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Gamma Scintigraphy: An Innovative Technique for *In Vivo* Tracking of Gastroretentive Drug Delivery Systems



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ABSTRACT

The gastrointestinal tract (GIT) is usually the preferred site of absorption for most therapeutic agents due to the convenience of administration, patient compliance, and cost. Although much about the performance of a system can be learned from *in-vitro* release studies using conventional and modified dissolution methods information about the behavior of pharmaceutical dosage forms *in-vivo* can be obtained using radionuclide incorporated into the dosage form. The best-known radionuclide imaging technique is gamma scintigraphy. Gamma scintigraphy provides a noninvasive method to see the *in-vivo* fate of a pharmaceutical dosage form. Controlled-release (CR) dosage forms have been extensively used to improve therapy with several important drugs. On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which remain in a gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste and enhance the solubility of drugs that are less soluble in high pH environment. Gamma scintigraphy has emerged as a useful technique for illustrating *in-vivo* evaluation of novel drug delivery systems. These assessments are especially powerful when combined with conventional pharmacokinetic (PK) assessment in a 'pharmacoscintigraphic study', as they allow the behavior of the dosage form in the GIT to be correlated directly with the arrival of the drug in the systemic circulation, and can be used to explain anomalous PK data in individual subjects.

INTRODUCTION:

Despite rapid growth in the novel routes for delivery, the majority of therapeutic agents are still administered orally [1]. To enhance patient compliance and treatment efficiency, several investigators across the globe have been focusing on either novel routes of drug delivery or reducing the multiple dosing regimens to once-daily products in the form of controlled release formulations [2]. Although much about the performance of drug delivery systems can be learned from *in-vitro* release studies using conventional and modified dissolution methods; however, information about the *in-vivo* behavior of dosage forms can be obtained using radionuclide incorporated into the dosage form. The best-known radionuclide imaging technique is gamma scintigraphy [3]. The technique had already been used for many years in studying the physiology of the gastrointestinal tract. The idea was originally to gain information about the anatomy and physiology of the human body using radionuclides that localize in specific organs. Soon after, it was discovered that the same basic procedure can be utilized in drug studies. The first applied studies of gamma scintigraphy in the context of peroral pharmaceutical dosage forms were carried out in the 1970s [4, 5]. Pharmaceutical gamma scintigraphy takes a step forward beyond the traditional anatomical imaging because the movements of drug molecules or delivery systems are monitored continuously. Therefore, it is also called functional imaging [6]. To support the introduction of novel, controlled release dosage forms, regulatory bodies have increasingly accepted imaging technologies to validate proof of the concept over the past 10 years. Among all the modalities available, i.e., X-rays, nuclear medicine (gamma scintigraphy and positron emission tomography), magnetic resonance imaging, and ultrasound, gamma scintigraphy has become preeminent as a tool in the assessment of oral, pulmonary, and ophthalmic dosage forms. Advances in this technology have allowed faster acquisition, and new computing techniques have allowed better characterization, of the pharmacokinetics of the radiopharmaceuticals incorporated in the formulation. Parallel to this, applications of scintigraphy in the study of drug formulations generated new expertise quite separate from the diagnostic arena. Now radiology and nuclear medicine are utilizing this knowledge to obtain better imaging agents and in many respects, the two paths crisscross to the mutual benefit of both camps [7].

This incisive and versatile technique has been recognized to be a valuable approach in the evaluation of oral drug delivery systems. It is a non-invasive method capable of providing reliable and precise information in terms of the transit time of dosage forms across the gastrointestinal tract (GIT). Time and site for the disintegration of dosage forms can be

revealed accurately using this procedure. Moreover, the effect of different conditions such as the presence of food, diseased state as well as the size of formulations can also be explored with imperative details. In the current scenario, it has become a common practice to evaluate the *in vivo* performance of various drug delivery systems in healthy volunteers or patients using this imaging technique [8, 9, 10].

GAMMA RADIATION:

Physicists credit French physicist Henri Becquerel for discovering gamma radiation. In 1896, he discovered that uranium minerals could expose a photographic plate through a heavy opaque paper. Roentgen had recently discovered X-rays and Becquerel reasoned that uranium emitted some invisible light similar to X-rays. He called it “metallic phosphorescence”. In reality, Becquerel had found gamma radiation being emitted by radium-226. Radium 226 is part of the uranium decay chain and commonly occurs with uranium [11].

Gamma rays are electromagnetic radiation of high frequency (very short wavelength). They are produced by sub-atomic particle interactions such as electron-positron annihilation, neutral pion decay, radioactive decay, fusion, fission, or inverse Compton scattering in astrophysical processes. Gamma rays typically have frequencies above 10^{19} Hz and therefore energies above 100 KeV and wavelength less than 10 picometers, often smaller than an atom. Gamma radioactive decay photons commonly have energies of a few hundred KeV and are almost always less than 10 MeV in energy [12]. Gamma radiation is one of the three types of natural radioactivity. Gamma rays are electromagnetic radiation, like X-rays. The other two types of natural radioactivity are alpha and beta radiation, which are in the form of particles. Gamma rays are the most energetic form of electromagnetic radiation [13]. Properties of various radioactive radiations are given in Table No. 1.

Table No. 1: Nature of radioactive radiations

Radiation	Mass	Electric charge	Velocity
Alpha particle	Relatively heavy	Double positive	Relatively slow
Beta particle	About 8,000 times lighter	Negative	Less than the velocity of light
Gamma rays	None	None	$3 \times (10)^8$ m/s in free space

GAMMA SCINTIGRAPHY [14, 15]:

Gamma scintigraphy was introduced by Griffith in 1966 for observing the gastric emptying time [16] but the fate of pharmaceuticals was determined by this technique in 1976 [4, 5, 6]. Gamma scintigraphy is a technique whereby the transit of dosage form through its intended site of delivery can be non-invasively imaged *in-vivo* via the judicious introduction of an appropriate short-lived gamma-emitting radioisotope. In gamma scintigraphy, radiopharmaceuticals tagged with formulations are administered internally, for example intravenously or orally. Then, an external detector (gamma camera) captures and forms images from the radiation emitted by the radiopharmaceuticals. This process is unlike a diagnostic x-ray where external radiation is passed through the body to form an image. The observed transit of 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. Figure No. 1 gives an idea about the basic principle of this technique.

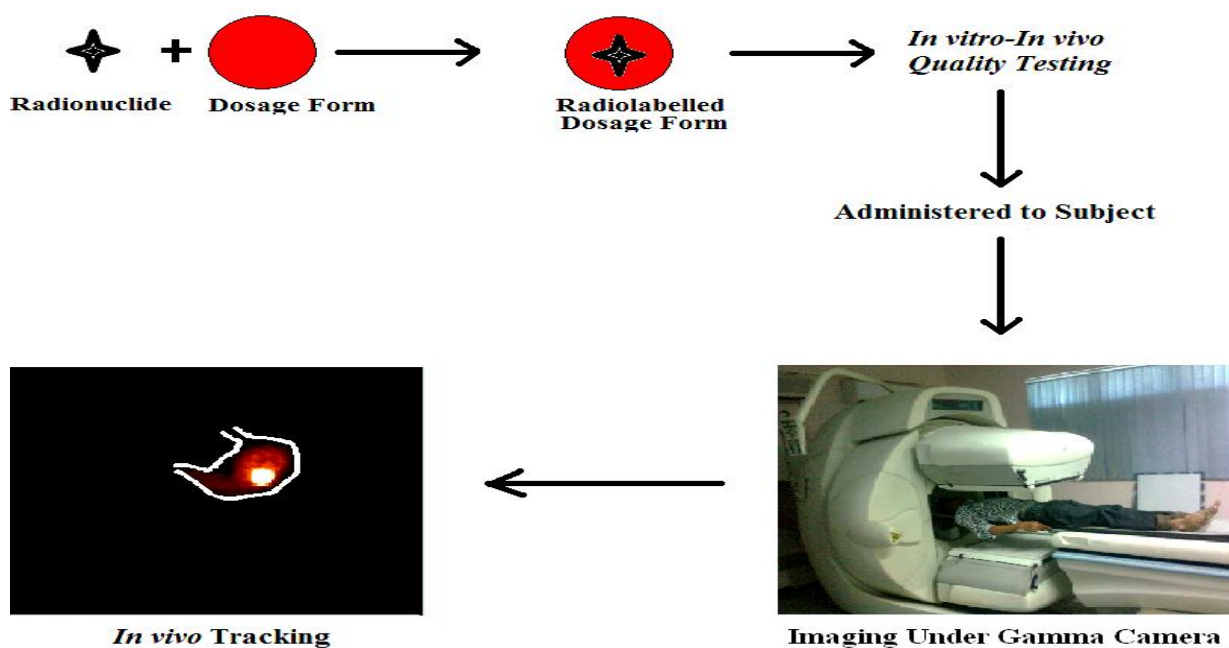


Figure No. 1: Principle of gamma scintigraphy

Protocols employing scintigraphy must be well planned since the technique is complex and costly involving expensive instrumentation and requiring highly trained personnel. Experiments often involve a team of scientists including radiochemists, imaging specialists, and experts in pharmaceuticals. Personnel capable of interpreting scintigraphic problems and devising protocols to deal with sources of error such as motion, scatter, and attenuation are

essential [17]. This growing role for imaging is leading to greater involvement of radiologists in clinical trials and increased integration of radiological science into clinical research [18]. Various advantages of gamma scintigraphy are summarized in the following text. [19]

- *In-vivo* evaluation of dosage forms is feasible under normal physiological conditions.
- Qualitative as well as quantitative observations can be recorded which is not viable with other approaches.
- Non-invasive.
- Very little radiation exposure to the participating subjects compared to roentgenography (X-ray method).
- Combining the imaging information with pharmacokinetic data known as 'pharmacoscintigraphy' provides valuable knowledge about the release and absorption mechanism in a more realistic way.
- In the case of oral dosage forms, altered gastrointestinal transit due to the presence of food, individual variation, physiological or pharmacological factors, may influence bio-availability. Disintegration, erosion, or drug release may be premature or delayed *in-vivo*. Gamma scintigraphy combined with knowledge of physiology and dosage form design can help explain these variables [20].
- Other possible routes that can be imaged include: parenteral [21], rectal [22, 23], pulmonary [24, 25, 26], ophthalmic [27, 28] etc.
- Also, functional in biodistribution studies of several new drugs radiolabelled with ^{99m}Tc . Biodistribution pattern has been established in an easy, cost-effective, and reproducible manner for various drugs including ciprofloxacin, sparfloxacin, and isoniazid [29].
- This approach is also being widely employed in brain targeting [2], tumor imaging [30, 31, 32, 33, 34], gene therapy [35], bone targeting delivery systems [36], etc.

BASIC PHYSIOLOGY OF STOMACH:

To understand the transit of dosage forms through the GIT, it becomes a necessity to know its basic physiology with special emphasis on the stomach where the GRDFS retain and exhibit their action. The GIT is essentially a tube about nine meters long that runs through the middle

of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum, and ileum), and large intestine (consisting of the cecum, appendix, colon, and rectum). The basic structure of the gastrointestinal wall is similar in the stomach and the intestines, although variations exist between different sections of GIT. The GI wall consists of four layers: an inner mucosa, a middle layer known as the submucosa, and on the outer section, the muscularis externa, composed of layers of smooth muscles covered with connective tissue (the serosa) [37]. The stomach is continuous with the esophagus at the cardiac orifice, and with the duodenum at the pyloric orifice. The part of the stomach above the cardiac orifice is the fundus; the main part is the body and the lower part, the pyloric antrum. At the distal end of the pyloric antrum, there is the pyloric sphincter, guarding the opening between the stomach and the duodenum. When the stomach is inactive the pyloric sphincter is relaxed and open, when it contains food the sphincter is closed [38]. The stomach secretes about 2 L of hydrochloric acid per day. The concentration of hydrogen ions in the stomach's lumen may reach 150 mM, 3 million times greater than the concentration in the blood [39]. Hydrochloric acid makes the stomach contents very acidic. This is (somewhat) dangerous since both hydrochloric acid and the protein-digesting enzymes can digest the stomach itself, causing ulcers. However, as long as enough mucus is made, the stomach is 'safe' and will remain unharmed [40]. The GIT is in a state of continuous motility consisting of two modes, inner digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GIT. Gastric motility is controlled by both neural and hormonal signals. Nervous control originates from the enteric nervous system as well as the parasympathetic and sympathetic systems. Several hormones have been shown to influence gastric motility, for example, both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach [41]. The inter-digestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence [42, 43, 44].

MMC is further divided into four consecutive phases as described by Wilson and Washington, represented in Figure No. 2 [44].

Phase I (basal phase): it is a quiescent period that lasts for 30-60 minutes with rare contraction.

Phase II (pre burst): It consists of intermittent action potential and gradually increases in intensity and frequency as the phase progress and lasts for about 40-60 minutes.

Phase IV (burst phase): This is a shorter period of intense, large regular distal and proximal gastric contractions (4-5 contractions per minute) lasting for about 4-6 minutes. This cycle is also known as the “housekeeper wave” since it sweeps undigested gastric contents from the stomach to the intestine.

Phase IV: This phase is about 0-5 minutes, it occurs between the last part of phase III and the beginning of phase I.

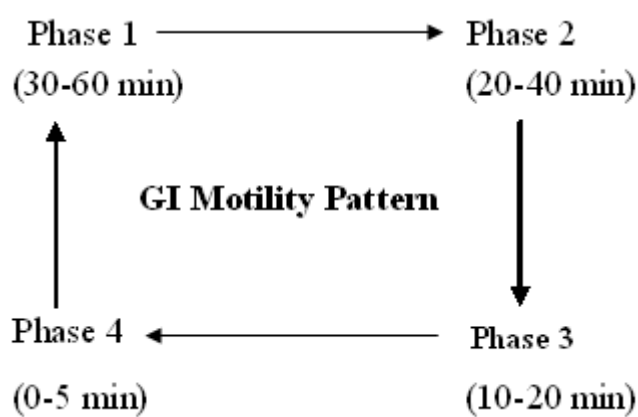


Figure No. 2: Gastrointestinal motility pattern.

Gamma scintigraphy is often the gold standard for transit studies [45] and has an important clinical value in the study of the digestive tract [46]. The main advantages are represented by the possibility to evaluate, in a relatively non-invasive manner, the transit time of specific components of physiological meals as well as of some digestive secretions. These techniques are generally well accepted by the patients and results are largely not operator dependent [47]. The patient or volunteer takes a meal that is radiolabeled with a radioisotope, which appears in blue when viewed through a gamma detection camera. The gamma camera is situated outside the body and can detect the meal inside the body from the radio emissions of radionuclide mixed with the food [48]. ^{99m}Tc (Technetium) radiolabeled eggs and ^{99m}Tc -DTPA (Indium-diethylenetriaminepentaacetic acid) are commonly used for this purpose, ^{99m}Tc -DTPA fulfills the criteria as an ideal agent for measuring gastric emptying time whereas water is labeled with ^{111}In -DTPA to evaluated liquid emptying [49, 50]. Using computer graphics, three-dimensional visualization of the data can be developed. The display enables viewing from any angle and should be of value in assessing the effect of variables on

the transit of pharmaceuticals and other materials [51]. It was reported from a study that, in the case of a solid test meal from which radiolabel could be eluted, the free label would empty considerably faster than the remaining solid material [52].

FACTORS AFFECTING GI TRANSIT STUDIED BY MEANS OF GAMMA SCINTIGRAPHY

Gamma scintigraphy has been applied by investigators to demonstrate various factors that may affect the GI transit and gastric emptying process, some of these studies are discussed here:

Davis et al. measured the gastrointestinal transit of pharmaceutical dosage form in 201 normal subjects using gamma scintigraphy. Solutions, small pellets, and single units (matrix tablets and osmotic pumps) were administered with different amounts of food in the stomach, ranging from fasted state to heavy breakfast. Gastric emptying was affected by the nature of dosage form and the presence of food in the stomach. Solutions and pellets were emptied even when the stomach was in the digestive mode, while single units were retained for long periods, depending on the size of the meal. In contrast, measured intestinal transit times were independent of the dosage form and fed state. The small intestinal transit time of about three hours has implications for the design of dosage forms for the sustained release of drugs in specific positions in the gastrointestinal tract [53]. Davis et al. also studied the effect of density on the gastric emptying of single and multiple-unit dosage forms. It was found that the use of density as a means of altering the gastric residence time of pharmaceutical dosage forms (multiple and single units) has little or no value using the gamma scintigraphic technique. The major factor determining the gastric emptying of single units is the presence of food [54].

Normal aging seems to reduce the propulsive capacity of the colon, whereas gastric and small intestinal motility is not affected [55]. Majaverian et al. studied the effects of gender, posture, and age on the gastric residence time of an indigestible solid: pharmaceutical considerations. By application of gamma scintigraphy, it was concluded that evaluation of these physical/biological parameters has important implications in the design of various sustained-release dosage forms [56].

Marathe et al. assessed the effect of altered gastric emptying and gastrointestinal motility on the absorption of metformin in healthy subjects. Scintigraphic data indicated that

pretreatment with metoclopramide decreased gastric emptying time and increased gastrointestinal motility while pretreatment with propantheline had the opposite effect [57].

Basit et al. assessed the effect of polyethylene glycol 400 (PEG 400) on gastrointestinal transit. The findings demonstrated that PEG 400 had a marked accelerating effect on small intestinal liquid transit [58].

Van Nieuwenhoven et al. investigated the effect of different dosages of guar gum on gastric emptying and small intestinal transit of a consumed semisolid meal. It was concluded that the addition of guar gum to a semisolid meal up to a dosage of 4.5 g does not affect gastrointestinal transit [59].

Adkin et al. studied the effects of pharmaceutical excipients on small intestinal transit. Effects of three iso-osmotic pharmaceutical excipient solutions of sodium acid pyrophosphate, mannitol, and sucrose on gastrointestinal transit were investigated in eight healthy male volunteers. Dual isotope gamma scintigraphy was used to assess the transit behavior of the tablets and solutions. There were no significant differences in the transit times of non-disintegration tablet preparations when co-administered with each solution [60].

Hence, gamma scintigraphy offers a variety of studies for evaluating GI transit and factors influencing it.

SOURCES OF RADIOISOTOPES:

Various sources of radioisotopes are shown in Table No. 2 along with their half-life used in gamma-scintigraphy. Notice that some of these have a relatively short half-life. These tend to be the ones used for medical diagnostic purposes because they do not remain radioactive for very long following administration to a patient and hence results in a relatively low radiation dose [61].

Table No. 2: Illustration of radionuclides used in gamma-scintigraphy

Radionuclide	Half-life (approx.)	Principle photon energy (Kev)	Type(s) of emitted radiation
^{81m} Kr (Krypton)	13 sec	191	Positron, beta particles, and gamma radiation
^{99m} Tc (Technetium)	6.02 h	140	Gamma radiation
¹¹¹ In (Indium)	2.8 d	173, 247	Beta particles
¹²³ I (Iodine)	13 h	160	Gamma radiations, free of beta particles
¹³¹ I (Iodine)	8.05 d	360	Gamma and beta particles

Choice of a suitable radionuclide for scintigraphic studies can be ascertained by considering the following major factors [1, 62]:-

- Emitted radiations must be well-suited for *in-vivo* applications.
- These radiations should be within the detection range of gamma camera i.e. between 100 and 200 KeV.
- Its half-life must be adapted to the duration of the experiment to avoid exposing unnecessarily the volunteer to radioactivity after completion.
- Tracer must not alter the behavior of the dosage forms under investigation.
- Cost and availability also affect the selection of proper radionuclide.

RADIOLABELLING OF DOSAGE FORMS:

Before imaging gastroretentive drug delivery systems, the dosage form must be radiolabeled. Once a suitable nuclide is selected, a proper agent must be selected to carry the isotope. Chelating agents such as diethylenetriaminepentaacetic acid (DTPA) [50], colloids e.g. sulphur colloid [63], polystyrene resin [64], and cellulose macromolecules [65] etc. are also utilized. The radionuclide is incorporated into the formulation using an appropriate method so that it acts as a marker for a particular event. This is usually the release of a drug, but in some cases, the radionuclide is required to be retained in the formulation to investigate the fate of

the dosage form itself [66]. Radiopharmaceuticals labeled with ^{99m}Tc are most widely employed. Using gamma-emitting radioisotopes compounded into GRDF has become the state of art for evaluation of GIT times in healthy volunteers [67]. Emitted rays can be imaged using a 'gamma camera' of scintillation counter, combined with a computer to process the image, and thereby dosage forms can be tracked in the GIT. A major advantage of this technique is its high safety profile, as it is accompanied by relatively low doses of radiation.

Radiolabelling techniques [66, 68]:

Several approaches are available and widely used for different radiolabelling techniques. Predominant ones are briefly described in the following text and shown in Figure No. 3.

(a) Whole dose radiolabelling: Involves incorporation of radiolabeled carrier particles uniformly within the formulation matrix during manufacture. This is particularly important when a key objective is to assess the release of drug from the dosage form over time.

(b) Point radiolabelling: Sometimes known as 'drill and fill' where radiolabeled carrier particles are inserted into a hole drilled within the surface of the tablet, which is then subsequently sealed. Radiolabel acts as a marker for location in the GIT and provides some information on the integrity of the dosage form. Examples- InteliSite[®] [69] and Enterion[™] capsule [70].

(c) Surrogate marker: It is not always necessary to directly radiolabel a multiparticulate formulation. Instead, a second population (e.g. ion exchange resin or non-pareil beads), labeled with a suitable radionuclide, is mixed with drug pellets. It is used for some multi-particulate systems. Production-scale batches cannot be radiolabeled by conventional method because of a large amount of radioactive isotope needed and the radiation exposure to the manufacturing personnel. Hence, the neutron activation method was developed by Parr et al. to radiolabel intact dosage forms. The study was carried out with ^{138}Ba , ^{170}Er , and ^{152}Sm as isotopes [71].

(d) Neutron activation gamma scintigraphy: The procedure incorporates a small amount of a stable (nonradioactive) isotope in the dosage form by mixing it with the other excipients at the time and site of its manufacture [72]. Properties of radionuclides employed in neutron activation shown in Table No. 3.

Table No. 3: Properties of radionuclides utilized in neutron activation based scintigraphy [73]

Stable nuclide	Natural abundance (%)	Neutron capture cross-section (barn)*	Radionuclide	Half-life	Gamma energies	Photon gain (%)	Daughter nuclide
¹³⁸ Ba	71.7	0.4	¹³⁹ Ba	83 min	166	22	¹³⁹ La (stable)
¹⁷⁰ Er	14.9	9.0	¹⁷¹ Er	7.5 hr	112 124 296 308	20 9 28 64	¹⁷¹ Tm (T _{1/2} =1.9 ↓) ¹⁷¹ Yb (stable)
¹⁵³ Sm	26.7	210	¹⁵³ Sm	47 h	97 103		¹⁵³ Eu (stable)

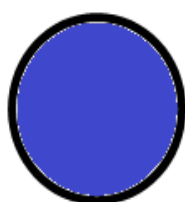
* 1 barn=10⁻²⁸m²

Abbreviations: Ba = Barium, Eu = Europium, Er = Erbium, La = Lanthanum, Sm = Samarium, Tm = Thulium, Yb = Ytterbium

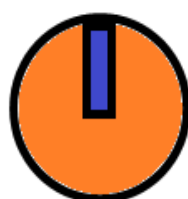
Neutron activation offers the advantage of allowing the manufacturing process to be performed at the usual site, the stable isotope is converted to a radioactive isotope (making it appropriate for gamma scintigraphy) by a short exposure to a neutron flux. The most commonly used is ¹⁵²Sm; in this case, ¹⁵²Sm is activated to ¹⁵³Sm to convert the isotope into gamma-emitting material [1]. Digenis et al. studied the dual-isotope imaging of neutron-activated erbium-171 and samarium-153 and the *in-vivo* evaluation of a dual-labeled bilayer tablet by gamma scintigraphy. The results demonstrated that this dual-label procedure is sensitive enough to monitor simultaneously the behavior of two discrete regions of the same unit dose in the gastrointestinal tract of man [74]. In the case of complex dosage forms, such as enteric-coated tablets, labeling is best undertaken by the addition of a non-radioactive tracer such as a samarium-152 oxide or erbium-170 oxide followed by neutron activation of

the final product [75]. Brunner *et al* used this technique to determine the gastrointestinal transit of samarium-153 mesalazine pellets versus tablets in male healthy volunteers [76].

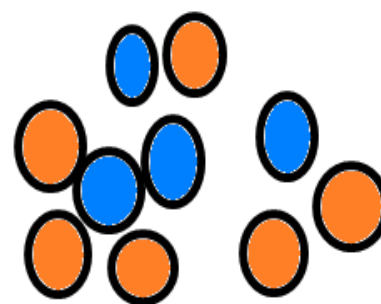
Burke *et al.* developed a novel method to radiolabel gastric retentive formulation for gamma scintigraphy assessment. The retention of two radionuclides, indium (^{111}In) and samarium (^{153}Sm), with and without further processing to improve radiolabel performance was evaluated in simulated gastric pH *in-vitro*. The most successful formulation from *in-vitro* screening was further evaluated in preclinical and clinical studies. A simple, yet robust radiolabel was developed for gastric retentive formulation to be evaluated pre-clinically or in a clinical setting by entrapping the radionuclide in an insoluble polymer through a simple polymer melt process [77]. Terán *et al.* performed scintigraphic studies to assess the release, both *in-vitro* and *in-vivo*, of radiotracers from tablet formulations. Four different tracers with differing physicochemical characteristics were evaluated to assess their suitability as models for drug delivery. Two hydrophilic tracers, $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid ($^{99\text{m}}\text{Tc}$ -DTPA), $^{99\text{m}}\text{Tc}$ -ethyl cysteinyl dimer ($^{99\text{m}}\text{Tc}$ -ECD) and two lipophilic tracers, $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) and $^{99\text{m}}\text{Tc}$ -sestamibi ($^{99\text{m}}\text{Tc}$ -MIBI) were used as drug models. This study demonstrated that significant differences in release patterns, depending on the model chosen. Careful choice of drug model, together with substantial *in-vitro* validation is essential to reduce *in-vivo* studies and make significant savings of human and financial resources [78].



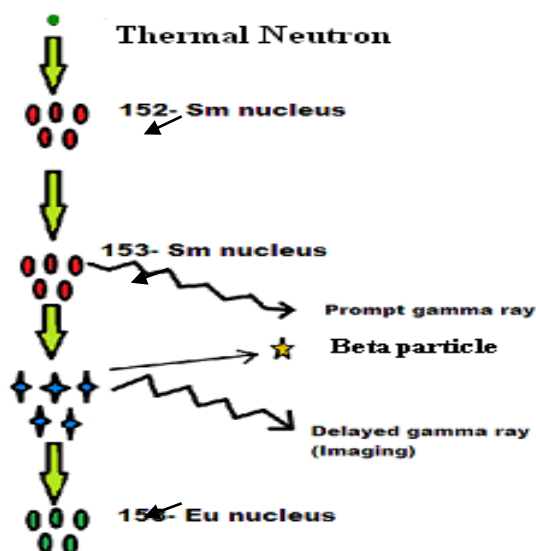
(a) **Whole dose radiolabelling**



(b) **Drill and fill**



(c) **Surrogate marker**



(d) Neutron activation method

Figure No. 3: Various radiolabelling techniques

Before each study, radiolabelling validation measurements are carried out to show that the drug delivery characteristics are unaltered by the labeling process and that the radiolabel acts as a marker for the drug across the full range of particle size band [79, 80, 81]. Once the radiolabelling method has been validated, scintigraphic data can be recorded *in vivo*.

Instrumentation Aspects [62, 82]:

Gamma scintigraphy relies on the detection of radiation emitted from a radionuclide. Nuclear imaging is mostly conducted with planar or SPECT (single-photon emission computed tomography) cameras and by using radionuclides that emit gamma radiation with energies between 100 and 250 KeV [19]. A schematic representation of the detector of a gamma-ray camera is shown in Figure No. 4. The apparatus used for this detection is a gamma camera. Gamma camera also called a scintillation camera or Anger camera, is a device used to image gamma radiation emitting radioisotopes, a technique known as scintigraphy. The applications of scintigraphy include early drug development and nuclear medical imaging to view and analyze images of the human body or the distribution of medically injected, inhaled, or ingested radionuclides emitting gamma rays [83]. It is provided with a scintillator which transforms the gamma radiation into emission of light. Inorganic crystals are best suited for the detection of gamma rays [84]. The intensity of the light produced is proportional to the energy deposited in the crystal by the gamma-ray [85]. The most commonly used scintillator is a monocrystal of sodium iodide activated by thallium. In neutron, X-ray, and gamma-ray

optics, a collimator is a device that filters a stream of rays so that only those traveling parallel to a specified direction are allowed through. Collimators are used in neutron, X-ray, and gamma-ray optics because it is not yet possible to focus radiation with such short wavelengths into an image through the use of lenses as routine with electromagnetic radiation at optical or near-optical wavelengths [86]. A collimator made of lead is placed immediately in front of the crystal to stop any radiations arriving at an angle. Electronic circuitry is provided for amplifying the light signal produced in the crystal, and for quantifying the intensity of the incident gamma rays and locating its origin. Photomultiplier is used for this purpose, photomultipliers are members of the class of vacuum tubes, and more specifically phototubes, are extremely sensitive detectors of light in the ultraviolet, visible, and near-infrared ranges of the electromagnetic spectrum. These detectors multiply the current produced by incident light by as much as 100 million times [87]. It is thus possible to determine the distribution of the tracer on an image formed as a matrix of pixels. This image is subsequently computer-processed to determine accurately the distribution of the tracer in the body, in the so-called 'regions of interest'. One of the drawbacks of this method is that although the image has the appearance of an anatomical image, it portrays in fact phenomena that are pure of a physiological nature. For this reason, when evaluating a tablet that does not disaggregate in the gastrointestinal tract, a second tracer needs to be administered concomitantly in a solution, so that the contour of the tract may be outlined and the tablet located accurately.

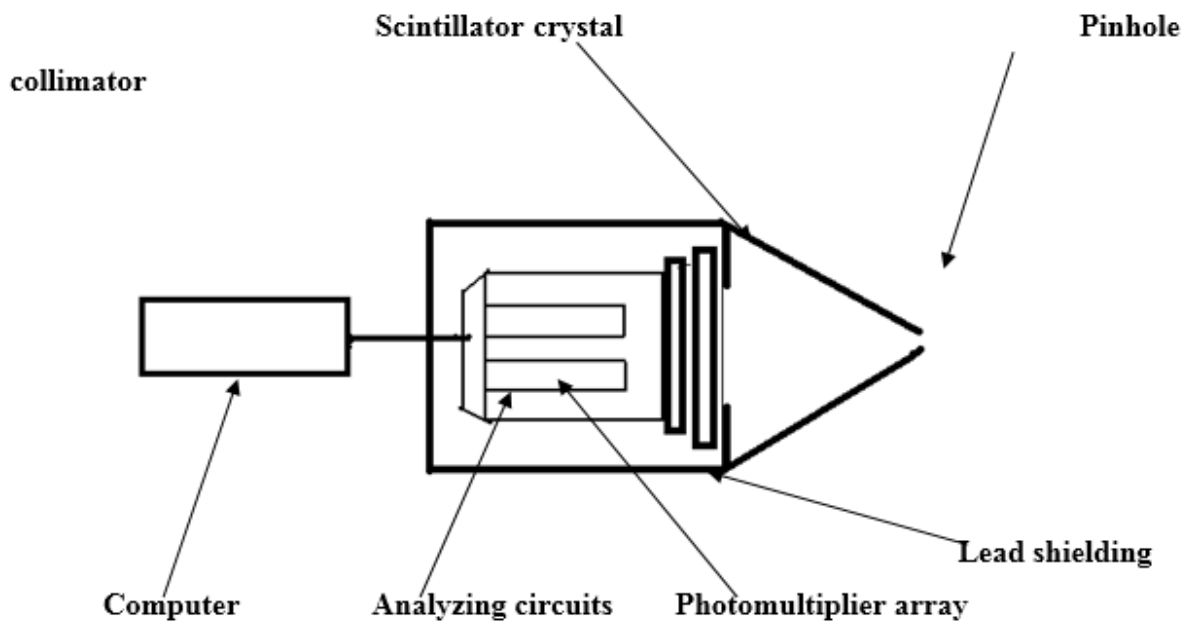


Figure No. 4: Pictorial representation of Gamma-ray camera

The camera provides two-dimensional or planar images of the distribution of radioactivity in the subject. The planar images, however, provide a good depiction of the position of the radiotracer. For this reason, radiolabeled drug delivery systems are best studied with a planar camera. Often, gamma cameras are dual-headed with one camera above and one camera beneath the table. The camera could also be located within a large, doughnut-shaped scanner. Dual-headed cameras, which allow simultaneous acquisition of anterior and posterior images, have become more common [7]. If planar imaging cannot provide the required deposition details, then SPECT should be considered. SPECT is a technique for producing cross-sectional images of radionuclide distribution in the body. This is achieved by imaging the organ at different angles (e.g. 64 or 128 images/180⁰ or 360⁰) using a rotating gamma-camera. The acquired raw data are then processed by high-speed computers [88]. Tomographic images produced by SPECT allow the construction of three-dimensional volume or surface-calculated structures. The time of image acquisition is also fast because of the presence of more numbers of sodium iodide crystals. However, the resolution of the SPECT images is not as good as the planar camera.

Gamma imaging tools are also available for imaging gamma scintigraphy e.g. Scin Cam, Scin Win, Scin view.

- Scin Cam: It is a hardware and software used to acquire images from a gamma camera.
- Scin Win: It helps in analyzing the images.
- Scin View: It is used in the presentation of analyzed images [89].

GASTRORETENTIVE DRUG DELIVERY SYSTEMS:

Oral administration is the most versatile, convenient, and predominant mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake [90]. Approximately 50 % of the drug delivery systems available in the market are oral drug delivery systems [91]. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period at a predetermined and controlled rate [92]. Drugs that are easily absorbed from the GIT and have a short half-life are eliminated quickly from the blood circulation. To overcome this problem, oral CR formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period [93]. Gastric emptying of dosage forms is an extremely variable process and the

ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the GIT. Drug absorption from the GIT is a complex procedure and is subject to many variables [94]. Scintigraphic studies determining gastric emptying rates revealed that orally administered CR dosage forms are subjected to two complications that of short gastric residence time and unpredictable gastric emptying rate. In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). These systems are known as gastroretentive drug delivery systems [95]. Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine [96, 97]. These approaches have gained considerable interest because they are economical and easy to deliver in conventional forms such as specialized tablets, capsules, powders, microspheres, granules, and films [2]. After oral administration, such a dosage form would be retained in the stomach and release the drug in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs [98]. GRDF releases medications in a controlled manner which extends the absorption phase of drugs characterized by a limited and narrow absorption window at the upper part of GIT or drugs intended to treat local ailments in the gastroduodenal. This mode of administration may prolong the period in which the blood drug concentrations are within therapeutic levels and improve therapy [97]. Thus one of the most feasible approaches for achieving prolonged and predictable drug delivery profiles in the GIT is to control the GRT, using GRDF that will provide us with new and important therapeutic options [99]. The need for GRDF has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.

Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, e.g., in the treatment of peptic ulcer disease. The GRDDS extends significantly the period over which the drugs may be released. Thus, they not only prolong design intervals but also increase patient compliance. This application is especially effective

in the delivery of sparingly soluble and insoluble drugs [100]. In general, an appropriate candidate for CR GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper part of GIT. The first GRDDS was suggested by Johnson and Rowe in 1971 [101], since then several systems have been pursued to increase the GRT of dosage forms by employing a variety of concepts [102] i.e. floating dosage forms [103, 104, 105], expandable/swelling of dosage form [106, 107], sedimentation of pellets/high-density system [108] and mucoadhesive/bioadhesive systems [109, 110, 111]. Figure No. 5 represents the major approaches for gastric retention of GRDDS.

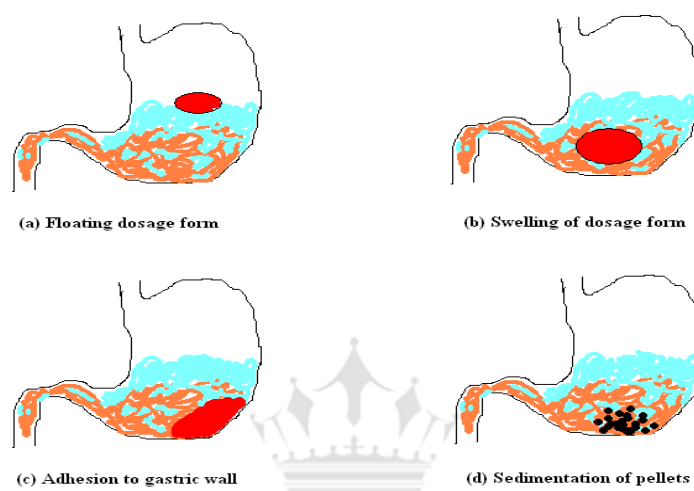


Figure No. 5: Approaches for Gastric Retention

Various advantages of gastroretentive drug delivery systems have been illustrated in the subsequent content: [91, 100, 112, 113, and 114]:

- These systems are advantageous for drugs absorbed through the stomach e.g. antacids, antiulcer agents, etc.
- Enhances the bioavailability and therapeutic efficacy of a drug with a narrow absorption window in the upper part of GIT (pahwa).
- Acidic substances like aspirin cause irritation on the stomach wall when coming in contact with it. Floating formulations may be useful for the administration of aspirin and other similar drugs.
- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. furosemide.

- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics, e.g. β -lactam antibiotics (penicillins and cephalosporins).
- Increasing GIT time thereby increasing bioavailability of sustained-release delivery systems indented for once-a-day administration, therefore GRDDS have the potential to enable many drugs to provide less frequent dosing e.g. ofloxacin.
- Retention of the drug in the GRDDS at the stomach minimizes the amount of drug that reaches the colon.
- When there is a vigorous intestinal movement and a short transit time as might occur in a certain type of diarrhea, poor absorption is expected. Under such circumstances, it may be advantageous to keep the drug in the floating condition in the stomach to get a relatively better response.
- Reduced frequency of dosing for drugs with a relatively short biological half-life, enhancing patient compliance, and thereby improving therapy.
- Drugs that are P-glycoprotein substrate and do not undergo oxidative metabolism, such as digoxin, GRDDS may elevate absorption compared to the immediate and CR dosage forms.

SALIENT APPLICATIONS IN GASTRO RETENTIVE DRUG DELIVERY TECHNOLOGY:

Gamma scintigraphy is an imaging modality that enables the scientific community worldwide to visualize *in-vivo* performance and behavior of various drug delivery systems under normal physiological conditions in a non-invasive manner. [115]. In the present scenario, it has become an established practice and is being extensively utilized by several investigators to monitor the concert of novel drug delivery systems within human GIT. Various researchers have utilized this innovative and sophisticated technology in the evaluation of gastroretentive drug delivery systems including raft forming agents [116-118]. Few of these findings are summarized in a chronological manner (Table No. 4).

Table No. 4: *In vivo* gastroretentive properties of GRDDS studied by gamma scintigraphy

Author	GRDF (drug)	Subject	<i>In vivo</i> scintigraphic studies
Guan et al. [119]	Gastric-resident osmotic pump tablet (famotidine)	Beagle dogs	It was observed that the system can remain in the stomach for an extended period of 7 h after administration compared with conventional tablets.
Yao et al. [120]	Gastro-mucoadhesive delivery system (furosemide)	Human Volunteers	Provided evidence for the validity of the hypothesis that the drug fiber provided better gastro-mucoadhesive properties.
Jain et al. [121]	Concanavalin microspheres (clarithromycin)	Albino rabbits	The prolonged residence time of over 6 h.
Ma et al. [122]	Floating microspheres (diltiazem HCL)	Human Volunteers	Formulation remained and clumped together in one mass for 5 h until the end of the study period.
Zou et al. [123, 124]	Floating and pulsatile release capsule	Human Volunteers	The pulsatile release capsule achieved a rapid release after lag time <i>in vivo</i> , which was longer than that <i>in vitro</i> .
Yao et al. [125]	Gastro-mucoadhesive delivery system (riboflavin)	Human Volunteers	Gamma imaging provided evidence for good mucoadhesive properties.
Sonar et al. [126]	Bilayer and floating bioadhesive tablets (rosiglitazone maleate)	Human Volunteers	The formulation remained in the stomach for approximately 8 h.
Jain et al. [127]	Floating microspheres	Albino rabbits	Administered microspheres remained floating and distributed in

	(repaglinide)		the stomach contents for a 6 h period.
Ali et al. [128]	Floating capsule (celecoxib)	Albino rabbits	An optimized hydrodynamically balanced system capsule was retained in the gastric region for a prolonged period.
Ali et al. [129]	Hydrodynamically balanced system (metformin)	Albino rabbits	The formulation remained buoyant during 5 h of study in rabbits.
Badve et al. [130]	Floating-pulsatile beads (diclofenac sodium)	Albino rabbits	Gamma scintigraphy studies determined on rabbits showed gastro retention of beads up to 5 h.
Jain et al. [131]	Floating microspheres (orlistat)	Albino rabbits	Optimized formulation remained floating and distributed in stomach contents for 6 h.
Sakkinen et al. [132, 133, 134]	Mucoadhesive chitosan granules	Human Volunteers	Chitosan studied had exhibited marked mucoadhesive capacities <i>in vitro</i> ; the retention at the site of adhesion in human GIT was relatively short and not sufficiently reproducible.
Dhumal et al. [135]	Bilayer floating tablets (cefuroxime axetil)	Human Volunteers	The floating matrix layer of the bilayered tablet after the disintegration of the immediate-release layer was found to have a GRT of 6 h.
Stops et al. [136]	Floating beads	Human Volunteers	Results indicated that prolonged gastric retention was achieved with citric acid as compared to retention in the absence of citric acid.
Chauhan et al. [137]	Floating granules (risedronate)	Human Volunteers	A study of matrices in human Volunteers showed that the formulation remained in the stomach

			for about 6 h.
Shimpi et al. [138]	Floating granules (diltiazem HCL)	Human Volunteer	Formulation remained in the stomach for about 6 h.
Sakkinen et al. [139]	Mucoadhesive microcrystalline chitosan granules	Human Volunteers	<i>In vivo</i> mucoadhesive of microcrystalline chitosan formulations are erratic, and that the formulations studied are not reliable GRDDS.
Billa et al. [140]	Xanthan gum matrices (diclofenac sodium)	Human Volunteers	Gastric emptying was delayed with food intake.
Whitehead et al. [141]	Multiple-unit floating Dosage Form i.e freeze-Dried calcium alginate	Healthy Volunteers	A prolonged gastric retention time of over 5.5 h was achieved in all subjects for floating formulations.
Washington et al. [142]	Pectin containing anti-reflux formulation	Human Volunteers	Greater than 50 % of the formulation remained in the fundal region of the stomach for 3 h.
Atyabi et al. [143]	Microspheres fabricated by ion exchange resins	Human Volunteers	Showed significantly prolonged GRT.
Desai et al. [144]	Floating tablets (theophylline)	Human Volunteers	The presence of food significantly increased gastric retention and tablet density did not appear to make a difference in the GRT.
Oth et al. [145]	Bilayered floating Capsule	Human Volunteers	The average GRTs were 199±69 min after the succession of meals.
Xu et al. [146]	Floating Tablets (gentamicin sulfate)	Human Volunteers	It was shown that the gastric retention time of all subjects taking gentamicin-HBS under fed and fasted conditions were all over 4 h.
Kholsa et al.	Bioadhesive pellets	Human	The pellets emptied from the

[147]	of polycarbophil	Volunteers	stomach rapidly and in an exponential manner. Polycarbophil did not retard the gastric emptying of pellets.
Wilson et al. [148]	Osmotic tablets	Young and elderly healthy subjects	The units were observed to move through the GIT at about the same rate as the release contents, arriving at the caecum on average 7 h after dosing.

PHARMACOSCINTIGRAPHIC APPROACH:

This advanced approach integrates gamma scintigraphy technique and pharmacokinetic data to assess the behavior of dosage form in subjects under investigation. Instead of relying on pharmacokinetic findings alone, it is better to unite these parameters with the technique of gamma scintigraphy to investigate the performance of dosage forms in humans [149]. In practice, it is not feasible to perform blood sampling at quick succession throughout the entire study period, and thus the use of gamma scintigraphy is ideal as it provides the visual information required regarding tablet disintegration time, which can act as a trigger to begin pharmacokinetic blood sampling. Furthermore, scintigraphic images combined with pharmacokinetic data are a powerful tool in the interpretation of unusual or unexpected pharmacokinetic profiles, allowing identification of gastrointestinal location and behavior of the formulation at the time of a particular pharmacokinetic event.

Sato et al. pharmacoscintigraphic evaluated riboflavin containing micro ballons for a floating controlled drug delivery system in healthy humans. The intragastric of ^{99m}Tc labeled micro ballons (MB) and nonfloating microspheres (NF) (control) following oral administration in fasted and fed humans was investigated by gamma scintigraphy. Simultaneously, the pharmacokinetic examination of riboflavin released from MB and NF was conducted in fasted and fed human subjects. MB was retained in the stomach up to 300 min compared with NF, which descended gradually into the lower part of the stomach within 90 min. In the fasted state, MB floated for approximately 60 min, after which it was removed rapidly via the cyclic activity referred to as the inter digestive migrating motor complex. It was concluded that MB is very useful for improving drug bioavailability, resulting in more sustained pharmacological action [150]. Goole et al. prepared sustained-release floating minitablets

containing levodopa and carbidopa, pharmascintigraphic, and pharmacokinetic evaluation on healthy human volunteers was done. The study showed that the new-sustained release floating mini-tablets were able to float on the surface of gastric fluid for more than 4 hours. They also provided a sustained pharmacokinetic profile of levodopa and carbidopa [151]. Cumming et al. also employed pharmacoscintigraphy to evaluate the single-dose pharmacokinetics, GIT, and release properties of a GABA receptor agonist from an endogastric therapeutic system (EGTS), in fasted and fed states in healthy volunteers. Gamma emitting radionuclide [153] was included in EGTS for pharmascintigraphic as well as pharmacokinetic analysis. Results suggested that the EGTS technology is an effective gastroretentive system for the delivery of therapeutic compounds [152]. Pharmascintigraphy studies in man can subsequently direct the oral development strategy of new compounds. This allows pharma to remain focused on developing oral product-preferred route of administration for patients (scrip magazine).

MISCELLANEOUS FACTORS AFFECTING GASTRIC RETENTION OF GRDDS EXPLAINED BY MEANS OF GAMMA SCINTIGRAPHY:

Other factors that might contribute to the variation in GRT of GRDDS have been briefly described in the below text.

Timmermans et al. studied the factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules utilizing gamma scintigraphy [153].

Fu et al. studied on bioadhesive property of carbomer 934 using a gamma camera in the dog. It was concluded that, in the dog, interactions between gastrointestinal mucus layer and adhesive material or nonadhesive material were significantly different. Carbomer 934 had a stronger *in vivo* bioadhesive property than ethylcellulose [154]. Jackson et al. performed a comparative scintigraphic assessment of intragastric distribution and residence of cholestyramine, carbopol 934P, and sucralfate for their mucoadhesive property. Using gamma scintigraphy it was concluded that cholestyramine had a comparable emptying time to carbopol and sucralfate but greater residence and wider distribution. It could provide a potential mucoadhesive drug delivery system targeting the gastric mucosa for the treatment of conditions such as *H. pylori* [155]. Kapil et al. evaluated the flow, compressive, and bioadhesive properties of various blends of poly (ethylene oxide). Two optimized formulations were subjected to gamma scintigraphy studies on Human Volunteers. Findings of gamma scintigraphy studies indicated a fourfold increase in the gastric retention time of

the optimized formulation vis-à-vis control formulation. It was also concluded that polyethylene oxide, in a concentration of 10-50 % (w/v) can be successfully employed in the manufacturing of gastroretentive tablets [156]. Harris et al. evaluated the gastric emptying and small intestinal transit of some potentially adhesive formulations in man by gamma scintigraphy. Two different capsule formulations were investigated, in combination with two potentially bioadhesive polymers and non-adhesive control. Small differences in oro-caecal transit were seen with certain combinations, but no dramatic effects on GI transit were observed [157].

Bechgaard et al. established the influence of transit time exerted by the density or diameter of pellets in six ileostomy subjects using gamma scintigraphy. It was reported that the diameter of pellets had a minor effect on gastrointestinal transit. The findings suggested the use of density as a means of modifying the period of absorption of controlled-release pellets [158, 159].

Strusi et al. studied the floatation behavior of systems obtained by modules assembled in the void configuration. *In-vivo* studies confirmed that the *in-vitro* floating ability of void configuration was also maintained in the human stomach where the system stayed for periods ranging from 2.5 to 5.0 h, depending on the food regimen and the sex of the subject [160].

Kedzierewicz et al. evaluated peroral silicone dosage forms in humans by gamma scintigraphy. To achieve a constant and predictable residence time in the stomach, three different formulations based on known concepts such as controlled swelling were investigated. The mini matrices provided at least 3 h retention, slabs exhibited 4 h 40 min retention. For the rods, the mean residence time in the stomach was around 4 h 20 min [161].

Agyilirah et al. compared the gastric emptying time of tablets coated with a cross-linked polymer that enabled them to balloon and float in gastric media with that of uncoated, non-disintegrating tablets in both fasted and fed states, with healthy volunteers using gamma camera scintigraphy. In the fed state, the balloon tablets prolonged the gastric emptying time by an average of 6 h over that of the uncoated tablets [162].

Dettmar et al. investigated the effect of omeprazole pretreatment on rafts formed by reflux suppressant tablets containing alginate. Raft formation and gastric residence, in the presence of ^{99m}Tc labeled meal, were assessed by gamma scintigraphy for 3 h after alginate tablet

administration. Pretreatment and co-administration with omeprazole had no significant effect on the raft-forming ability of alginate tablets [163].

Above investigational studies reveal that gamma scintigraphy offers vital and valuable information in studying the GRT, GET, and other significant factors affecting GRDDS.

RADIATION SAFETY:

Gamma rays have adequate energy to pass through the human body without interactions with the tissues, but they can ionize atoms in tissue or cause secondary ionizations by transferring energy to atomic particles such as electrons. The gamma rays can induce DNA alterations by interfering with the genetic material of a cell. DNA double-strand breaks are generally considered to be the most significant mechanism by which radiation causes cancer and hereditary disease [164]. Like any medicine, radiopharmaceuticals are prepared with great care. Before they are used, they are tested carefully and approved for use by the U.S Food and Drug Administration. The International Commission on Radiological Protection uses four risk classes of clinical studies utilizing radiation [165] categorized in Table No. 5.

Table No. 5: ICRP categories of social and corresponding societal benefits [165]

Level of risk	Risk category ^a	Corresponding effective dose range (adult; mSv) ^b	Level of expected societal benefit
Trivial	Category I (~10 ⁻⁶ or less)	< 0.1	Minor
Minor to moderate	Category IIa (~10 ⁻⁵) Category IIb (~10 ⁻⁴)	0.1-1	Intermediate to moderate
Moderate	Category III (~10 ⁻³ or more)	1-10	Substantial

^a Expressed as absolute risk probability (number of events/population).

^b To be kept below deterministic thresholds except for therapeutic experiments.

Although exposure to radioactivity in very large doses can be harmful, the radioactivity in radiopharmaceuticals is carefully selected by the nuclear medicine physician to be safe. The radioactivity given to a patient does not pose any demonstrable health hazard. The amount given is as small as it can be to achieve clear and accurate imaging results [166]. The risk of

the radiation is negligible compared to the information obtained from the scan. The radionuclide is safe and is quickly removed from the body, usually by the kidneys. [167]. Neil G. Hartman studied problems encountered with radiopharmaceutical products and concluded that hospital pharmacists should be aware of the possibility of the, albeit rare, adverse effects from radiopharmaceuticals. The medicines of patients who will be receiving a radiopharmaceutical should be assessed to establish if there are any potential drug interactions [168].

The most biological damaging forms of gamma radiation occur in the gamma-ray window, between 3 and 10 MeV, with higher energy gamma rays being less harmful because the body is relatively transparent to them [7]. Current guidelines for radiation exposure are based upon the conservative assumption that there is no safe level of exposure. In other words, even the smallest exposure is assumed to have some probability of causing a late effect such as cancer or genetic damage. This assumption has led to the general philosophy of not only keeping exposures below recommended levels or regulatory limits, but of also maintaining all exposures “as low as is reasonably achievable” (ALARA) [169, 170]. This is a fundamental tenet of current radiation safety practice and is a regulatory requirement to be followed by all occupational users of radioactive materials and radiation producing devices. Annual dose limits of gamma radiations are shown in Table No. 6.

Table No. 6: Annual dose limits [171]

Annual external dose limits	Rems*
Whole-body, active blood-forming organs, lens of the eye, and gonads	
Single-dose	3
Annual total dose commitment	5
Other organs	
Single-dose	5
Annual total dose commitment	15

Abbreviation: Rems, Rontgen Equivalent Man.

* For a research subject under 18 years of age, the radiation dose shall not exceed 10 % of the above-stated limits.

The International Commission on Radiological Protection (ICRP) recommended an average permissible whole-body radiation dose of 0.1 rem/week and 5 rem/year (radiation protection procedures, International Atomic Energy Agency, safety series, No. 38, pp 40-45, 1978) [14]. These limits still hold valid and are considered to be safe from the health point of view of the individuals. The level of radioactivity used in gamma scintigraphy is very low and it gives a radiation dose to participating subjects that are well below the maximum permissible dose. Hence, it can be considered that the radionuclides used in gamma scintigraphy are harmless at the level they are used. In case of any adverse reaction to radiopharmaceuticals, Sampson suggested its treatment [172]. A worldwide effort should be made to report as many cases as possible of adverse events and false-positive reactions with radiopharmaceuticals [173].

CONCLUSION AND PROSPECTS:

Gamma scintigraphy provides a non-invasive means of acquiring *in vivo* information under normal physiological conditions. The quantity of radionuclide needed to fit into a formulation makes it suitable for use in a gamma scintigraphy study is minuscule and does not compromise the functioning characteristics of the delivery system. Scintigraphy is currently an effective technique that the pharmaceutical scientist has in the interpretation of the *in vivo* behavior of the gastroretentive drug delivery system. Vital information regarding the extent, rate, site, and mode of drug release along with morphology of drug delivery systems in subjects under the ethical norms can be obtained using this technique. Innovations in this technology have allowed the researchers with faster acquisition and better characterization of various radiopharmaceuticals. The reliability and reproducibility of this approach make it an acceptable technique worldwide with diverse advantages and applications. It is anticipated that continued advancements and newer applications of this imaging technique will play a vital role in tracking of sophisticated new generation drug delivery systems. Furthermore, the relevance of this highly developed technology equipped with all desired characteristics for effective and successful mapping of various new delivery systems would be an appropriate futuristic endeavor in times to come.

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