A FLOATING DOSAGE FORM FOR VALACYCLOVIR

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Abstract: *A set of process method has been developed for the determination of valacyclovir in tablet dosage forms. The method was based on the charge transfer reactions of Valacyclovir with 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone. The absorbance of the highly intensive coloured solution was measured at 205 to 450 nm against reagent blank treated similarly. In certain cases Beer's law is obeyed in the concentration range of 20-100 µg/ml. Statistical analysis proves that the proposed method is reproducible and selective for the routine analysis of pharmaceutical formulations of Valacyclovir.*

In a trendy Literature survey revealed that few instruments like Spectrophotometric methods, HPLC methods, and LC-MS methods for biological fluids are reported in the literature for the determination of VAL in Bulk, pharmaceutical formulations and serum samples. The aim of the present work was to develop a simple and economic liquid chromatographic method that would be suitable for determination of VAL and its impurities in bulk and dosage form. The proposed method is found to be simple, accurate, reproducible and suitable for routine determination of VAL from its pharmaceutical dosage form.

The major work was to formulate a gastroretentive dosage form of Valacyclovir, an anti viral drug.

Keywords: *Gastroretentive forms, floating, Mucoadhesive, Floating systems, Hydrogels.*

Introduction

The methods or process which can be evaluated in the instrumentation like UV-Visible spectrophotometry is the technique of choice in research laboratories, hospitals and pharmaceutical industries due to its low cost and inherent simplicity. The objectives of the work are to develop new spectrophotometric method for its estimation in bulk and tablet dosage form with good accuracy, simplicity, precision and economy. Hence the present work deals with the spectrophotometric estimation of Valacyclovir using 2, 5-dichloro-3, 6-dihydroxy-1, 4-benzoquinone.

Valacyclovir is an antiviral drug, mainly acting by interfering with viral replication, reducing the physical severity of an outbreak associated lesions, and lowering the chance of transmission to others. Studies of vulnerable patient populations have indicated that daily use of antiviral such as Valacyclovir can help reduce Herpes reactivation rates.

Valacyclovir gastroretentive mucoadhesive tablets were prepared using polymers such as Carbopol 974P and hydroxy propyl methyl cellulose (HPMC) K^4M, in different proportions by wet granulation technique. Compatibility studies were performed by FTIR spectroscopy. The prepared granules were evaluated for bulk density, Carr's index, Hausner's ratio, friability, drug content uniformity, hardness, thickness and post compression parameters.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.

Prolonged gastric retention improves bioavailability, reduces drug wastage, and improves solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Materials and Methods: The oral route is considered to be the most promising route of drug delivery. Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. This result in a significant fluctuation in drug concentration hence the need for a gastroretentive drug delivery system. Technical advancements of maintaining the drug in the gastro intestinal tract is known as gastroretentive oral controlled released dosage form. By this approach, it is possible to prolong gastric residence time, thereby targeting site specific drug release in the upper gastro intestinal tract for local and systemic effects. It has considerable therapeutic advantages such as ease of administration, improved patient compliance, prolonged gastric emptying time and flexibility in formulation. The ability to maintain the delivery system to a particular location for an extended period of time has a great appeal for both local disease treatment as well as systemic drug bioavailability. To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system , low density systems, raft systems, incorporating alginate gels, bioadhesive or mucoadhesive systems, high density systems, super porous hydrogels and magnetic systems. Mucoadhesive dosage forms provide intimate contact between the dosage form and the absorbing tissue, which may result in high-localized drug concentration and hence, high drug flux across the absorbing tissue. Furthermore, intimate contact is likely to increase the total permeability of high molecular weight drugs such as peptides and proteins. By incorporating a permeation enhancer, drug absorption through the mucous membrane can be enhanced and thus increase the bioavailability of the drug. Using a combination of HPMC (K4M), Carbopol 974P, Microcrystalline cellulose and PVP, the development of a gastroretentive drug delivery system is hereby postulated. Since Valacyclovir has less absorption in the basic pH the gastroretentive dosage form will cause Valacyclovir to remain in the acidic pH of the stomach for a longer duration with the added benefit of improved absorption. Therefore an attempt has made to increase the oral bioavailability of Valacyclovir by retaining the dosage form in the stomach for a longer period of time.

Valacyclovir was obtained as a gift from Hetero laboratories, Hyderabad. Hydroxy propyl methyl cellulose (HPMC) K4M, Microcrystalline cellulose (MCC), Carbopol 974P, Polyvinyl pyrolidine (PVP), Talc, Magnesium Stearate, Lactose and Potassium chloride are purchased from SD Fine chemicals, Mumbai. Acetonitrile HPLC grade and Hydrochloric acid (HCl) was procured from Merck, Mumbai. Triple distilled water was obtained from Milli Q RO system.

Method development of calibration curve: A standard drug solution of Valacyclovir was prepared by dissolving 10mg Valacyclovir in 10 ml volumetric flask containing 1.2 pH HCl and volumes was adjusted with 1.2 pH buffer to the

concentration of 1000µg/ml. From this 2.5 ml solution was withdrawn and diluted to 25 ml to get a concentration of 100µg/ml. Further, from 100µg/ml, aliquots of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml were pipetted into 10 ml volumetric flasks. The volume was made up with 1.2 pH HCl buffer to get the final concentration of 10, 20, 30, 40, and 50µg/ml respectively. The absorbance was measured at 255 nm

Compatibility studies of Fourier transform infrared spectroscopy:

Infrared spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 to 400 cm-1 in a Perkin Elmer FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of pure drug and polymers which were matched to detect any appearance or disappearance of peaks, using FTIR peak matching method.

Factors Affecting Floating in Gastric Retention:
Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties from the stomach;[7] hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves. It has been demonstrated using radio labeled technique that there is a difference between gastric emptying times of a liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (91 mm) indigestible objects from stomach was dependent upon interdigestive migrating myoelectric complex. When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increase in size during the housekeeping wave and allows the sweeping of the indigestible

solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed. Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from "all or none" effect. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulations. Size and shape of dosage unit also affect the gastric emptying. Garg and Sharma[9] reported that tetrahedron- and ring-shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter. of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period [10].Over the last two decades, numerous gastroretentive dosage forms have been designed to prolong gastric residence time. They may be broadly classified as

- **Floating Drug Delivery Systems:** Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floats on the gastric contents, the drug is released slowly at the desired rate from the system

- **High-Density Systems:** Basically, gastric contents have a density close to water (¨1.004 g cm-3). When the patient is upright small high-density pellets sink to the bottom of the stomach as shown in Figure 6, where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g cm-3 seems necessary for significant prolongation of gastric residence time [19,20] and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients. Although encouraging results were reported in ruminants [20,21,22], effectiveness in human beings was not observed [23] and no system has been marketed.

- **Expandable Systems:** This is a class of gastroretentive systems capable of expanding in stomach. The expanded structure is trapped in stomach for prolonged period leading to sustained drug release and subsequent controlled absorption in stomach and intestine. These systems are administered perorally in the form of capsule bearing the dosage form in folded and compact configuration. When exposed to gastric environment capsule shell breaks and the dosage form attains its expanded structure, which is retained in stomach for longer time. Advantages of these systems include easy formulation, simple in operation and reproducible results; however, they suffe from serious drawback like clogging of pylorus end of stomach

- **Hydrogels and Superporous Hydrogels**: Hydrogels offer a promising approach to gastric retention. These materials have a

swelling ratio of over 1000. They can be made by cross linking watersoluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Superporous hydrogels have unique superswelling properties combined with pore sizes in the range of few hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min, which is an important requirement for gastric retention devices based on size.

Floating or Bioadhesive Systems: Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. The potential sites for attachment of any bioadhesive system lead to the development of various mucoadhesive drug delivery systems such as buccal sublingual, vaginal, rectal, nasal, ocular and gastrointestinal drug delivery systems

Formulation of floating Tablets: The composition of bioadhesive Valacyclovir tablets. All ingredients were powdered and made into a wet mass by adding binder (PVP dissolved in Polyvinyl Alcohol) and mixed for 10 minutes to obtain a uniform mixture. Wet mass was passed through sieve #60 and granules obtained are dried in an oven at 40^{o} The volume was made up to 100 ml with 1.2 pH HCl buffer and filtered. From the above solution, 25 ml aliquot was pipette into a 100 ml volumetric flask and the volume was made with 1.2 pH HCl buffer. From this, 1 ml and 2 ml were pipetted into a 25 ml volumetric flask with 1.2 pH HCl buffer respectively. The absorbance was measured at 255 nm. This procedure was repeated thrice and the mean value obtained. C for 30 min. Magnesium stearate and talc were added to dried granules. Each tablet weighing 150mg was prepared by compression method using 8 mm flat punches in Rimek Mini Press Tablet compression machine. The present study was carried out to develop gastro retentive mucoadhesive tablets of Valacyclovir in order to enhance absorption and bioavailability by increasing gastric retention time of the dosage form. In this case, ten formulations of mucoadhesive tablets were prepared using polymers such as Carbopol 974P, HPMC K4M, MCC, PVP and Lactose in different concentrations and compared with conventional tablets. The detailed composition of each formulation is given in the Table. 1. Post compression parameters Post compression parameters such as appearance, thickness, hardness, friability, drug content uniformity, weight variation and swelling index were performed for the prepared tablets. Drug content uniformity Twenty tablets were weighed and powdered. A quantity equivalent to 150mg of Valacyclovir was weighed accurately and taken in a 100 ml volumetric flask. 50 ml of 1.2 pH HCl buffer was added and sonicated for 5 min.

In Vitro Dissolution Studies:

The tablets were so fixed to the paddle as to release the drug from the exposed side only In vitro dissolution studies were carried out in USP XXIV type II apparatus (Electrolab, Mumbai). The dissolution media was 900 ml 1.2 pH HCl at 37^0 C ± 0.5^0 Release kinetics of the prepared mucoadhesive tablets was evaluated using models such as zero order kinetics (cumulative percentage of drug release versus time), First order kinetics (log cumulative percentage of drug remaining to release versus time) and Higuchi (fraction of drug release, log Mt/Mi versus log time). The most suitable model for the drug release was predicted on the basis of regression coefficient i. e., nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism. Formulation Design. C with stirring speed of 50rpm for 24 h. The sample of 5 ml was withdrawn at predetermined time intervals of 0, 1, 2, 4, 6, 8, 12 and 24 h. An equivalent amount of fresh media was replaced. The withdrawn samples were filtered and analyzed by Ultra violet (UV) spectrophotometer (Shimadzu, UV 1700) at 255 nm using 1.2 pH HCl buffer as a blank. The drug content was calculated using the equation generated from standard calibration curve. Drug release in cumulative % from different formulations versus time was compared

Method of analysis The bioanalytical calibration curve samples and plasma samples were injected into RP-HPLC with above chromatographic conditions and the chromatograms were recorded. The quantification of the chromatogram was performed using peak area

Chromatographic Conditions The stationary phase used in RP-HPLC was Hibar C18 (250 X 4.6 mm, 5 µm). The mobile phase used was acetonitrile: Phosphate buffer (pH 3.8) in a ratio 05:95. The flow was maintained to be 1.0 ml/min and the sample volume used was 20 µl. Rheodyne injector of 7725 i was used. Acyclovir was used as IS and its run time was 6.9 min and drug run time was 13.1 min. Gradient pump with PDA detector with isocratic elution mode was used. Buffer strength was 25 mM and data station was LC-20AD

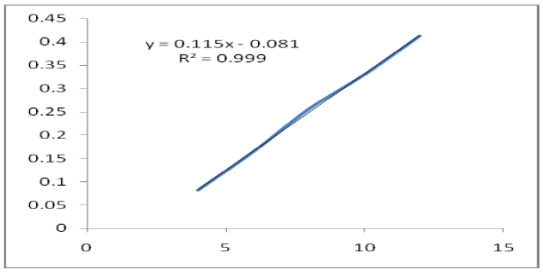
Preparation of standard and sample Valacyclovir solutions Standard stock solution of Valacyclovir Valacyclovir (10 mg) working standard was accurately weighed, transferred into a 10 ml volumetric flask, dissolved in Millipore water and made up to the volume with the same solvent to produce a 1mg/ml concentration of Valacyclovir. The stock solution was stored in a refrigerator at –20^oC ± 2^o C until analysis. The stock solution was diluted to suitable concentrations to obtain calibration curve standards. Standard stock solution of IS Acyclovir (10 mg) working standard was accurately weighed, transferred into a 10 ml volumetric flask, dissolved in Millipore water and made up to the volume with the same solvent to produce a 1mg/ml concentration of Acyclovir. The stock solution was stored in refrigerator at –20^o C ± 2^o The bioanalytical curve of Valacyclovir was developed by spiking 0.5 ml of Valacyclovir into a mixture of 0.5 ml of IS (Acyclovir), 0.5 ml of plasma and 0.5 ml of 10% perchloric acid (protein precipitating agent). The spiking was done in such a way that the test samples produced a concentration of 400, 200, 100, 50, 20, and 10 µg/ml. The concentration of IS was maintained at 100 µg/ml. These solutions were labeled and stored at –20 ± 2°C until analysis. C until analysis. Calibration standards curve was prepared for the concentration from 10-400 µg. Preparation of calibration curve standards Preparation of plasma samples Plasma samples (0.5 ml) obtained from study subjects were transferred into 2.0 ml

eppendorf tubes to which, 0.5 ml of IS and 0.5 ml of 10% perchloric acid was added. The resulting solution was vortexed for 10 min. The solution was centrifuged and clear supernatant liquid is separated and analyzed.

In vitro residence time of Valacyclovir optimized formulation (B^3) The ideal batch depending upon the in vitro release profile selected was B3 and subjected for in vitro residence time study, and it was found that the batch B3 formulation resided for 24h with continuous time interval swelling and erosion.

Pharmacokinetic Studies Optimization of chromatographic conditions Blank plasma, standard and sample solutions were injected and the chromatograms were recorded. The optimized conditions and the mobile phase used for estimation provided a well defined separation between the drug, internal standard and endogenous components. The blank plasma samples showed no interference at retention time of the drug and internal standard. Estimation of plasma samples from the rabbit was carried out using the optimized chromatographic conditions. The standard and sample solutions were injected and chromatograms were recorded. The calibration curve was constructed routinely for spiked plasma containing Valacyclovir and internal standard. Figure.8 represents the calibration curve data. The zero hour (pre-dose) samples of all subjects showed no interference at the retention time of both Valacyclovir and IS. The response factor of the standard and sample solutions was calculated. The concentration of Valacyclovir present in plasma samples were calculated

Validation of the Method: Linearity The linearity of peak areas versus different concentrations was evaluated for VAL over the range of g/mL and for



Calibration Curve of Valacyclovir hydrochloride

all the related substances over theμ25-500 range of 0.3μg/mL to 6μg/mL. The correlation coefficient (r^2) for VAL and each related substances was calculated.

Specificity The analyte should have no interference from other extraneous components and be well resolved from them. To determine the specificity of the method, the mixture of reference standard VAL and the related substances was injected and chromatogram was recorded. The sample solution (pharmaceutical dosage form) was then injected and the chromatogram was obtained. The sample chromatogram was compared with the standard chromatogram.

Precision Precision of the method was studied in terms of repeatability and intermediate precision. Repeatability Repeatability was performed by analyzing six separate VAL solutions of concentration 50 μg/mL that were prepared by spiking the related substances to give 1 μg/mL of each of V1, V2 and V3. The %R.S.D for each related substance was evaluated. Intermediate precision The intermediate precision of the method for VAL and related substances was determined on three separate sample solutions prepared by spiking the related substances by two different analysts on two different days. The mean values of results for each day and for each analyst were compared. Accuracy (Recovery studies) To ensure the accuracy of method, recovery studies were performed by standard addition method at 80 %, 100 % and 120 % levels of drug concentrations, to

the preanalyzed samples and they were re-analyzed. Accuracy of the method for all the related substances was determined by analyzing VAL sample solutions spiked with all the related substances at three different concentration levels of 1%, 2% and 4% of sample concentration each in triplicate.

Pharmacokinetics data The pharmacokinetic data of C3 and B3 formulations were shown in Table. 6 and Figure. 9. The mean plasma concentration of C3 and B3 was found to be 545.19 and 567.26 respectively.

In **vivo evaluation method:**

The study of residence in gastrointestinal transit time became necessary to evaluate the drug-release pattern at various levels of GIT by tracking the location of the dosage form. This provided the insight for formulation of a programmable drug dosage form, which would then release the drug at specific levels of the GIT. In earlier days for measurement of in vivo GRT, x-ray studies were used.[52] Radiographs of BaSO4 were taken after ingestion of the dosage form, to locate the floating and non-floating (fabricated) dosage forms at various periodic time intervals.

Heidelberg capsule technique was introduced for monitoring GRT by radiotelemetry.[53-57] Ewe et al.[58] developed a new method for studying a large variety of physiological, pathophysiological and pharmacological questions concerning gastrointestinal transit by a metal sphere of 6 mm diameter, which can be located accurately in the body by a metal detector at a distance of 2-12 cm from the abdominal surface. This procedure had a correlation of r = 0.99, with pH-sensitive radiotelemetering Heidelberg capsule for recording gastric emptying. Presently, in vivo evaluation of floating dosage forms is done by gamma scintigraphy (GS). GS is a technique, whereby the transit of a dosage form through its intended site of delivery can be noninvasively imaged in vivo via the judicious introduction of an appropriate short-lived gamma-emitting radioisotope. The observed transit of the dosage form can then be correlated with the rate and extent of drug absorption. Information such as the site of disintegration or dispersion can also be obtained. Specific site delivery in the GIT can be done by using the InteliSite capsule. The InteliSite capsule is a radiofrequency-activated, nondisintegrating drug-delivery device. It is capable of noninvasive controlled delivery of drug formulations to the GIT for determining regional differences in drug absorption and bioavailability. Radiolabeling permits determination of the capsule location within a specific region of the GIT via GS. When the capsule reaches the desired location in the GIT, external activation opens a series of windows to the capsule drug reservoir. The release and degree of dispersion of the solution or powder contents from the capsule can be visualized. The transit of dosage form or the site of release of drug can be easily correlated with drug absorption. It facilitates neutron activation and standard radiolabeling techniques with regulatory compliance and expert consultation. Success in formulation and development depends on defining the variables that affect the performance of a drug-delivery system. Often, in vitro testing methods are not predictive of in vivo results. For oral dosage forms, altered gastrointestinal transit due to individual variation in physiologic or pharmacologic factors or the presence of food may influence bioavailability. Disintegration, erosion or drug release may be premature or delayed in vivo. Similarly, altered deposition or clearance from other routes of

administration such as nasal, ocular or inhalation may explain drug absorption anomalies. GS combined with knowledge of physiology and dosage form design helps to define these variables. The resulting insight can be used to accelerate the formulation development process and help ensure success in early clinical trials. Standard radiolabeling techniques will incorporate the radioactive marker in a finished product shortly before dose administration. Alternatively, neutron activation is a technique in which a small amount of stable isotope is incorporated in the dosage form at the time of manufacture. The stable isotope is then converted to a radioactive isotope appropriate for GS by a short exposure to a neutron flux.[59] Hence, GS is a rapid and effective method for determining the rate and extent of drug absorption within specific regions of the GIT under pharmaceutically and physiologically relevant conditions and also it saves time and avoids wastage of resources during the drugdevelopment process by defining formulation objectives. The radionuclides are used because it is not possible to radiolabel drug molecules for GS. A radionuclide must therefore be used in a carrier or in the formulation, which is having radiation energy (Ideal about 150 KeV) with suitable half-life period. Also it should be easily available and should emit only pure gamma rays. Furthermore, it should be nontoxic and nonabsorbable (for nonparenteral routes). The metal ion nuclides are most commonly used radionuclides[Table 3].[60-62] 99mTechnetium (99mTc) is the most popular nuclide due to its optimum energy, easy availability (through portable generator), versatile chemistry, low radiation dose and short half-life period.

Conclusion: Drug absorption in the GIT is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Floating dosage forms promises to be a potential approach for gastric retention. These systems consisting of swelling and expanding systems, floating and inflating systems and bioadhesive systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. This review summarizes the various attempts, which have been made to develop a floating system, in vitro and in vivo evaluation studies and application of floating dosage forms.

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