed using any dosage form with GI fluid's (floating) buoyancy feature. After a waiting (lag) time, the new dosage form's density falls below that of gastric fluid. This waiting (lag) period is determined by the pace of swelling of the formulation's polymer, which in turn depends on the polymer's type, the presence of wicking agents or swelling enhancers, the viscosity grade, etc. In order to enhance the floating behaviour (floating lag time and floating duration), an extra characteristic, such as effervescence, was added to this swelling-based delivery system. The dosage form contains a mixture of different effervescent ingredients, such as sodium bicarbonate, citric acid, and tartaric acid. Carbon dioxide is released as a result of a chemical reaction when these excipients come into contact with the GI fluid and is then confined inside the gellified hydrocolloid system. As a result of these swelling and effervescence combinations, the dosage form achieves an effective lower density than the GI fluid and moves higher, maintaining buoyancy for a prolonged amount of time.

3. In-vitro assessment of mixed-approach

(i) Being a novel formulation with a combined approach, evaluation parameters should continue to ensure safe, effective and patient convenience formulation.

(ii) To assure the *in-vivo* performance regarding floating lag time, duration and choice of appropriate formulation, in-vitro evaluations of solubility enhanced- gastroretentive formulation are necessary. General compression factors such hardness, friability, description, uniformity of content, weight variation, and dissolution *in vitro* drug release are part of the standard evaluation procedures for tablet dosage forms.

(iii) De-ionized water and gastric fluid (simulated) have been utilised to assess gastroretention behaviour such as gastric retention time for any GRDDS. Polymeric dosage forms deposited in a suitable dissolution medium are examined for swelling features and rate of swelling for at least 7 to 12 hours to ensure drug release and retention mechanism. At the conclusion of the study, measurements of the enlarged tablet's size and weight growth will be made.

(iv) SEM (scanning electron microscopy) is utilised to visualise the surface morphology of the dosage form under microscopic examination, preferably at various magnifications.

(v) For the gastro-retentive beads and microspheres, the formulations' composition and related processing parameters are optimised utilising further tests such particle size measurement, drug loading, and drug entrapment effectiveness.

(vi) In *in-vitro* evaluation tests, spectrophotometers, optical microscopes, and particle size analyzers are frequently employed. [25,16.]

4. In-vivo Assessment of combined approach

Over the past two to three decades, drug delivery research has seen widespread use of oral gastro-retentive delivery systems. Although only a small number of these have been supported by *in-vivo* findings, there are a few instances of effective combination formulations for the mode in animals[7].

Studies in Animals[22]

(i) Utilizing unfolding membranes with enlarged dimensions and high stiffness, formulation scientists created a controlled release gastroretentive formulation of Levodopa. Beagle dogs who had received a unique formulation pretreatment were used in an *in-vivo* investigation. The dosage form's location was identified by X-ray analysis after the new formulation was injected. Blood samples were frequently taken at regular intervals and checked for drug activity. It was discovered that the drug's optimised controlled release gastroretentive drug delivery system was able to sustain therapeutic Levodopa concentrations (>500 ng/ml) for 8 hours. Comparing the mean absorption time to the standard controlled release formulation, it was noticeably longer.

(ii) Calcium silicate is employed as a porous carrier and eudragit as a polymer in the formulation of microspheres. In order to conduct the organ distribution investigation, rats were employed, and a

water-based suspension of floating microspheres was given orally. The rats were euthanized after 6 hours of gastric retention, which was confirmed by gamma scintigraphy, and their organs were separated (stomach and intestinal region). When compared to commonly available tablets, the test compound's relative bioavailability was determined to be 3.17 times higher, and its uniform organ distribution was also discovered. [3,24,26].

(iii) To determine the therapeutic effectiveness of floating calcium alginate beads containing 5-flurouracil, an *in-vivo* anti-tumour investigation was conducted. In mice, it was discovered that the multi-unit floating delivery system was able to minimize the occurrence of stomach tumours by 74 percent, whereas a standard tablet dosage form was only able to lower this incidence by 25 percent.

(iv) Polymers like HPMC and ethyl cellulose were used as the release-delayed materials in the solvent evaporation procedure used to create the drug-loaded microspheres. Microspheres of cefpodoxime proxetil were made as GRDDS. Cefpodoxime proxetil suspension and cefpodoxime proxetil microspheres were given orally to two groups of male albino rats at a dose of 10 mg/kg. Blood samples were drawn periodically from the retro-orbital region, centrifuged individually, and then subjected to HPTLC analysis. In comparison to the commercial suspension, the medication incorporated into the microspheres had a 1.5 times greater relative bioavailability as a consequence of this investigation.[24].

Studies in Humans

(i) For administering the API losartan, a gastro-retentive formulation based on the mechanism of swelling and effervescence was created using a combination of polymers including hydroxyethyl cellulose, sodium CMC and sodium bicarbonate. In an *in vitro* experiment, tablets were discovered floating for more than 16 hours before ballooning to a diameter of 2 centimetres in just 3 hours. Additionally, the tablets demonstrated a pH-dependent drug release over a 24-hour period. When compared to the quick release market formulation, the improved tablets' bioavailability increased by about 164 percent when tested on healthy human volunteers. The gastro-retentive floating tablets (GRFT) generated positive results as anticipated: Maximum residence time (MRT), Tmax, and Cmax values were higher & lower respectively, than those of the marketed formulation.[24,26.]

(ii) Cefuroxime axetil gastro-retentive tablets outperformed normal tablets in terms of antibiotic treatment effectiveness, according to formulation scientists. The basis for newly developed and improved tablets was a mechanism that combined swelling with effervescence. The optimised tablets could be held for 225–30 minutes in human participants, according to *in-vivo* radiographic investigations, which are consistent with an *in-vitro* floating time of more than 12 h with a floating lag duration of less than 30 seconds. Eight human volunteers were given the same tablets to test. Based on *in-vivo* performance, an important difference between test and reference was seen in t1/2, Cmax, Tmax, AUC0, and mean residence duration. The floating tablets of cefuroxime axetil increased relative bioavailability by 1.61 times when compared to the reference tablets.[24,26].

These *in-vivo* tests on humans and animals have conclusively shown that gastroretentive formulations are superior to conventional ones.

5. Future challenges with GRDDS

The key difficulty in developing GRDDS is keeping the formulation in the stomach or upper part of the small intestine for an extended period of time until all the medications have been completely released at a predetermined rate. The duration of the gastric emptying process varies greatly. It primarily relies on the dosage form as well as whether the patient is fed or fasting, among many other variables. The type of food, caloric amount, gender, and age are some physiological barriers and factors that significantly affect how quickly the stomach empties. Meals with a high calorie and fat content significantly slow down the emptying of the stomach. Under conditions of feeding, indigestible polymers or fatty acids can alter the stomach's pattern of motility and thereby lower the rate at which the stomach empties. During digestion, the pylorus is around 2 to 3 mm in size, and during the interdigestive phase, its diameter increases to 12.8 7.0 mm. Therefore, for any particle to enter the duodenum through the antrum, its diameter must be less than 5 mm. For any GRDDS, the pylorus size restriction is crucial to stomach retention. [24]

Other things to think about in this situation include how the pylorus of an animal, like a dog or a rabbit, differs from the human in terms of size and peristaltic movement. Other variables that affect the efficacy of the dose form include body mass index (BMI), size and shape of the formulation, and the patient medical history. A single unit gastro-retentive dosage form may finally leave the stomach before the dosage form becomes functional because of the lag period and the gastric emptying sequence. Therefore, in order to create an ideal GRDDS, it is necessary to solve issues with the stomach's gastric emptying rate as well as sustain a proper drug release rate for a long time before it is metabolised[6,27].

6. Conclusion

To overcome the limitations of low soluble and low permeability of class IV drugs a mixed approach of increasing solubility and intestinal permeability is explored in this review, with the help of various available studies in the form of review and research work. Work on solubility enhancement is somewhat common but a mixed approach is a unique idea for formulators. Different traditional and unique strategies are detailed to increase solubility, whereas a gastro-retentive drug administration strategy has lately become extremely popular in the area of oral drug delivery to increase absorption. It is a newly developed strategy to keep the dosage form in the stomach for a prolonged time and release the medication in a controlled form that can address several issues with traditional oral delivery, such as solubility and poor bioavailability. To create GRDDS, a number of cutting-edge techniques are being used, such as gastro-retention, magnetic field assistance, plug swelling systems, muco-adhesion techniques, and floating systems with effervescence or without it. Gamma scintigraphy, MRI, and X-rays are common methods for measuring in-vivo gastric residence time. It is still very difficult to evaluate the overall *in-vivo* efficacy of tiny animals like mice and rats. Numerous positive *in-vitro* findings have been obtained for gastro-retention procedures in trials using beagle dogs, rabbits, and humans. The hurdles that prevent more GRDDS from being made accessible on the market, however, include their many benefits, significant subject variability in GI physiological condition, impact of meals, and different rates of gastric emptying period.

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