Journal of Food and Drug Analysis
1993, 1(3) : 235-244

藥物食品分析
第一卷　第三期

Pharmacoscintigraphy : Techniques for Studying Drug Release And Absorption in Humans

KEITH KEWI-HANG CHAN

Pharmaceuticals Division, CIBA-GEIGY Corporation, 444 Sawmill River Road, Ardsley, New York 10502, U.S.A.

ABSTRACT

In vivo drug release and absorption in the gastrointestinal tract are governed by a complex process subject to many variables. Extensive efforts were spent in studying the durg and manipulating the excipient and mechanical design of the formulation but little is known regarding the physiological factors that influence the release and absorptive processes.

Understanding of the behavior of formulation inside the GI tract has been made by gamma scintigraphy using a single isotope. However, the technique is suffering from several limitations : (1) anatomical location of the object is difficult to determine; (2) quantification of radioactivity is difficult due to tissue attenuation and movement of isotope; (3) cannot distinguish between a radionuclide present as a solid or as a solute; (4) preparation of the radiolabeled dosage forms are problematic; and (5) neither the drug nor the excipients can be labeled with nuclide. These problems can be partly alleviated by using dual isotopic, geometric mean measurement, perturbed angular correlation, neutron activation, and pharmacokinetic techniques. Combining several scintigraphic techniques with pharmacokinetics can drastically improve the quality of the data. Thus, the term pharmacoscintigraphy was coined.

The application of pharmacoscintigraphy can be further supplemented by other techniques such as stable isotope with gas chromatography-mass spectrometry, pH monitoring and gastrointestinal intubation. Those techniques can be used either independently or simultaneously with pharmacoscintigraphy to provide us with a full picture of durg release and absorption in humans.

Key words : Drug Release, Drug Absorption, Pharmacokinetics, Pharmacoscintigraphy

INTRODUCTION

In vivo drug release and absorption from its oral formulation is important in the field of drug development. Absorption can determine the time course of pharmacological action, whereas durg release can drastically affect the rate of drug absorption. Numerous mathematical methods in the field of pharmacokinetics have been developed for determining in vivo absorption rate [1-4]. Unfortunately, these methods are based on the appearance of drug in the systemic circulation and only can provide indirect information regarding drug release and absorption in the gastrointestinal (GI) tract.

Once a drug is administered, its release and absorption from the GI tract are governed by a

complex process subject to many variables. The physico-chemical characteristics of a drug and the disign of pharmaceutical formulation are key determents. Pharmaceutical scientists spend extensive efforts in studying the drug and manipulating the excipient and mechanical design of the formulation. However, little is known of the physiological factors that influence the release and absorption processes. Therefore, the development and design of the dosage form are usually empirical.

Over the past 10 years, significant contribution to the understanding of the behavior of formulations inside the GI tract has been made by the advent of external gamma scintigraphy. Combining scintigraphic and pharmacokinetic techniques (termed pharmacoscintigraphy) further advances our knowledge on how the drug and its formulation interact with the GI environment. Another factor of interest is how long the formulation remains in that environment where drug release and absorption can take place. This report briefly reviews the historical development and current applications of pharmacoscintigraphy in the field of drug delivery.

METHODOLOGY DEVELOPMENT

I . *Classical Single Isotopic Scintigraphy*

The technique of gamma scintigraphy is well established within the field of nuclear medicine to monitor pathological conditions such as brain, thyroid, adrenal, pulmonary, renal and hepatic functions [5,6], When the technique is applied to study the in vivo behavior of dosage forms, a small amount of radionuclide (e.g., Tc-99m, In-111, In-113m, I-123, I-125 and I-131) is incorporated into the formulation. The behavior of the formulation can then be monitored by external gamma camera. The gamma camera consists of a detector linked to a computer. The image of radioactivity distribution within the field of view is stored as a pixel matrix on a minicomputer for later analysis. Gamma camera imaging can be carried out by using either static imaging, in which single acquisitions are stored, or dynamic imaging, in which a sequence of data of varying frame time can be obtained. The latter technique is used to follow rapid processes, such as drainage of an aqueous formulation from the stomach. For in vivo dosage form evaluation, both imaging techniques may be used.

An important advantage of scintigraphic technique is that the field of view can be arbitrarily divided up into areas, and then the amount of isotope within these areas can be quantified, and hence the distribution of the radioactivity in the GI tract can be followed. The technique was first used to study the behavior of capsule in vivo in 1977 [7]. To date, gamma scintigraphy has been used to investigate the behavior of a wide variety of dosage forms such as solutions, small pellets, single unit matrix tablets, and osmotic pumps [8-12]. The technique has also been applied to other areas such as the in vivo behavior of buccal formulation [13], suppositories [14], enemas [15-17], esophageal transit of tablets and capsules[18,19],ocular drug delivery [20], intravaginal administration of microspheres [21], nasal sprays [22], and aerosols [23,24].

The classical scintigraphic procedure for oral dosage form is simple but suffers from the following limitations and drawbacks:

(I). *Anatomical location of the object is difficult to determine.*

The anatomical position of the GI tract is relatively easy to identify especially when solution formulation is used. Stomach can be identified when the solution is first administered and large intestine can be identified because of its unique shape. However, for non-disintegrating dosage forms, identification of the object's position in the GI tract becomes difficult. An external marker can serve as a common reference point to facilitate the identification of the object in the GI tract by comparing images taken at different times.

The small intestine is convoluted, folding back on itself, and hence the position cannot be accurately identified. The limitation can be over-

come by using a sophisticated 3-dimensional technique [25]. The images were taken from the front and the side, and then one can construct a three dimensional coordinate geometry to calculate the position of the dosage form. Images were aligned by placing a square array of markers visible in each image. Because of its complicated procedure, the use of this method is not widespread.

(II). *Attenuation of radioactivity by various tissues and movement of the isotope in the anterior-posterior plane.*

Attenuation is a problem for low-engergy gamma emitters. Air does not attenuate gamma rays, but various tissues attenuate to a variable degree. The combination of attenuation and movement of the isotope in the anterior-posterior plane within the body produces a significant error. Calculation of the geometric mean of anterior and posteior counts allows a partial correction for this error [26,27]. Hard gamma emitters such as In-113m do not have the problem of attenuation, but the counting efficiency is lower.

(III). *The technique cannot distinguish between a radionuclide present as a solid or as a solute.*

Since the nuclide is not incorporated into the drug or excipient, the disintergration and dissolution processes cannot be separated. This problem may be somewhat orercame by the use of perturbed angular correlation technique [28-30].

(IV). *Preparations of radiolabeled dosage forms are problematic.*

The preparation of raidolabeled solutions or suspensions is relatively simple since most nuclides can be chelated with various hydrophilic and lipophilic agents. However, complications may occur in the preparation of radiolabeled solid dosage forms. Some of the problems are:

1. The production time may be too long to be amenable to labeling with short-lived radionuclides.

2. Special decontamination procedure or equipment may be required.

3. The labeling procedure may compromise the intergrity of the dosage form.

4. On-site small scale preparation is not practical and is limited to the handling of a small quantity of materials. The products may not accurately represent the same dosage forms produced under industrial scale up conditions.

Recently, a procedure for incorporating a small quantity of nonradioactive precursor into the dosage form and subsequently activating it into a radioactive nuclide following neutron activation has been described. The technique is a powerful alternative and will be discussed in section III.

5. Neither the drug nor the excipients can be labelled with nuclide.

Neither the drug itself nor the excipeints can be easily labelled with the radionuclide. Therefore, the behavior of the radionuclide observed may or may not represent the disintegration or the release of the drug. In the last several years, an increasing number of studies has used plasma drug level determination concurrently with scintigraphy. The quality of data has been drastically improved and the term pharmacoscintigraphy was coined and will be discussed in Section IV.

II. *Dual Isotopic Gamma Scintigraphy*

Some problems discussed in Section I can be partly alleviated by the administration of a second radiopharmaceutical. Typical application of dual isotopic gamma scintigraphy involves using one nuclide with lower energy to outline the anatomy of the GI tract (e.g., a solution of Tc-99m) and another nuclide with higher energy to study the behavior of the formulation of interest (e.g., tablet labelled with In-111). The two nuclides do not have to be administered simultaneously. The images of one nuclide can be overlayed on top of the images of another nuclide by computer and the position of the dosage form can be accurately determined.

Alternately, and perhaps more importantly, separate formulations can be labelled with two

different nuclides and administered together. Most gamma cameras are able to separate gamma emissions on the basis of different photopeak energies so that two isotopes may be monitored simultaneously and independently. This simultaneous dual isotopic technique greatly enhanced the applicability of gamma scintigraphy in biopharmaceutical research. Since each formulation can now be tracked simultaneously and independently within the same subject [31,32] ,this technique can be used to investigate a single or a combination of physiological and biopharmaceutical events as well as a variety of factors affecting those events. It has been recognized for many years that movement through the gut exhibits considerable intra- and intersubject variability. The simultaneously dual isotopic approach is particularly valuable in these situations where various factors can be studied in the same subject at the same time.

When two isotopes are administered simultaneously, the scatter-down effect from the high energy isotope to the low energy isotope window has to be corrected by mathematical technique. The correction is made by subtracting a fixed proportion of one channel from the other. This correction factor is a fixed calculable function of the isotopes and will not vary within the course of the study. The correction factor for commonly used radionuclides such as Tc-99 m/In-111 has been reported [33].

III. *Neutron Activation Gamma Scintigraphy*

One of the problems in using scintigraphy is that the preparations of radiolabeled dosage forms are generally problematic (Section I.5).

Recently, a procedure for incorporating a small quantity of non-radioactive precursor into the dosage form has been described [34-37]. The precursor is subsequently activated into a radioactive nuclide following neutron activation. The procedure can be easily performed in any nuclear reactor facility. Several rate-earth elements in the Lanthanide series (i.e., barium, erbium and samarium) seem to be the best choices because of their chemical stability, lack of toxicity, low dosimetry of radionuclide produced, high natural abundance, large neutron capture cross-section, and decay to a stable nontoxic isotope. More importantly, their pharmacology and toxicology have been extensively studied [38,39]. The oxide is the most common form of these elements used in biopharmaceutical studies due to their low water solubility, thus limiting its absorption into the body. Barium oxide was used for early studies but the short half-life of Ba-139 (83 .6 min) precludes its use in the long termed GI study. The cost of enriched Er-170 oxide has risen sharply over the years and became prohibiting to use. The commonly used precursor to date is enriched Sm-152 oxide, and recnetly gaining popularity is another element, Ytterbium (Yb-174), and its oxide [40].

The effect of exposing the dosage form to an intense thermal neutrol flux has to be evaluated before the study [41,42]. As in the dual isotopic study when two isotopes are used, the scatter-down effect and its mathematical relationship have to be determined. The correction factors for Er-171/Sm-53 and Yb-175/Sm-153 have recently been reported [40,43-45].

IV. *Pharmacoscintigraphy Using Single or dual Isotopes and Neutron Activation*

Early scintigraphic studies are useful in providing information regarding behavior of formulation in the GI tract. Over the last several years, increasing number of studies has been reported using the combination of pharmacokinetics and scintigraphy [46-56]. The quality of data has drastically improved.

One of the most important additions to gamma scintigraphy is the correlation of the plasma concentration-time profile with the position of the formulation, since it allows the identification of the GI tract region from where the drug is absorbed. One typical use of this technique is to examine possible sources of variablility observed in the plasma profile, for example, an erratic gastric emptying of the formulation [49]. Another application is to correlate bioavailability with GI transit using external scinti-

graphy with neutron activation technique [46].

A landmark study was carried out by the use of osmotic type delivery system filled with the drug [55]. The exterior of the unit was radiolabeled and administered with a non-absorbed redionuclide labelled marker to outline the GI tract. The results of the study clearly demonstrated that the drug is well absorbed in the colon. The reason for the reduction in extent of bioavailability in some subjects is due to the reduced residence time of the unit in the colon.

FUTURE TRENDS

The application of pharmacoscintigraphy has become increasing sophisticated in recent years. Other techniques can also be incorporated into the study to improve the quality of data generated. A recent study demonstrated this multipronged approach[56]. A stable isotope (N-15) suspension and nonstable isotopic formulation (OROS tablet) were administered simultaneously and the drug concentrations from each formulation were determined by gas chromatography/ mass spectrometry (GC/MS). The tablet was administered with Tc-99m DTPA (diethylenetraminepentaacieitc acid) in water to outline of the GI tract. The edge of OROS tablet was glued with In-111 mixed with ion-exhange resin powder adhesive. This study illustrates the value of improved pharmacokinetic interpretation using stable isotope/GC/MS technology with simultaneously dual isotopic scintigraphy. The problems of intra- and inter-subject variability can now be avoided. The study results demonstrate that the drug was released and absorbed efficiently throughout the stomach and small intestine. However, systemic absorption was reduced when the system was situated in the colon. Rapid and premature expulsion of the dosage form was the leading cause of reduction in bioavailability in some subjects.

It is undoubtedly that pharmacoscintigraphy has greatly advanced our understanding of the behavior of dosage forms and it will continue to do so. Our knowledge can further be advanced when pharmacoscintigraphy is used in conjunction with other techniques such as pH monitoring and GI intubation [57-62]. These techniques can be used either independently or simultaneously with pharmacoscintigraphy to provide more information regarding drug release and absorption. Ultimately, it should be possible to explain all the factors in the sequence between drug release and absorption and consequently improving the clinical outcomes.

REFERENCES

1. Cutler, D. 1981. Assessment of Rate and Extent of Drug Absorption. Pharmac. Ther. 14: 123-160.
2. Gibaldi, M. and Perrier, D. 1982. Absorption Kinetics and Bioavailability. In "Pharmacokinetics" 2nd Edition, Marcel Dekker, New York, U.S.A. pp. 145-198.
3. Wagner, J.G. 1975. Absorption Plots and Estimation of Absorption Rate Constants. In "Fundamentals of clinical Pharmacokinetics" . Drug Intelligence Publications, Inc., Hamilton, Illinois, U.S.A. pp. 173-202.
4. Chan, K.K.H. and Gibaldi, M. 1985. Assessment of Drug Absorption After Oral Administration. J. Pharm. Sci. 74:388-393.
5. Chilton, H.M. and Witcofski, R.L. 1986. Nuclear Pharmacy: An Introduction to the Clinical Application of Radiopharmaceuticals . Lea & Febiger, Philadelphia, P.A., U.S.A.
6. Kelly, J.D. 1984. Choice of Radionuclide for Scintigraphy. In "Radionuclide Imaging in Drug Research" . Wilson, C.G., Hardy, J.G. , Frier, M. and Davis, S.S. (eds). Croom Helm Ltd., London. pp.39-59.
7. Casey, D.L., Beihn, R.M., Digenis, G.A. and Shambhu, M.B. 1976. Method for Monitoring Hard Gelatin Capsule Disintergration Times, in Humans Using External Scintigraphy. J. Pharm. Sci. 65:1412-1413.
8. Wilson, C.G. and Hardy, J.G. 1982. Radionuclide Imaging in Drug Research. Croom

Helm Ltd., London.
9. Davis, SS, Hardy, J.G. and Fara, J.W. 1986. Transit of Pharmaceutical Dosage Forms Through the Small Intestine. Gut. 27:886-892.
10. Fell, J.T. and Digenis, G.A. 1984. Imaging and behavior of Solid Dosage Forms in Vivo . Int. J. Pharm. 22:1-15.
11. Davis, S.S. 1989. Small Intestine Transit. In "Drug Delivery to the Gastrointestinal Tract" . Hardy, J.G., Davis, S.S. and Wilson, C.G. (eds.) Ellis Horwood, Chichester, England. pp. 49-62.
12. Wilson, C.G. and Washington, N. 1988. Assessment of Disintegration and Dissolution of Dosage Forms in Vivo Using Gamma Scintigraphy. Drug Devel. Ind. Pharm. 14: 211-281.
13. Davis, S.S., Kennerley, J.W., Taylor, M.J., Hardy, J.G. and Wilson, C.G. 1983. Scintigraphic Studies on the In Vivo Dissolution of a Buccal Tablet. In "Modern Concepts in Nitrate Delivery Systems" . Goldberg, A. A.J. and Parson, D.G. (eds). Royal Society of Medicine. International Congress and Symposium Series No. 54. pp.29-37.
14. Jay M., Beihn, R.M., Digenis, G.A., Deland, F.H., Caldwell, L. and Mlodozeniec, A.R. 1985. Disposition of Radiolabeled Suppositories in Humans. J. Pharm. Pharmacol. 37:266 -268.
15. Hay, D.J., Sharma, H. and Irving, M.H. 1979. Spread of Steroid-Containing Foam After Intrarectal Administration. Br. Med. J. 1:1751-1753.
16. Farthing, M.J.G., Rutland, M.D. and Clark, M.L. 1879. Retrograde Spread of Hydrocortisone Containing Foam Given Intrarectally in Ulcerative Colitis. Br. Med. J. 2:822-824.
17. Jay, M. Digenis, G.A., foster, T.S. and Antonow, D.A. 1986. Retrograde Spreading of Hydrocortisone Enema in Inflammatory Bowel Disease. Dig. Dis. Sci. 31:139-144.
18. Channer, K.S. and Virjee, J.P. 1985. Effect of Surface Coating of Tablets on Oesophageal Transit. Br. J. Pharm. Pract. 7:9-10.
19. Channer, K.S. and Virjee, J.P. 1986. The Effect of Size and Shape of Tablets on Their Oesophageal Transit. J. Clin. Pharmacol. 26: 141-146.
20. Wilson, C.G. 1987. Scintigraphic Evaluation of Polymeric Formulation for Ophthalmic Use. In "Ophthalmic Drug Delivery. Biopharmaceutical, Technological and Clinical Aspects" . Saettone, M.S., Gucci, G. and Speiser, P. (eds.) Fidia Research Series, Vol. 11. Liviana Press. Padova, Italy.
21. Digenis, G.A., Jay, M., Beihn, R.M., Tice, T .R. and Beck, L.R. 1984. External Scintigraphy in the Study of Long-Acting Contraceptive Delivery Systems. In "Long-Acting Contraceptive Delivery Systmes" . Zatuchni, G.I., Goldsmith, A., Shelton, J.D. and Sciarra. J.J. (eds.) Harper and Row, New York, U.S.A. pp. 173-177.
22. Lee, S.W., Hardy, J.G., Wilson, C.G. and Smelt, G.J.C. 1984. Nasal Sprays and Polyps . Nucl. Med. Commun. 5:697-703.
23. Smith, M.F., Bryant, S., Welch, S. and Digneis, G.A. 1984. Labeling Suspended Aerosol Particles with Short-Lived Radionuclides for the Determination of Particle Deposition. J. Pharm. Sci. 73:1091-1094.
24. Vidgren, M.T., Karkkainen, A., Paronen, T. P. and Karjalainen, P. 1987. Respiratory Tract Deposition of 99m-Tc-Labeled Drug Particles Administered via a Drug Powder Inhaler. Int. J. Pharm. 39:101-105.
25. Kaus, L.C., Fell, J.T., Sharma H. and Taylor D.C. 1984. On the Intestinal Transit of a Single Non-Disintegrating Object. Int. J. Pharm. 20:315-323.
26. Tothill. P., McLoughlin, G.P. and 1Heading, R.C. 1978. Techniques and Errors in Scintigraphic Measurements of Gastric Emptying. J. Nucl. Med. 19:256-261.
27. Hardy, J.G. and Perkins, A.C. 1985. Validity of the Geometric Mean Correction in the Quantification of Whole Bowel Transit. Nucl Med. Commum. 6:217-224.
28. Beihn, R.M. and Digenis, G.A. 1981. Non-Invasive Dissolution Measurement Using Perturbed Angular Correlation. J. pharm. Sci

. 70:1325-1328.

29. Jay, M., Fell, J.T. and Digenis, G.A. 1985. Studies on the Dissolution of Drugs From Tablets Using Perturbed Angular Correlation . Pharm. Res. 2:75-81.

30. Jay, M., Beihn, R.M., Snyder, G.A., McClanahan, J.S., Digenis, G.A., Caldwell, L. and Miodozeniec, A. 1983. In Vitro and In Vivo Suppository Studies with Perturbed Angular Correlation and External Scintigraphy. Int. J. Pharm. 14:343-347.

31. Hardy, J.G., Wilson, C.G. and Wood, E. 1985, Drug Delivery to the Proximal Colon. J. Pharm. Pharmacol. 37:874-877.

32. Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G. 1984. A Comparative Study of the Gastrointestinal Transit of a Pellet and Tablet Formulation. Int. J. Pharm. 21:167-177.

33. Davis, S.S., Stockwell, A.F., Taylor, M.J., Hardy, J.G., Walley, D.R., Wilson, C.G., Bechgaard, H. and Christensen, F.N. 1986. The Effect of Density on the Gastric Emptying of Single- and Multiple-Unit Dosage Forms. Pharm. Res. 3:208-213.

34. Parr, A., Jay, M. Digenis, G.A. and Beihn, R.M. 1985. Radiolabeling of Intact Tablets by Neutron Activation for In Vivo Scintigraphy. J. Pharm. Sci. 74:590-591.

35. Parr, A. and Jay, M. 1987. Radiolabeling of Intact Dosage Forms by Neutron Activation : Effects on In Vitro Performance. Pharm. Res. 4:524-526.

36. Parr, A., Beihn, R.M. and Jay, M. 1986. Radiolabeling of An Enteric-Coated Tablet by (n,r) Radioactivation of Erbium-170 for Scintigraphic Imaging. Int. J. Pharm. 32:251-256.

37. Degenis, G.A., Parr, A.F. and Jay, M. 1989. Neutron Activation Methods for Evaluation of Pharmaceutical Dosage Forms. In "Drug Delivery to the Gastrointestinal Tract. Hardy , J.G., Davis, S.S. and Wilson, C.G. (eds.). Ellis Horwood Ltd., Chichester, England. pp .111-120.

38. Haley, T.J. 1965. Pharmacology and Toxicology of the Rare Earth Elements. J. Pharm . Sci. 54:663-670.

39. Bruce, D.W., Hietbrink, B.E. and DuBois, K .P. 1963. The Acute Mamalian Toxicity of Rare Earth Nitrates and Oxides. Toxicol. Appl. Pharmacol. 5:750-759.

40. Sandefer, E.P., Digenis, G.A. and Beihn, R. M. 1991. Neutron Activated Ytterium-175 for Dual Label Scintigraphy Studies with Samarium-153: An Alternative to Erbium-171. Pharm. Res. 8:S-133.

41. Parr, A. and Jay, M. 1987. Radiolabeling of Intact Dosage Forms by Neutron Activation: Effects on In vitro Performance. Pharm. Res. 4:524-526.

42. Parr., A.F., Digenis, G.A., Sandefer, E.P., Ghebre-Sellassie, I., Lyer, U., Nesbitt, R.U. and Scheinthal, B.M. 1990. Manufacture and Properties of Erythromycin Beads Containing Neutron-Activated Erbium-171. Pharm, Res. 7:264-269.

43. Alioth, C., Tendolkar, A., Buch, A., Combs, M., Benneche, P., Mulder, R., Barr, W., John, V. and Chan, K. 1990. Preparation of Erbium and Samarium Hydrogel Beads Suitable for Human Gamma Scintigraphic Studies. Pharm. Res. 7:S-198.

44. Combs, M.J., Mulder, R.U., Alioth C., Croft , B.Y., Chan, K., Teates, C.D. and McCallum, R.W. 1991. Optimization of Anger Camera Window Settings Using Er-171 and Sm -153 in Gastrointestinal Imaging. Abstract, Soc. Nucl. Med. Meeting, Cincinnati, Ohio, June 11-14.

45. Digenis, G.A., Sandefer, E.P., Beihn, R.M. and Parr, A.F. 1991. 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. Pharm. Res. 10:1335-1340.

46. Parr, A.F., Beihn, R.M., Franz, R.M., Szpunar G.J and Jay, M. 1987. Correlation of Ibuprofen Bioavailabilility with Gastrointestinal Transit by Scintigraphic Mointoring of 171-Er-Labeled Sustained-Release Tablets. Pharm. Res. 4:486-489.

47. Feely, L.C. and Davis, S.S. 1989. Correlation of Phenylpropanololamine Bioavailability with Gastrointestinal Transit by Scintigraphy Monitoring of In-111 Labelled Hydroxypropylmethylcellulos Matrices. Pharm. Res. 6: 274-278.
48. Wilson, C.G., Washington, N., Greaves, J.L. , Kamali, F., Rees, J.A., Sempik, A.K. and Lampard, J.F. 1989. Bimodal Release of Ibuprofen in a Sustained-Release Formulation : A Scintigraphic and Pharmacokinetic Open Study in Healthy Volunteers Under Different Conditions of Food Intake. Int. J. Pharm. 50 :155-161.
49. Wilson, C.G., Parr, G.D., Kennerley, J.W., Taylor, M.J., Davis, S.S., Hardy, J.G. and Rees, J.G. 1984. Pharmacokinetics and In Vivo Scintigraphic Monitoring of a Sustained Release Acetylsalicylic Acid Formulation. Int. J. Pharm. 18:1-8.
50. Davis, S.S., Khosla, R., Wilson, C.G., Washington, N., Leslie, S.T. and Malkowska, S. 1990. The Gastrointestinal Transit of a Controlled Release Fromulation of Indomethacine. Int. J. Pharm. 50:191-196.
51. Wilson C.G., Washington N., Hardy J.G. and Bond, S.W. 1987. The Influence of Food on the Absorption of Acyclovir : A Pharmacokinetic and Scintigraphic Assessment. Int. J. Pharm. 38:221-225.
52. Graffner, C., Wagner, Z., Nilsson, M.I. and Widerlov E. 1990. Plasma Concentrations of Remoxipride and the Gastric Transit of In-111 Marked Extended-Release Coated Spheres. Pharm. Res. 7:54-58.
53. Wilding, L.R., Davis, S.S., Sparrow, R.A., Ziemniak, J.A. and Heald, D.L. 1991. Pharmacoscintigraphic Evaluation of a Sustained Release Diltiazem Formulation. Pharm. Res. 8:S-133.
54. Wilding, L.R., Davis, S.S., Bakhshaee, M., Stevens, H.N.E., Sparrow, R.A. and Brennan, J. 1992. Gastrointestinal Transit and Systemic Absorption of Captopril From a Pulsed-Release Formulation. Pharm. Res. 9: 654-657.
55. Davis, S.S., Washington, N., Parr, G.D., Short, A.H., John, V.A., Lloyd, P. and Walker, S.M. 1988. Relationship between the Rate of Appearance of Oxprenolol in the Systemic Circulation and the Location of an Oxprenolol Oros 16/260 Drug Delivery System Within the Gastrointestinal Tract As Determined by Scintigraphy. Br. J. Clin. Pharmacol. 26:435-443.
56. Wilding, I.R., Davis, S.S., Hardy, J.G., Robertson, C.S., John, V.A., Powell, M.L., Leal , M., Lloyd, P. and Walker, S.M. 1991. Relationship Between Systemic Drug Absorption and Gastrointestinal Transit After the Simultaneous Oral Administration of Carbamazepine as a Controlled-Release System and as a Suspension of 15N-Labelled Drug to Healthy Volunteers. Br. J. Clin. Pharmacol. 32:573-579.
57. Chan, K.K.H., Mojaverian, Ziehmer, B. and John, V.A. 1990. Application of Radiotelemetric Technique in Evaluating Diclofenac Sodium Absorption After Oral Administration of Various Dosage Forms to Healthy Volunteers. Pharm. Res. 7:1026-1032.
58. Betlach, C.J., Straughn, A.B., Meyer, M.C., Bialer, M., Vashi, V.I., Lieberman, P. and Gonzalez, M. 1991. The Effect of Raising Gastric pH with Ranitidine on the Absorption and Elimination of Theophyllin From a Sustained-Release Theophylline Tablet. Pharm. Res. 8:1516-1519.
59. Hardy, J.G., Evans, D.F., Azki, I., Clark, A. G., Tonnesen, H.H. and Gamst, O.N. 1987. Evaluation of an Enteric-coated Naproxen Tablet Using Gamma Scinitgraphy and pH Monitoring. Int. J. Pharm. 37:245-250.
60. Chan, K., Buch, A., Glazer, R., John, V.A. and Barr, W. 1990. Site Differential Gastrointestinal Absorption of Benazepril HCL in Humans. Pharm. Res. 7:S-209.
61. Godbillon, J., Evard, D., Vidon, N., Duval, M., Schoeller, J.P., Bernier, J.J. and Hirtz, J. 1985. Investigation of Drug Absorption From the Gastrointestinal Tract of Man. III. Metoprolol in the Colon. Br. J. Clin. Pha-

rmacol. 19:113s-118s.

62. Brennan, J., O'Donnell, D., Zinny, M., Jain, N., Ivashkiv, E. and Arnold, M. 1991. The Comparative Bioavailability of Captopril After Colonic Infusion and Oral Administration in Healthy Volunteers. Proc. 92nd Meeting, Amer. Soc. Clin. Pharmac. Ther. San Antonio, Texas. p.9.

Correspondence to : Keith Kwei-Hang Chan

Accepted for Publication : September. 7.1992

Journal of Food and Drug Analysis. 1993. 1(3)

Pharmacoscintigraphy：

研究藥物在人體的釋放與吸收之技術

陳 桂 恒

摘 要

藥物在體內胃腸道內的釋放與吸收其程序相當複雜，受許多變數影響。在藥物的研究，賦形劑的處理與處方的機械性設計方面已有相當多的努力，然而影響釋放與吸收程序的生理因素方面則所知有限。

處方於胃腸道內的情形可用伽瑪放射性測定儀測定單同一位素而得知，然而，此技術有所限制：(1)標的物於胃腸中的位置難以確定，(2)由於組織的衰減與同位素的移動而難以定放射性的量，(3)難以區分放射性核種是固態或溶解物，(4)放射性標識的劑型難以製備，(5)無論是藥物或賦形劑都無法以核種標識。上述這些問題某部份則可以雙同位素，等比中項測定，角度變動係數，中子活性及藥動技術予以克服，數種放射性技術(scintigraphic techriques)與藥動(pharmacokinetics)的結合，可徹底地改進數據資料的品質，因此，新名詞〝pharmacoscintigraphy〞於焉而生。

pharmacoscintigraphy之應用可更進一步以其他的技術補足，如定安性同位數與氣相屬析質譜，酸鹼值檢查，及胃腸道插管，這些技術可單獨使用或同時與pharmacoscintigraph使用，以提供吾人有關人類藥物釋放與吸收之完整狀況。