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Review Articles

DRUG RELEASE FROM LIPID-BASED DOSAGE FORMS. I

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INTRODUCTION

Whilst the great majority of medicines for internal use are administered as solid unit dosage forms or as water-based liquid preparations, some dosage forms utilize lipid material. Many rectal dosage forms are traditionally formulated in a lipophilic base and the fusion of this base is a necessary preliminary to drug release. The soft gelatin capsule, by its very nature, requires that the active principle be dissolved or dispersed in a liquid in which the hydrophilic shell is insoluble. The use of lipophilic liquids as the vehicle in oral dosage forms may cause problems in formulation, flavouring, etc., but is often employed if the active principle is unstable in the presence of water. Oil-based intramuscular injections are well known, particularly as prolonged release preparations.

The administration of medicinal agents in conjunction with lipid material, whether as foodstuffs or formulation aids, is not without therapeutic hazards. Oils and fats have long been known to increase the absorption and toxicity of male fern extract (Martindale, 1977a), while deficiency in fat-soluble vitamins has been attributed to malabsorption of the vitamins due to the presence of polyunsaturated fats or liquid paraffin (Sinclair, 1967). A corollary of the latter effect is the enhancement of the effect of orally administered anticoagulants brought about by malabsorption of vitamin K (Becker, 1952). Conversely, reduction in the efficacy of anticoagulants has been attributed to lipid liquids such as ethchlorvynol (Martindale, 1977b) and a dimethicone additive in cooking oil (Talbot and Meade, 1971). The effects of food on the bioavailability of drugs have been recently reviewed by Welling (1980).

The significance of these and other reports is that in some cases absorption of the medicinal agent is increased by the presence of a lipophilic solvent, and in some cases it is decreased. It is thus apparent that the prediction of an effect depends on the particular combination of drug substance and lipid involved, and this in turn has implications in the formulation of dosage forms of which lipid is an integral part.

PARENTERAL PRODUCTS

Non-aqueous injections undoubtedly originated as an answer to the problem of administering lipophilic, water-insoluble drugs. A solution of the drug in a lipid solvent provided an elegant presentation, but the principle gave rise to what was probably the first bioavail-

ability problem, in that the duration and intensity of biological response was dependent on the nature of the solvent and on the pro-drug form in which the drug was given. Despite the ancient origins of this dosage form, the problems are still not fully understood. However, empirical rules have developed, so that it is now roughly known what will constitute a successful oily injection. The problems, their solution, and methods used to investigate the mechanism of action, can be illustrated by reference to testosterone, which is inactive by mouth, and has a solubility in water too low for injection as an aqueous solution.

Deanesly and Parkes (1936) investigated the effect of testosterone dissolved in arachis oil on the weights of prostate and seminal vesicles in castrated rat. Biological response varied with the nature of the solvent, arachis oil was about as effective as castor oil, but olive oil was less so, and in mineral oil, testosterone was inactive. The best response was obtained using propylene glycol as solvent. The biological response to the arachis oil solution was enhanced by adding 10% of palmitic acid, an observation which led to the preparation of testosterone esters as possible androgens, on the assumption that esterification of testosterone with palmitic acid had occurred in situ. This move was fortunate, but also fortuitous, since palmitic acid exhibited the same synergism with androstanedione, which has no hydroxyl groups to esterify (Parkes, 1936), and since testosterone palmitate was later shown (Miescher et al., 1936) to be androgenically inactive. They examined the effects of 11 testosterone esters on capon's comb and on prostate and seminal vesicles in rat. Single intramuscular injections of ester in sesame oil produced longer, more intense activities in rat than testosterone. With the lower n-fatty acid esters, intensity and duration of action increased with increasing molecular weight. This work inspired the practice of using esters in oily injections as pro-drugs of the active species. The influence of palmitic acid has not been exploited, probably because its effect is less than that resulting from esterification.

A study of steroid esters currently used in oily injections enables us to make generalizations regarding the choice of esterifying acid for a required duration of therapeutic effectiveness. Thus the recommended dosage of the acetates of deoxycortone and testosterone suggests that esters of acetic acid give a rapid onset of action, and should be administered daily. Propionates are effective for longer periods, requiring 2 or 3 injections a week, and the interval between doses increases progressively as the homologous series is ascended. Oestradiol undecanoate is the highest ester in common use, and falls into the general pattern, having a recommended interval of 3 weeks between doses. These predictions are neither meant to be precise, nor to suggest that an ester of a new steroid must fall into the same range as other esters of the same acid. The solvent is frequently not specified in official formularies and descriptive literature, or at best leaves a wide range from which to choose. Thus for example, the British Pharmacopoeia usually states that the drug should be dissolved in 'ethyl oleate, or other suitable ester, in a suitable fixed oil, or any mixture of these'. The solvent effects observed by previous workers (Deanesly and Parkes, 1936; Albrieux and Prego, 1943; Tanaka et al., 1974) appear either to have been forgotten, or ignored.

Oily injections were originally formulated for drugs which were inactive by mouth and insoluble in water. Non-toxic, water-miscible co-solvents and solubilizing agents are now available, providing means of administering such drugs in aqueous media. The remaining

benefit of lipid solvents is that a prolonged response can be achieved if a suitable ester is chosen, and is dissolved in a suitable lipid solvent. This approach is sometimes used with drugs which are water-soluble and orally active, particularly neuroleptic drugs. Fluphenazine enanthate, for example, when injected intramuscularly in sesame oil, significantly inhibited conditioned avoidance in rats from 1 day to nearly 3 weeks after administration (Sanseigne et al., 1968). In comparison, fluphenazine hydrochloride, which is water-soluble and orally active, induced an immediate response, which was lost within 2 days when given intraperitoneally in aqueous solution. Fluphenazine enanthate therefore provides a useful treatment for psychosis, a condition notorious for poor patient compliance after leaving hospital, with the result that the patient relapses and has to be readmitted. Fluphenazine enanthate injections can be coordinated with routine visits to the outpatients' department. Fluphenazine decanoate, also in sesame oil, has an even more prolonged action. Clopenthixol is chemically related to fluphenazine, and has similar pharmacological properties. Its effect is relatively transient, but its decanoic acid ester dissolved in vegetable oil provides a slow-release intramuscular injection.

Possible rate-controlling steps in the prolongation of action are the hydrolysis of the ester to produce the biologically active parent alcohol, and the release of drug from a lipid deposit in the muscle. The latter has been followed by injecting one gastrocnemius muscle of each of a group of rats with labelled drug solution, and comparing activities in treated and untreated legs after prearranged time intervals (James et al., 1969; van der Vies, 1970). The elimination process is first-order, so that rates could be compared in terms of half life, and showed that the rate is retarded by esterification, and is an inverse function of molecular weight.

Hydrolysis rates have attracted the attention of very few workers (van der Vies, 1965; James et al., 1975). James et al. (1975) found that the overall androgenic effects (areas under the time–response plots) of 5 testosterone esters were logarithmically related to the logarithms of the catalytic constants for their enzymatic hydrolysis in vitro. However, the significance of the correlation was obscured by the observation that catalytic constants were related to distribution coefficients in the same way as overall androgenic effects.

A process involving partition of a drug between lipid and circulating plasma infers that elimination rate is related to distribution coefficient. Lipid–water distribution coefficients of esters of steroids and other high molecular weight alcohols are difficult to determine experimentally, because of their low aqueous solubilities. Parameters related to distribution coefficient have therefore had to be used, for example the ratio of the solubilities in the two solvents (solubility ratio) (James et al., 1969; Chaudry and James, 1974). R_m values of chromatography are logarithmically related to distribution coefficient (Bate-Smith and Westall, 1950). They are assumed to be related to distribution coefficients (α) of other systems through Eqn. 1 (Collander, 1951), which is expressed here for two systems, A and B; a and b are constants.

$$\log \alpha_A = a \log \alpha_B + b \qquad (1)$$

Special methods have had to be developed, because compounds relevant to this review are highly lipophilic and with most chromatographic systems, give rise to R_f values outside

the normally acceptable range. Boyce and Milborrow (1965) described a thin-layer technique for estimating paraffin–water distribution coefficients for low polarity solutes, which was later used to compare times of maximum effect of testosterone esters with R_m values (Biagi et al., 1971). Bowen et al. (1970) determined R_m values with a reverse-phase paper chromatography system (Bush, 1961). These have been correlated with half-lives and times of maximum effect of testosterone esters in rat (James, 1972). Gas, paper and thin-layer chromatography methods of expressing distribution coefficients have been compared, with particular reference to their use in predicting androgenic activities of testosterone esters (James et al., 1972).

Eqn. 1, upon which the chromatography techniques depend, is not as general as was first anticipated, and the problems have been discussed by Leo et al. (1971). Van der Vies (1970) avoided these difficulties by applying the actual injection solution to the chromatography paper and using plasma as the mobile phase. His results for a group of steroid esters did not correlate with in vivo half-lives in muscle, but followed the same rank order.

James et al. (1969) determined the biological half-lives from the muscle of application and from whole bodies of rats, after intramuscular injection of ethyl oleate solutions of [4-^{14}C]testosterone and its formate to valerate esters. Half-lives from whole body were approximately double those from muscle, and while ethyl oleate–water distribution coefficients varied with carbon number in a similar manner to half-lives in whole rat and times of maximum effect in rat and fowl, half-lives in muscle did not. It was suggested that release from the depot in the muscle was not the rate-determining step, but was followed by storage at another site, probably fatty tissue, from which the steroid was gradually released. The reason the rates of elimination from muscle did not correlate with distribution coefficients was attributed to the ethyl oleate being absorbed from the muscle at a rate similar to that for the steroids. Deanesly and Parkes (1933) showed that appreciable quantities of olive and arachis oils are absorbed from subcutaneous tissue within two days of injection into rat. Support for a second body depot comes from Samuel (1966) who pointed out that a distribution coefficient favouring lipids leads to concentration in fatty tissue. Plotz and Davies (1957) detected significant levels of progesterone in body fat after intramuscular injection, and Steinetz et al. (1967) found significant quantities of ethynyloestradiol cyclopentyl ether in the various fat depots of castrated female rats after intramuscular administration. Fotherby and James (1972) suggested that a level in body fat below detectable concentration could still be high enough for the total amount retained in the body to be substantial.

Van der Vies (1965) gave an intramuscular injection of nandrolone decanoate, dissolved in arachis oil, to rats, and determined the rate of elimination from the muscle. He calculated the blood levels of nandrolone which would be anticipated at intervals after one oily, intramuscular injection, assuming that they were dependent on release from an oily depot in the muscle. On administering 21 consecutive aqueous, intravenous injections, having varying potencies based on his calculations, he obtained responses in good agreement with those obtained with the single intramuscular injection. However, 21 equal injections, having the same total strength as the 21 injections in the simulated treatment, produced a similar response. Thus, whilst the results favour a mechanism involving slow release from a depot, they do nothing to establish what the depot is. Nandrolone phenyl-

propionate behaved in the same way. An interesting observation was that only 10 $\mu g\ ml^{-1}$ of ester and 2.4 $\mu g\ ml^{-1}$ of alcohol were found in the blood, $1\frac{1}{2}$ min after intravenous injection of 1 mg of nandrolone phenylpropionate; 50 g rats were used, which means that the total blood content was less than 10% of the administered dose. A rapid extraction by other body tissues, possibly fat, could account for this discrepancy.

Chaudry and James (1974) investigated the effects of intramuscular injections of nandrolone esters in ethyl oleate. Bimodal time–response plots were obtained, in which the times of the second maximum correlated with the corresponding ethyl oleate distribution coefficients, but those of the first maximum did not, and it was suggested that the first part of the time–response plot represented release from a muscle depot, and the second from body fat. Similar plots have been obtained for the lower n-fatty acid esters of nandrolone (Ng, 1974), and fluphenazine decanoate in sesame oil appears to give a similar time–response profile (Florence et al., 1978).

Aaes-Jorgensen et al. (1977) studied the distribution and elimination of clopenthixol in dogs and rats, following intramuscular injection of a solution of the decanoate ester in viscoleo (a thin vegetable oil) solution. Clopenthixol was distributed in the tissues almost entirely as the free alcohol, and it was concluded from this that the maintenance of drug levels was due to the slow release of the lipophilic ester from an oil depot in the muscle, followed by hydrolysis. It is significant, however, that clopenthixol decanoate was found in other organs, indicating that some ester had escaped hydrolysis while transported in the blood. The hydrolysis results quoted showed the rate to be sufficiently slow to permit this. Plasma and faeces levels indicated a half-life in dog of 10 days, compared with 4–5 days calculated from release rate from the site of injection, and a similar discrepancy could be detected in the rat results. The differences can be explained by the existence of a second depot, although its location is uncertain. Similar results were obtained with flupenthixol decanoate in dog and rat (Jorgensen et al., 1971), and with [^{14}C]fluphenazine enanthate and decanoate administered in sesame oil to dogs (Dreyfuss et al., 1976).

Tanaka et al. (1974) studied the intramuscular absorption of methylisonicotinate, isonicotinamide, sulphanilamide and [^{14}C]testosterone from oily solutions in the rat. Methyl oleate, tributyrin and diethyl phthalate were used as solvents. Clearance from the injection site was first-order for all 4 drugs from each of the solvents. Two concentrations were employed, and found to have the same effect on clearance rates. With methylisonicotinate and sulphanilamide, absorption rate was directly related to distribution coefficient. The process therefore appears to take the form of an equilibrium between the oily injection and the surrounding aqueous environment. It was speculated that this behaviour would apply to all drugs having moderate lipid solubility ($K_{o/w}$ = 1–13).

The in vivo absorption rate of isonicotinamide was not related to distribution coefficient, and it was suggested that this was because of its low lipid solubility. Using the same statement in reverse, the relatively high aqueous solubility, coupled with the large difference between the volumes of the blood and the injection, provides conditions in which the blood will behave as a sink. The result is that equilibrium between the blood and the injection is never established, so that the distribution coefficient is irrelevant, and the rate-determining factor is the migration of the drug from oil to water. The distribution coefficient of testosterone was also unrelated to absorption rate. This was considered to be a general characteristic of drugs having 'extremely high partition coefficients', and a

consequence of the low solubility in tissue fluid. It is thus evident that the precise mechanism of absorption from oily intramuscular injections has yet to be evaluated. The evidence suggests a rate-limiting step involving release from a depot, but it is not clear whether the depot is at the site of injection or elsewhere in the body. It is probable that both factors operate, and that their relative importance depends on the properties of the drug and solvent.

RECTAL DOSAGE FORMS

Though probably dating from the seventeenth century, the lipid-based solid suppository is still widely used. Like other lipid dosage forms, an essential preliminary to drug absorption is the release of the drug from its vehicle, followed by dissolution in an aqueous liquid. However, other factors are present which pose added complications. Firstly, fusion of the suppository mass must occur before a significant degree of drug release can be achieved. Secondly, conditions for the partition of the drug into an aqueous medium may be unfavourable, as the water content of the rectum is low (about 2–3 ml in the adult). Since this is not dissimilar to the volume of the average suppository, a phase–volume ratio of about one is present, which does not favour rapid drug release. In addition, the water is present as mucus of relatively high viscosity, thereby retarding diffusion of the drug molecules, and a low buffer capacity which may not favour the dissolution of ionisable molecules.

A further factor is that many suppositories contain medicaments which are insoluble or only partly soluble in the lipid base. Drug release may then be controlled by factors governing the passage of solid particles across an oil–water interface, such as particle size, degree of agglomeration, particle solubility in both phases and the presence of substances which may affect the interfacial tension of the system (Crommelin, 1979).

Finally, the site of absorption in the rectum may govern the therapeutic response to the drug. The upper part of the rectal submucosa is fed by the superior haemorrhoidal vein which empties into the portal vein, whilst the lower part is fed by veins which lead to the inferior vena cava. It has been suggested that drugs absorbed in the lower rectum will bypass the liver and thereby avoid metabolism by the so-called first-pass effect. However, this theory assumes that when administered, a suppository will remain in the lower part of the rectum and not migrate, even after melting, to areas drained by the portal vein. The evidence for such an assumption is by no means conclusive (Rutten-Kingma et al., 1979).

The literature is replete with reports of the evaluation of numerous combinations of drugs and suppository bases (Senior, 1974). However, in view of the complications involved in this form of therapy, it is not surprising that many reports are contradictory, and high degrees of correlation between in vitro tests, animal studies and performance in humans are comparatively rare.

Many reports on bioavailability from suppository systems typically compare the release of a relatively water-insoluble drug and a more soluble salt or derivative, using a lipid base and a water-miscible base such as polyethylene glycol or glycerol–gelatin mixtures (see for example, Schwartz and Bichsel, 1963; Neuwald and Ackard, 1966). Comparatively few reports examine in detail the role of the lipid base in controlling the release

of a substance dissolved in it. A number of authors have deduced from their findings that the rate of release of drug from the vehicle and transport to the rectal mucosa is essentially a function of the lipid–water partition coefficient of the solute, but in the experience of the present authors, this assertion is rarely supported by a determination of these partition coefficients, without which a quantitative evaluation of the results is virtually impossible.

Interaction between solutes and bases must not be overlooked, though here too evidence in the literature may be contradictory. For example, the presence of water in lipid bases has been shown by Muhlemann and Neuenschwander (1956) to reduce drug release, the suggested mechanism being the formation of a water-in-oil emulsion within the suppository, though Pennati and Steiger-Trippi (1958) have attributed the rapid release of sulphasomidine from Massuppol as being due to the presence of an emulsifier in that base.

Because of the possible interaction between drug and base, caution must be exercised in the extrapolation of in vitro data to in vivo situations. Puffer and Crowell (1973) found that sodium salicylate was released quicker from a number of polyethylene glycol mixtures in vitro than was salicylic acid. However, in a study in dogs using the same two substances, Lowenthal and Borzelleca (1965) found that release of sodium salicylate from polyethylene glycol suppositories was slower than that of salicylic acid. Kakemi et al. (1965) have also demonstrated a retarding effect of polyethylene glycol bases, in this case on the rectal absorption of some sulphonamides in the rat. Polyethylene glycol suppositories do not melt at body temperature, but rather dissolve, and so polyethylene glycol and sodium salicylate are both present as solutions in the rectal fluid. Such a situation will favour an interaction between the two solutes which will hinder absorption. However, such an interaction was not detected in vitro, since the analytical technique used by Puffer and Crowell would not distinguish between free salicylate and that bound to polyethylene glycol.

In an in vitro study of drug release from cetyl phthalate, Voight and Falk (1968) found that in general the release rate was proportional to the drug's solubility in water. However, the equation of high release rate with high water solubility should be viewed with caution, since it does not necessarily follow that substances which are freely soluble in water will have a low solubility in an oily medium. For example, two substances placed by Voight and Falk in the category 'very readily soluble' were atropine sulphate and resorcinol. The former has negligible lipid solubility, it will be present in the suppository as a suspension, and its release from the base will be controlled by those factors which govern the transfer of solid particles across an oil–water interface. On the other hand, resorcinol has an appreciable solubility in lipid, and it will be present in the suppository as a solution. In this case, release may well be controlled by partition coefficient and relative phase volume, i.e. completely different factors to atropine sulphate. For substances with intermediate solubility in the lipid phase, the drug will be present partly as a suspension and partly as a solution, and so both sets of factors will be operative.

Thus for meaningful comparative studies on either the release of different drugs from the same base or the same drug from different bases, caution must be exercised if some systems are solutions and some are suspensions, since factors controlling drug release from the dosage form will be different in each case. An appreciation of drug release from non-polar suspensions has only recently been made (Crommelin, 1979) and there has

been little effort to optimize drug release from non-polar rectal solutions by the use of distribution coefficient data.

REFERENCES

Aaes-Jorgensen, T., Overa, K.F., Bogeso, K.P. and Jorgensen, A., Pharmacokinetic studies on clopenthixol decanoate; a comparison with clopenthixol in dogs and rats. Acta Pharmacol. Toxicol., 41 (1977) 103–120.

Albrieux, A.S. and Prego, L.E., Activity of oestrogenic substances in solutions in various oils. Arch. Soc. Biol. (Montevideo), 11 (1943) 71–76.

Bate-Smith, E.C. and Westall, R.G., Chromatographic behaviour and chemical structure. I. Some naturally occurring phenolic substances. Biochim. Biophys. Acta, 4 (1950) 427–440.

Becker, G.L., The case against mineral oil. Am. J. Dig. Dis., 19 (1952) 344–348.

Biagi, G.L., Barbaro, A.M. and Guerra, M.C., Relationship between R_m values and biological activity of steroid esters. Experientia, 27 (1971) 918–919.

Bowen, D.B., James, K.C. and Roberts, M., An investigation of the distribution coefficients of some androgen esters using paper chromatography. J. Pharm. Pharmacol., 22 (1970) 518–522.

Boyce, C.B.C. and Milborrow, B.V., A simple assessment of partition data for correlating structure and biological activity using thin-layer chromatography. Nature (London), 208 (1965) 537–539.

Bush, I.E., The Chromatography of Steroids, Pergamon, London, 1961, p. 62.

Chaudry, M.A.Q. and James, K.C., A Hansch analysis of the anabolic activities of some nandrolone esters. J. Med. Chem., 17 (1974) 157–161.

Collander, R., The partition of organic compounds between higher alcohols and water. Acta Chem. Scand., 5 (1951) 774–780.

Crommelin, D.J.A., In vitro release studies on drugs suspended in non-polar media. Ph.D. Thesis, University of Leiden, 1979.

Deanesly, R. and Parkes, A.S., The subcutaneous absorption of oils by rats and mice, with special reference to the assay of estrin. J. Physiol. (London), 78 (1933) 155–160.

Deanesly, R. and Parkes, A.S., Male hormones and the question of accessory substances. Lancet, (1936) 837–839.

Dreyfuss, J., Ross, J.J., Shaw, J.M., Miller, I. and Schreiber, E.C., Release and elimination of ^{14}C-fluphenazine enanthate and decanoate esters administered in sesame oil to dogs. J. Pharm. Sci., 65 (1976) 502–507.

Florence, A.T., Vezin, W.R., Ray-Johnson, M.L. and Stevens, H.N.E., Intramuscular formulations of fluphenazine and their duration of activity in the rat. J. Pharm. Pharmacol., 30 (1978) 28P.

Fotherby, K. and James, F., Metabolism of synthetic steroids. In M. Briggs and G.A. Christie (Eds.), Advances in Steroid Biochemistry and Pharmacology Vol. 3. Academic Press, London, 1972, pp. 67–165.

James, K.C., R_m values and biological action of testosterone esters. Experientia, 28 (1972) 479–480.

James, K.C., Nicholls, P.J. and Richards, G.T., Correlation of androgenic activities of the lower testosterone esters in rat with R_m values and hydrolysis rates, Eur. J. Med. Chem., 10 (1975) 55–58.

James, K.C., Nicholls, P.J. and Roberts, M., Biological half-lives of 4-^{14}C-testosterone and some of its esters after injection into the rat. J. Pharm. Pharmacol., 21 (1969) 24–27.

James, K.C., Richards, G.T. and Turner, T.D., A comparison of chromatographic methods for the assessment of the distribution coefficients of androgen esters. J. Chromatogr., 69 (1972) 141–149.

Jorgensen, A., Overa, K.F. and Hansen, V., Metabolism, distribution and excretion of flupenthixol decanoate in dogs and rats. Acta Pharmacol. Toxicol., 29 (1971) 339–358.

Kakemi, K., Arita, T. and Muranishi, S., Effect of water soluble bases on rectal absorption of sulphonamides. Chem. Pharm. Bull., 13 (1965) 969–975.

Leo, A., Hansch, C. and Elkins, D., Partition coefficients and their uses. Chem. Rev., 71 (1971) 525–616.

Lowenthal, W. and Borzelleca, J., Drug absorption from the rectum. J. Pharm. Sci., 54 (1965) 1790–1794.

Martindale, The Extra Pharmacopoeia, 27th edn., Pharmaceutical Press, London, 1977a, p. 106.
Martindale, The Extra Pharmacopoeia, 27th edn., Pharmaceutical Press, London, 1977b, p. 757.
Miescher, K., Wettstein, A. and Tschopp, E., The activation of the male sex hormones II. Biochem. J., 30 (1936) 1977–1989.
Muhlemann, H. and Neuenschwander, R.H., The use of some modern bases as suppository masses. Pharm. Acta Helv., 31 (1956) 305–309.
Neuwald, F. and Ackard, P., Drug absorption from preparations for rectal administration. Galenica Acta, 19 (1966) 179–189.
Ng, C.T., The influence of structure on the solubility profiles and biological activities of some androgen esters. Ph.D. Thesis, University of Wales, 1974.
Parkes, A.S., Increasing the effectiveness of testosterone. Lancet, (1936) 674–676.
Pennati, E. and Steiger-Trippi, K., The influence on absorption of rectally administered drugs by the suppository base. Pharm. Acta Helv., 33 (1958) 663–677.
Plotz, E.J. and Davies, M.E., Distribution of radioactivity in human maternal and fetal tissues following administration of progesterone-4-C^{14}. Proc. Soc. Exp. Biol. Med., 95 (1957) 92–96.
Puffer, H.W. and Crowell, W.J., Salicylate release characteristics of selected polyethylene glycol suppositories. J. Pharm. Sci., 62 (1973) 242–245.
Rutten-Kingma, J.J., Polderman, J. and de Blaey, C.J., Biopharmaceutical studies of fatty suspension suppositories I. Spreading in situ. Int. J. Pharm., 3 (1979) 39–53.
Samuel, L.T., The dynamics of steroid hormone distribution in the body, particularly the distribution of cortisol. In G. Pincus, T. Nakao and J.F. Tait (Eds.), Steroid Dynamics, Academic Press, London, 1966, pp. 385–391.
Sanseigne, A.J., Yale, H.L., Hess, S.M., Burke, J.C. and Horovitz, Z.P., New concept in phenothiazine therapy, fluphenazine enanthate and fluphenazine decanoate. Agressologie, 9 (1968) 309–313.
Schwartz, T.W. and Bichsel, K., Absorption of sulphasomidine from various suppository bases by humans. Pharm. Acta Helv., 38 (1963) 861–870.
Senior, N., Rectal administration of drugs. In A.H. Beckett, H.S. Bean and J.E. Carless (Eds.), Advances in Pharmaceutical Sciences, Vol. 4, Academic Press, London, 1974, pp. 366–435.
Sinclair, L., Rickets from liquid paraffin. Lancet, i (1967) 792.
Steinetz, B.G., Meli, A., Giannina, T. and Beach, V.L., Biliary metabolites of orally administered ethynylestradiol and its 3-cyclopentyl ether. Proc. Soc. Exp. Biol. Med., 124 (1967) 1283–1289.
Talbot, J.M. and Meade, B.W., Effect of silicones on the absorption of anticoagulant drugs. Lancet, i (1971) 1292.
Tanaka, T., Kobayashi, K., Okumura, K., Muranishi, S. and Sezaki, H., Intramuscular absorption of drugs from oily solutions in the rat. Chem. Pharm. Bull., 22 (1974) 1275–1284.
Van der Vies, J., On the mechanism of action of nandrolone phenylpropionate and nandrolone decanoate in rats. Acta Endocrinol. (Copenhagen), 49 (1965) 271–282.
Van der Vies, J., Model studies in vitro with long-acting hormonal preparations. Acta Endocrinol. (Copenhagen), 64 (1970) 656–669.
Voight, R. and Falk, G., Water solubility of drugs as a criterion for drug liberation from fatty substances. Pharmazie, 23 (1968) 709–714.
Welling, P.G., Effect of food on bioavailability of drugs. Pharm. Int., 1 (1980) 14–18.