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Pharmacoscintigraphy: An emerging technique for evaluation of various drug delivery systems

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ABSTRACT

Pharmacoscintigraphic technique provides a non invasive method to monitor the in vivo fate of a different pharmaceutical dosage forms. This advanced approach combines gamma scintigraphy and pharmacokinetic information to predict the behaviour of dosage form in subjects under investigation. It 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. These studies provide an insight into the outcome of delivery systems, its integrity as well as enable the relationship between in vivo performance and resultant pharmacokinetic parameters. The present manuscript highlights several applications of this advanced approach in the evaluation of various drug delivery systems. Radiolabelling phenomenon, scintillation camera and safety consideration aspects have also been discussed.

Keywords: Pharmacoscintigraphy, Drug delivery systems, *In-vivo* evaluation.

INTRODUCTION

In recent years, drug evaluation process has emerged as an advanced and sophisticated approach to enable large number of investigators globally with rapid and accurate means of predicting the *in vivo* performance of drug delivery systems. Information about the *in vivo* behaviour of dosage forms can be obtained using radionuclide tagged with dosage forms and the process is known as gamma scintigraphy. This radiolabelled method is a well established technique in medical practice for the past several decades. Moreover, instead of relying on pharmacokinetic data alone, it is better to combine it with the technique of gamma-scintigraphy or pharmacoscintigraphy to assess the performance of dosage form in man [1]. The coupling of gamma scintigraphy with usual pharmacokinetic methods makes it possible to correlate the information obtained on the distribution of medicament with complete absorption profile. The application of a conventional pharmacokinetic assessment to data obtained from gamma scintigraphic studies is called as pharmacoscintigraphy. Radionuclide tagged with drugs/formulations/devices can provide vital information regarding the extent, rate, site and mode of drug release and morphology of the drug delivery system during release in human under

ethical norms [2, 3]. Conclusions can also be drawn about the performance of the formulation, including: the ability of a formulation to target a specific location; the rate of erosion in comparison with *in vitro* dissolution data; the impact of absorption window on bioavailability [4]. The fundamental principle of pharmacoscintigraphy is depicted in figure 1.

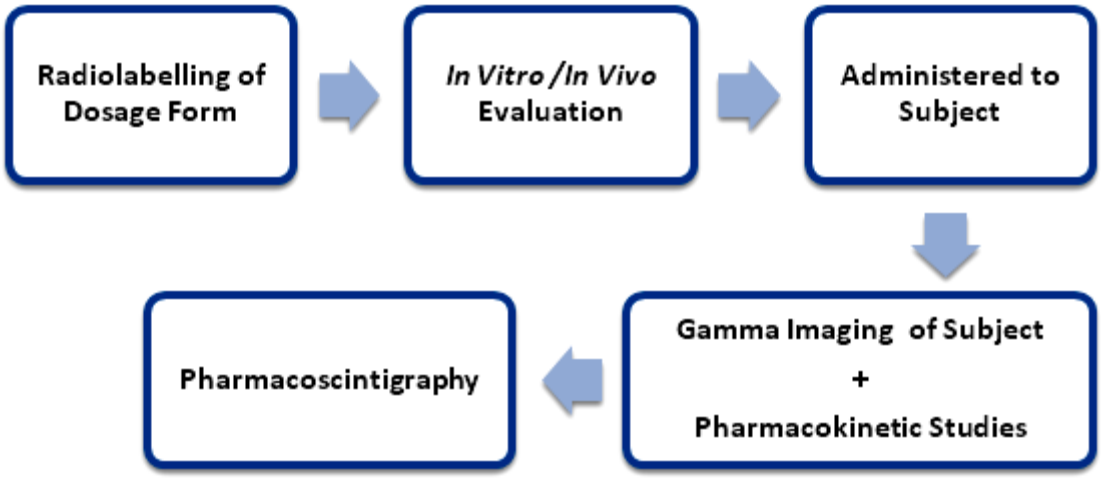

Figure 1: Fundamental principle of pharmacoscintigraphy

Following administration to healthy volunteers or patients, scintigraphic images are acquired at regular intervals. This is a non-invasive process and each image takes approximately 50 seconds to acquire. Images are acquired at 10-20 minutes intervals resulting in a series of snapshots of the dosage form in the gastrointestinal tract (GIT). Scintigraphic images are interpreted by experienced data analysts to identify key events such as gastric emptying, colon arrival, initial release of drug and so on, and to quantify processes such as rate of tablet erosion [1]. An increasing number of development groups are using pharmacoscintigraphic imaging to visualise the *in vivo* location/performance of drug formulations and to investigate their impact on simultaneous pharmacokinetic evaluation so as to fully establish the factors controlling *in vivo* drug disposition [5]. This incisive approach is capable of providing reliable and precise information along with diverse advantages and applications (figure 2).

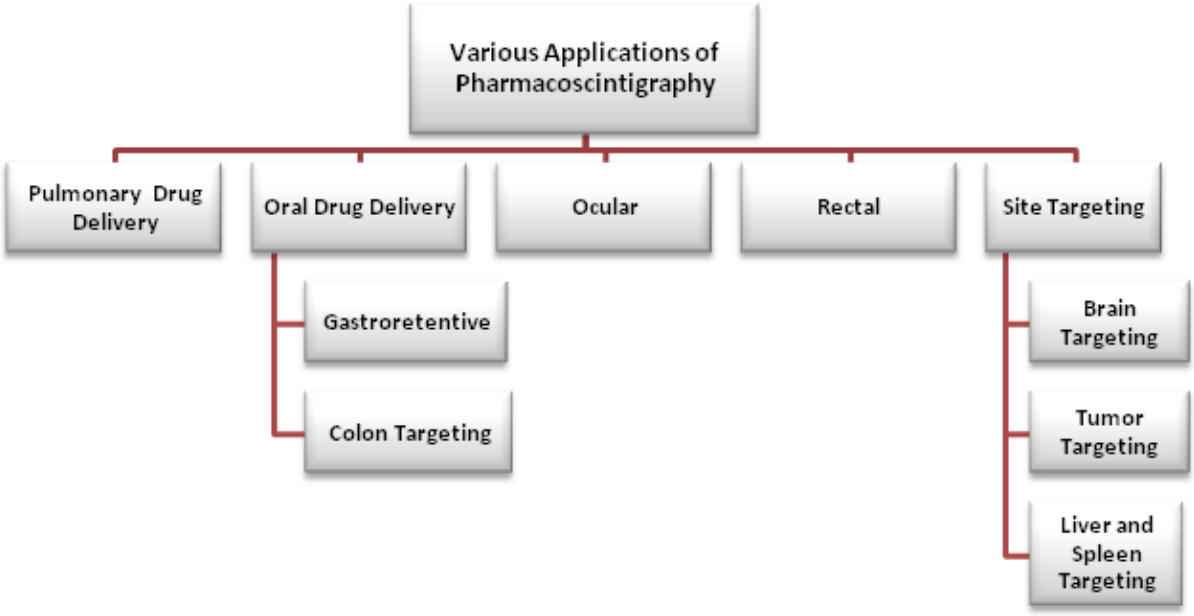

Figure 2: Various applications of pharmacoscintigraphy

Radiolabelling

Prior to imaging by this technique, the dosage form should be radiolabelled. Drug/formulations can be radiolabelled either by gamma emitting isotopes or by neutron activation technique. Emitted radiations are further captured by external detectors such as gamma cameras.

Labelling by Gamma-Emitting Isotopes

Radiolabelling of formulation involves utilization of a short-lived radioisotope that can spontaneously emit gamma radiation. The isotope is incorporated in the formulation as a salt (e.g., sodium pertechnetate) in normal saline. In this type of labelling, a reducing agent is used to reduce technetium, Tc (VII), into a lower valence state. The final solution is maintained in a buffered system, which is followed by incubation to enable labelling [6]. The most widely used reducing condition is the acidic stannous chloride or other stannous salts [7]. Various approaches for radiolabelling can be classified into whole dose radiolabelling, point radiolabelling and surrogate marker technique [8, 9]. Commonly used radionuclides are shown in table 1 along with their half-life [10].

Table 1: Commonly employed radionuclides

Radionuclide	Half-life (approx.)
^{81m}Kr (Krypton)	13 sec
^{99m}Tc (Technetium)	6.02 h
^{111}In (Indium)	2.8 d
^{123}I (Iodine)	13 h
^{131}I (Iodine)	8.05 d

Labelling by Neutron Activation Technology

This approach involves the incorporation of a stable isotope into the dosage form prior to its manufacture, followed by neutron irradiation of the intact dosage form (table 2). Neutron flux exposure is conducted for a very short time, generally 5-30 seconds. This exposure time has been shown to maintain the characteristics and integrity of the dosage form. Short period of time also prevents the degradation of drug under conditions of bombardment. Longer exposures may result in cross-linking of the polymers used in the dosage form. During this technique, thermal neutron irradiation converts the carefully selected stable isotopes (^{152}Sm or ^{170}Er) into radioactive gamma emitting isotopes (^{153}Sm or ^{171}Er) that can be detected by external imaging devices [11, 12, 13, 14].

Table 2: Properties of radionuclides utilized in neutron activation based scintigraphy

Stable nuclide	Natural abundance (%)	Radionuclide	Half-life	Daughter nuclide
^{138}Ba	71.7	^{139}Ba	83 min	^{139}La (stable)
^{170}Er	14.9	^{171}Er	7.5 hr	^{171}Tm ($t_{1/2}$=1.9y) ^{171}Yb (stable)
^{153}Sm	26.7	^{153}Sm	47 h	^{153}Eu (stable)

Ba- Barium, Eu- Europium, Er- Erbium, La- Lanthanum, Sm- Samarium, Yb- Ytterbium

Gamma Camera

Gamma scintigraphy relies on the detection of radiations emitted from a radionuclide. In this technique, gamma camera is used to image gamma radiation emitted from radioisotopes (figure

3). Nuclear imaging is predominantly carried out 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. The single photon emitting radioisotopes such as ^{99m}Tc and ^{111}In are widely used with these instruments. Gamma camera is composed of an array of photomultiplier tubes coupled to a sodium iodide crystal. The interaction of a gamma photon from the source with the crystal leads to the production of a flash and it is detected by photomultiplier. To ensure that radiation from the source is detected in straight line, a lead collimator is placed between the subject and the crystal. The camera provides two-dimensional or planar images of the distribution of radioactivity in the subject. The planar image provides a good depiction of the position of the radiotracer. For this reason, radiolabelled drug delivery systems are best studied with planar camera [15]. 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/ 180^0 or 360^0) using a rotating gamma-camera. The acquired raw data are then processed by high-speed computers [16]

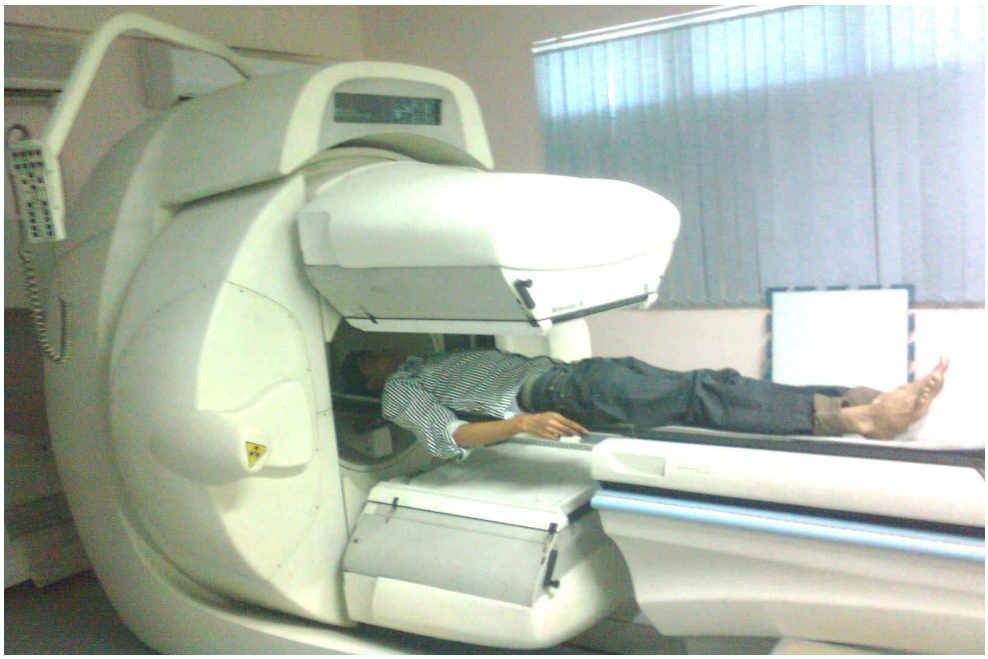

Figure 3: Scintigraphic studies under gamma camera

Oral Drug Delivery Systems

For decades, oral drug delivery has been the most convenient and usually employed route of drug delivery due to its ease of administration, least aseptic constrain and flexibility in the design of dosage form [17]. Combination of scintigraphy technique with pharmacokinetic studies (pharmacoscintigraphy) has become an important and crucial means of providing information about the transit and release behaviour of dosage forms with subsequent drug absorption pattern. Some pharmacoscintigaphy studies have been successfully applied in the avenue of oral controlled drug delivery. Few examples are described in table 3.

Table 3: Pharmacoscintigraphic evaluation of oral drug delivery systems

Drug	Formulation	Number of volunteers	Research envisaged	Pharmacokinetic data	Reference
Naproxen	Tablet	6	Tablet disintegration and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma	Hardy *et al* [18]
Theophylline	Tablet	6	*In vitro–in vivo* correlation	Correlation of absorption data with *in vitro* release kinetics	Sournac *et al* [19]
Aminophylline	Tablet	6	*In vitro–in vivo* correlation and relationship of dosage form position to serum concentration	Absorption of drug independent of tablet position and controlled by release from the tablet	Davis *et al* [20]
Naproxen	Multiple unit dosage form	8	Disruption of pellet coating and onset of absorption	Close correlation between tablet coat disruption and detection of drug in plasma	Hardy *et al* [21]
Naproxen	Tablet	12	*In vivo* performance of enteric coated tablets	Close correlation between tablet coat disruption and detection of drug in plasma	Wilding *et al* [22]
Carbamazepine	Oros system	8	Correlation of position in the GI tract with plasma concentration	Intrinsic crossover design using stable isotope technology. Decreased absorption from the colon.	Wilding *et al* [23]

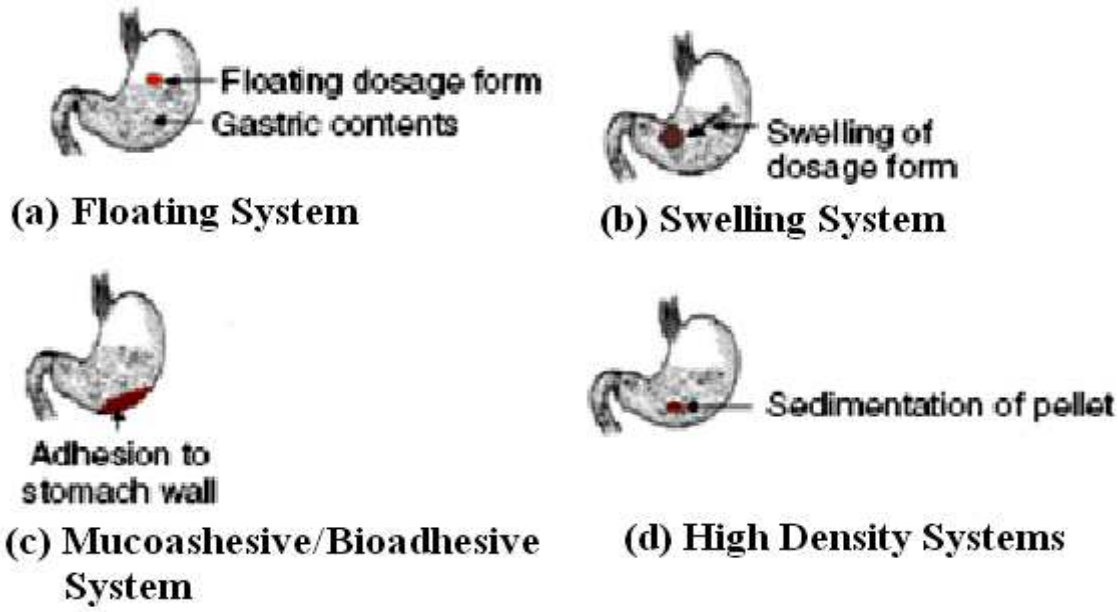

Figure 4: Classification of gastroretentive delivery systems

Gastroretentive Technology

Various 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, unpredictable gastric emptying times etc. These innovations are known as gastroretentive drug delivery systems [24]. Several approaches have been explored to retain the dosage form in the stomach including floating system, swelling system, bioadhesive system, high density system etc. (Figure 4). Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly in the stomach and upper small intestine [25, 26]. 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, etc. [27].

Gastroretentive drug delivery system offers numerous advantages over conventional drug delivery system. Some of these are discussed in the following text [28, 29]:

- Gastric retention of drug delivery system enhances the bioavailability and therapeutic efficacy of drugs with narrow absorption window in the upper part of GIT.
- Floating system has the property of retaining the dosage unit in the stomach for prolonged period of time. It provides controlled drug release behavior which offers the advantages of uniform and consistent blood level of medication.
- Site specific drug delivery improves local therapy in the GIT by increasing gastric residence time, optimize systemic absorption and minimize premature drug degradation. This approach would be highly beneficial in the treatment of *Helicobacter pylori* infection in peptic ulcer disease.
- Fluctuations are minimized due to continuous input of the drug following controlled release gastroretentive dosage forms administration.
- Minimizes or eliminates the side effects by delivering the drug at the active site.
- This system is advantageous in case when there is vigorous intestinal movement and a shorter transit time as might occur in certain type of diarrhoea, which results in poor absorption. Thus it helps to keep the drug in floating condition in stomach to get a relatively better response.
- Drugs from oral controlled release formulations are invariably and inadequately absorbed owing to short residence of their devices in GI tract. Gastroretentive dosage forms circumvent these hiccups by improving their GI retention.
- Prolongation of the total GI transit time reduces the number of doses in the regimen which improves patient comfort and compliance.

Table 4: Applications in gastroretentive drug delivery approach

Objective	Conclusion	Reference
Evaluation of the gastric retention time of the sustained release floating mini tablets (FMT) and of the marketed Prolopa® HBS 125 floating capsule in fed state.	Sustained release FMT were able to float on the surface of gastric fluid for more than 4 h.	Goole *et al* [30]
Intragastric of ^{99m}Tc labelled microballoons and non floating microspheres (control) following oral administration in fasted and fed humans.	Microballoons with improved drug bioavailability resulted in more sustained pharmacological action.	Sato *et al* [31]
Evaluation of the single dose pharmacokinetics, GI transit and on release properties of a GABA receptor agonist from an endogastric therapeutic system (EGTS), using pharmacoscintigraphy in fasted and fed states in healthy volunteers. Samarium-153 was included in EGTS for pharmacoscintigraphic as well as pharmacokinetic analysis.	Findings suggested that the EGTS technology is an effective gastroretentive system for the delivery of therapeutic compounds.	Cumming *et al* [32]

Pharmacoscintigraphy has proven to be a handy tool in the *in vivo* assessment of gastroretentive drug delivery systems (table 4)

Colon Targeting

In recent years, scintigraphic technique has become the most popular means of investigating the gastrointestinal performance of pharmaceutical dosage forms, especially site-specific dosage forms [33]. By means of gamma scintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which drug release takes place can be obtained [34]. These studies can also provide information about regional permeability in the colon. Findings about GI transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gamma scintigraphic studies. Good correlations between appearance of a drug in plasma and observed disintegration times can also be recorded [35]. Some pharmacoscintigraphic evaluation of colon targeting have been reported and described in table 5. Stevens *et al* used gamma scintigraphy to identify the site of release from a Pulsincap™ formulation, intended to release drug after a five-hour lag time. A good correlation was found between release times determined scintigraphically and pharmacokinetic profiles [36]. A correlation between pharmacokinetic and gamma scintigraphic data was also found when times and anatomical locations of break-up of colon-specific formulation were determined by Sangalli *et al* [37].

Table 5: Pharmacoscintigraphic evaluation of colon targeting technology

Drug/Dosage Form	Number of volunteers	Objectives	Conclusion	Reference
Dexamethasone/tablet	8	Ability of the naturally occurring polysaccharide (guar gum) to deliver a corticosteroid, dexamethasone, to the colon using pharmacoscintigraphy was evaluated.	Pharmacoscintigraphic data indicated that 72%–82% of the dexamethasone was delivered into the colon although not all the dexamethasone delivered into the colon was absorbed.	Kenyon *et al* [38]
5-ASA "TIME CLOCK" system	8	Simultaneous assessment of transit/disintegration using scintigraphic imaging and drug absorption via traditional pharmacokinetic evaluation.	Pharmacoscintigraphic findings provide "proof of concept" data for the colonic delivery of 5-ASA using enteric coated "TIME CLOCK" technology.	Steed *et al* [39]
Gaur gum matrix/tablets	6	To evaluate the efficiency of gaur gum in delivery to the colon	Tablet specifically disrupted and released the tablet contents in the colon	Satyanara-yan *et al* [40]
Indomethacin/ Gaur gum as a compression coat	6	To evaluate the efficiency of gaur gum as a coat in delivery to the colon	The tablet coat specifically disrupted and released the core tablet contents in the colon	Krishnaiah *et al* [41]
Inert HPMC capsules coated with two different polymers	8	To study the release of two Eudragit polymers and their effect on the capsule content release	The Eudragit L30 D55 was found to disrupt within the capsule, whereas the Eudragit FS30 D was found to disrupt in the colon	Cole *et al* [42]
Oseltamivir/ Enterion™ Capsule	9	To study specific sites of drug absorption	The proximal and distal bowel were the sites for absorption, and a modified release system was feasible	Charles *et al* [43]

Inert/tablets	20	To determine the anatomical site and time of disintegration of the tablets with different *in vitro* DT	No difference in the site and time of DT was seen, but colon targeting was observed	Goto *et al* [44]
Ranitidine/ Tablets	10	To assess feasibility of the formulation to target colon and determine the site of absorption	The formulation for targeting the colon is a feasible approach to assess the GI site absorption and colon targeting	Basit *et al* [45]
Inert/tablets coated with pectin- HPMC by compression coating	6	To study the colonic release of the coated tablets	The coat was disrupted in the colon in all of the individuals and hence the material can be used for coating tablets that release the contents in the colon	Hodges *et al* [46]

In essence, gamma scintigraphic evaluation of a colon-specific drug delivery system provides 'proof of concept', i.e. visualization of system disintegration event and ascertainment of disintegration location in the GI tract.

Pulmonary Drug Delivery Systems

The pulmonary route is preferred to all the others when it becomes necessary to treat reversible obstructions of the respiratory tract. Radionuclide imaging technique also plays an important function in the assessment of drug delivery via pulmonary route. This technique is capable of quantify accurately the amount of drug delivered from an inhaler device to the target site in the lungs. Measurement of local bioavailability at the site of action in the lungs is also possible. Furthermore, such investigational studies also provide a viable way for the determination of equivalence of two different inhaled products. For assessing the bioequivalence of inhaled asthma medication, this technique is more relevant than classical bioequivalence testing, more appropriate than *in-vitro* findings and more incisive than clinical response studies [47, 48]. Various objectives of this radionuclide imaging technique for drug products delivered via pulmonary route include [49]:

- To provide reliable and precise information on the amount and location of drug deposited in lung after inhalation.
- To reveal proof of concept in man for newer devices.
- To visualize the complex structure of the lungs in three dimensions.
- To compare the *in-vivo* drug delivery performance of different products in a more realistic manner.
- To establish the likely dose range of a newer inhaler device as compared to an established product.
- To present accurate information with regards to inhaler design modification and process engineering aspects.

Various scintigraphic studies have been carried out on the pulmonary route of drug delivery, mainly for the drugs employed in asthma. Various modes of this research have involved 2-dimensional planar imaging [50] and 3-dimensional SPECT studies of asthma inhalers [51]. Cass *et al* determined the sites of zanamivir deposition in the respiratory tract and the pharmacokinetics of zanamivir after oral inhalation from the Diskhaler device and from a prototype of a novel breath-activated device. Thirteen healthy volunteers were given dry powder zanamivir 10 mg formulated with ^{99m}Tc from the Diskhaler or the prototype device on separate days. Scintigraphic images of the chest and oropharynx were recorded. Pharmacoscintigraphy was confirmed as being a reliable technique for measuring zanamivir deposition in the

respiratory tract [52]. Weers *et al* investigated the inhalation of a liposomal formulation of amikacin in healthy male volunteers in terms of pulmonary deposition, clearance, and safety following nebulization with a commercial jet nebulizer. The liposomes were radiolabeled with ^{99m}Tc using the tin chloride labelling method. Lung deposition was determined by gamma scintigraphy in three healthy male volunteers at the following time points (0, 1, 3, 6, 12, 24, 48, and 72 h post-administration). It was concluded that inhalation of a single nominal dose of 120 mg liposomal amikacin results in prolonged retention of drug-loaded liposomes in the lungs of healthy volunteers. The treatment was well tolerated [53]. Newhouse *et al* evaluated the efficiency and reproducibility of pulmonary delivery of an investigational tobramycin PulmoSphere formulation (PStob) by a passive dry powder inhaler, and compared serum concentrations and whole-lung deposition with a commercial nebulized tobramycin product PStob was radiolabelled with ^{99m}Tc, and *in vitro* experiments confirmed it as a valid drug marker. The aerosol doses of PStob (25 mg and 150 mg) were well dispersed and tolerated. Serum drug concentrations matched scintigraphy data and were roughly twice that of the comparator [54].

Ocular Drug Delivery Systems

Delivery of medication to the human eye is an integral part of medical treatment [55]. Ophthalmic preparations, including solutions, suspensions, and ointments, can be applied topically to the cornea or instilled in the space between the eyeball and lower eyelid (the cul-de-sac or conjunctival sac of the lower lid) [56]. Conventional dosage forms such as solutions, suspensions, and ointments have well-known disadvantages. Taken together, all of these challenges indicate the potential need for the development of alternative methods to deliver drugs to the eye. Techniques have been developed to deliver drugs to the ocular site that include depot preparations such as inserts, gels, liposome-based products etc. Pharmacoscintigraphic studies have been effectively used to study the pharmacokinetics of such products [27]. Table 6 summarizes recent studies that have been performed by pharmacoscintigraphic technique in ocular drug delivery.

Table 6: Pharmacoscintigraphic studies in ocular drug delivery systems

Drug / formulation	Subjects	Objective	Reference
Timolol-maleate loaded chitosan/HPMC based polymer	NZ rabbits	To enhance ocular retention	Gupta *et al* [57]
HEC and gellan gum formulations	Humans, rabbits	To determine species-specific differences in the precorneal residence of two gelling agents in humans and rabbits	Greaves *et al* [58]
Polyvinyl alcohol films	Humans, rabbits	To study the precorneal residence of polyvinyl alcohol films	Fitzgerald *et al* [59]
Pilocarpine nitrate containing NODS	12 heathy humans	To study the rate of clearance of a soluble marker from a NODS	Greaves *et al* [60]
Pilocarpine nitrate eye drops	Healthy humans	To compare corneal contact time of various formulations containing viscosity modifiers	Meseguer *et al* [61]
Labelled octreotide	10 patients with Graves' ophthalmopathy	To predict the clinical response to corticosteroid therapy in patients	Colao *et al* [62]
Pluronic-based *in situ* gelling system with sodium hyaluronate	4 rabbits	To evaluate the residence of *in situ* gelling system	Wei *et al* [63]

HPMC: Hydroxypropyl methylcellulose, HEC: Hydroxyethyl cellulose, NODS: New ophthalmic delivery system, NZ: New Zealand.

Miscellaneous Applications

Pharmacoscintigraphy has also been proven to be useful tool in the evaluation of new drugs during developmental phase [64], characterization of new formulations/delivery systems [13, 65, 66], establishing bioequivalence of generic products, therapeutic drug monitoring [67- 68], dosage forms intended for rectal route [70-71] and in various site/organ targeting studies (table 7).

Table 7: Site/organ specific studies utilizing gamma scintigraphy

Drug/formulation	Route of Administration	Subjects	Site targeted	Reference
Chondroitin sulphate-nanocontructs	Intravenous	Mice	Ehrlich ascites tumor (EAT)	Pathak *et al* [73]
N-(2-Hydroxypropyl)methacrylam-ide copolymers	Intravenous	Mice	Bone-targeting	Wang *et al* [74]
Stealth liposomes loaded with methotrexate	Intravenous	Albino mice	Liver, spleen, kidney, and EAT	Subramani-an *et al* [75]
Leuprolide-loaded liposomes	Intravenous	Balb/C mice and albino NZ rabbits	EAT	Murthy *et al* [76]
Chitosan-labelled nanoparticles	Intravenous	NZ rabbits albino mice	Liver and spleen	Maitra *et al* [77]
Etoposide solid lipid nanoparticles	Subcutaneous, intravenous, intraperitoneal	Strain A mice	Lymphoma	Reddy *et al* [78]
Zolmitriptan mucoadhesive microemulsions	Intranasal	Swiss albino rats	Brain	Vyas *et al* [79]
5-flurouracil hydrophobized nanogel	Intravenous	Strain A mice	Brain	Soni *et al* [80]
Sumatriptan/ mucoadhesive microemulsion	Intranasal	Swiss albino rats	Brain	Misra *et al* [81]
Risperidone/nanoemulsion/ mucoadhesive nanoemulsion	Intranasal	Swiss albino rats	Brain	Kumar *et al* [82]
Tacrine/mucoadhesive microemulsion	Intranasal	NZ Rabbits	Brain	Misra *et al* [83]

NZ: New Zealand.

Safety Considerations

Like any medicine, radiopharmaceuticals are prepared with utmost care and concern. Before utilizing, they are tested carefully and should be approved for use by the U.S Food and Drug Administration. The International Commission on Radiological Protection recommended an average permissible whole body radiation dose of 0.1 Rem per week and 5 Rem per year (radiation protection procedures, International Atomic Energy Agency, Safety Series, 1978). These limits are considered to be safe for the health point of view of individuals. The level of radioactivity used in scintigraphic study is very low and it gives a radiation dose to participating subjects which is well below the maximum permissible dose [16]. Hence, it can be considered that the radionuclides used in scintigraphic studies are harmless at the level they are used. However, high costs associated with the equipment and material, strict environment controls, highly skilled labor, and unpredictable effect of radiation on the drugs and their pharmacokinetics, limit the use of this technique [27].

CONCLUSION AND FUTURISTIC PROSPECTS

Pharmacoscintigraphic technique is an elegant approach to gain insight of the actual *in vivo* distribution pattern of dosage form along with the assessment of pharmacokinetic information. Although agreement between *in vitro* and *in vivo* data is sometimes good, but *in vitro* data alone may not predict *in vivo* performance of drug delivery adequately in some situations. This versatile technique has been widely employed by large numbers of research centres across the globe in several drug evaluation processes. This promising approach is also useful in the evaluation of novel carrier-based drug delivery systems administered by different routes. Owing to constant improvements in the gamma ray detection technology, the amount of tracer incorporated is also sufficiently low. 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, 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 endeavour in times to come.

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