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DRUG RELEASE FROM LIPID-BASED DOSAGE FORMS. II

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ORAL PREPARATIONS

Oily medicaments have been administered orally since early times; castor oil, liquid paraffin and fish liver oils are particular examples. They are unpleasant to take, and the sensation can be masked by sealing the oil in a soft gelatin capsule, which dissolves in the stomach. Whilst considerable interest has been directed towards the bioavailability of solids from tablets, little attention has been paid to the effects of the oily environment on the absorption of drugs presented in soft gelatin capsules.

Crounse (1961) reported a nearly doubled serum griseofulvin concentration when administered to human subjects, following a high fat breakfast. A natural extension of this was to compare a suspension in corn oil with the powder, when given orally to rat (Kraml et al., 1962). Increased availability was again observed with the oily suspension, resulting in plasma levels approximately double those obtained with equivalent aqueous suspensions. Carrington and Bates (1973) obtained similar results when comparing aqueous suspensions of griseofulvin with suspensions in corn oil in rat, but found even higher plasma levels when the drug was dispersed in an oil in water emulsion. In contrast, Bloedow and Hayton (1976), in examining the effects of hexadecane, oleyl alcohol, triolein and trioctanin on the bioavailability of griseofulvin in rats, found that in comparison to administration in water, the rate of absorption was either decreased or unchanged by the presence of the lipids. It is unfortunate that these authors did not examine the effects of corn oil, since there is no way of establishing whether their results are in direct contradiction to the previous work, or are different because corn oil has a specific effect on griseofulvin.

Mantilla-Plata and Harbison (1975) examined the effect of corn oil on the availability of Δ9-tetrahydrocannabinol in mice, and recorded considerably reduced plasma levels in comparison with those obtained with 1% polysorbate 80 in saline as vehicle. Similarly L-diphenylmethyl-4-[(6-methyl-2-pyridyl)methyleneamino]piperazine was found to have anticonvulsant activity in mice when administered intragastrically in aqueous suspension, but had no effect when given as a suspension in corn oil (Sanvordeker and Bloss, 1977). The biological availability of flufenamic acid after oral administration of the drug in both hard and soft gelatin capsules was studied in dogs and humans (Angelluci et al., 1976). The soft gelatin capsules, which contained a mixture of vegetable oils, lecithin and beeswax as vehicles, produced consistently higher plasma concentration–time plots. No significant difference between plasma levels was observed following administration of diazepam,

either as a powder in hard gelatin capsules, or a solution in medium chain triglyceride in soft gelatin capsules, using 4 human subjects. The failure to distinguish between the two preparations could have been due to intersubject variation associated with the small number of patients examined. Repeated administration to an individual subject indicated faster absorption and a more uniform absorption rate (Yamahira et al., 1979).

In a bioavailability study to the antimalarial α-(dibutylaminomethyl)-6,8-dichloro-2-(3′,4′-dichlorophenyl)-4-quinolinemethanol, blood levels of 5 beagle dogs indicated that delivery was better from soft gelatin capsules containing a solution of the free base in oleic acid, than from hard gelatin capsules containing the hydrochloride (Stella et al., 1978). Fischler and coworkers (1973) studied the plasma concentrations of chlormethiazole in man after administration of tablets containing chlormethiazole edisylate, capsules containing chlormethiazole base in arachis oil and a syrup containing the edisylate. The peak plasma level was higher, and was reached more rapidly from the syrup than from the capsules, which in turn gave a quicker and higher plasma level than the tablets. The rank order of blood levels remained significant up to 70 min after administration. The superiority of the aqueous solution was also demonstrated with ephedrine when administered to dogs (Lin et al., 1974). About half the dose from the soft gelatin capsule containing a solution in mineral oil was excreted in the urine over the first 48 h, compared with three-quarters from the aqueous solution.

The oral bioavailabilities of steroids are usually enhanced by the presence of lipids (Kim and Ivy, 1952). In tests on the contraceptive efficiency of megestrol acetate, 15 pregnancies occurred in 1290 cycles when tablets were given, but there was only 1 pregnancy in 599 cycles when the drug was dissolved in arachis oil and administered in soft gelatin capsules (Avendano, 1970). The behaviour is not always so simple. Bruni and Galletti (1970) measured the urinary excretion of pregnanediol and allopregnanediols after oral administration of quingestrone to a human volunteer. Recovery was greater when oil was administered concurrently. However, when the experiment was repeated substituting progesterone for quingestone, the oil had no effect.

A selection of androstanolone and testosterone esters, methyltestosterone and androstanolone, when given orally in oil solution to rats, all produced a greater increase in weight of seminal vesicles, prostate and levator ani, compared with aqueous suspensions (Alibrandi et al., 1960). In complete contrast, the biological activities of prednisolone, prednisone and their esters were greater in aqueous suspension than in oily solution. Bruni et al. (1966, 1973) examined the effects of sesame oil on 17-ketosteroid excretion in an adult male, after oral administration of androstenedione and its cyclopentyl enol ether. The oil had no effect on androstenedione, but produced a 50% increase in the 17-ketosteroid level from the ether.

Absorption from lipid solution is considered to involve liberation of the drug from the vehicle into the aqueous luminal fluid, followed by passage through the gastrointestinal wall. Armstrong et al. (1979) determined in vitro rates of release and distribution coefficients of a range of benzoic and phenylacetic acids between either isopropyl myristate or octanol and water, and compared them with the bioavailabilities in rat. Absorption in vivo followed an inverse rank order to lipid solubility, but was related to the in vitro solvent–water transfer rate constant, rather than the distribution coefficient. The inference was therefore that availability was dependent on the concentration of drug in

solution in the gastrointestinal fluid, which in turn was dependent on the rate of supply from the oily phase. In other words, lipid and aqueous phases in vivo were not in equilibrium. Similar results were obtained with methyltestosterone in rat (Davies, 1977). Availabilities, as indicated by blood, bile and gastrointestinal fluid concentrations, were inverse functions of the solubilities in the solvent vehicles, which were blends of octanol and octane.

The above observations are not surprising, since the more the drug favours the lipid phase, the more reluctant it will be to migrate to the aqueous gastrointestinal fluid. It therefore seems a contradiction that highly lipophilic drugs such as androstenedione-3-cyclopentyl ether (Bruni et al., 1966) and ethynyloestradiol-3-cyclopentyl ether (Steinetz et al., 1966) are absorbed more readily from oils than from aqueous suspensions. Bloedow (1974) described the first stage of absorption of fixed oils and fats as hydrolysis at the oil–water interface, followed by solubilization in bile salt micelles, which penetrate into the intramicrovillus spaces of the intestine, and suggested that a poorly water-soluble drug could be carried with its lipid solvent along this route. Androstadiene-3-cyclopentyl ether and ethynyloestradiol-3-cyclopentyl ether could follow this route. Evidence favouring this suggestion is that the absorption of ethynyloestradiol-3-cyclopentyl ether is considerably retarded in the absence of bile. The less lipophilic a drug, the less readily will it be transported by this mechanism. Ethynyloestradiol, with two hydroxyl groups, has a significant hydrophilic influence, hence the failure of its rate of absorption to increase when administered in oily solution (Steinetz et al., 1966). The same consideration explains why the biological activities of progesterone (Bruni and Galletti, 1970) and prednisolone (Alibrandi et al., 1960) are not improved by administration in oil solution.

A further complication is that after absorption, fatty acids containing 14 or more carbon atoms are considered to be taken up in the lymph, and those containing 8–12 carbon atoms enter the systemic circulation through the portal vein (Bloom et al., 1951). Bloedow (1974) has suggested that lipophilic drugs follow one or both of these routes, depending on the nature of the drug. By analogy with the fatty acids, one anticipates that the lymph process favours the more lipophilic drugs. Results obtained with ethynyloestradiol and ethynyloestradiol-3-cyclopentyl ether support this view (Giannina et al., 1966). Only about 0.5% of the administered dose was found in 24-h lymph samples of rats after administration of ethynyloestradiol, whether as aqueous suspension or in sesame oil, but 7.5% ethynyloestradiol-3-cyclopentyl ether was found when the ether was given in sesame oil. Aqueous solutions of the ether gave lymph concentrations of only 1.5%. Esterification of testosterone to the undecanoate resulted in considerable increase in oral activity in man (Horst et al., 1976) and rat (Coert et al., 1975), and could be increased further by dissolving the ester in oil. Testosterone undecanoate was found exclusively in the lymph, but free testosterone and androstanolone, resulting from metabolism of the ester, were found exclusively in the portal circulation (Horst et al., 1976).

Solvent-assisted dyeing (Beal et al., 1960) has been used in the textile and cosmetic industries for many years (Tucker, 1971). An acid dye in an aqueous bath, for example, requires an elevated temperature to be permanently fixed to wool fibres, but in the presence of benzyl alcohol, the process can be carried out at ambient temperature. The physical properties of the solvent are critical in that it must be sufficiently insoluble in

water to form a separate phase, yet be slightly miscible with water, and it must also be a good solvent for the dye, but not a better solvent than wool. The solvent is believed to function as a carrier between the dye bath and the fibre. It has been suggested that percutaneous absorption can follow this mechanism (Goldenburg, 1976), and it is possible that a similar process occurs in the intestinal absorption of drugs dissolved in lipid solvents.

Several papers have appeared describing drug release from emulsions. Although heterogeneous systems are outside the scope of this review, some of these papers are worthy of mention, because they help to throw light on the mechanisms of drug absorption from lipid solutions. Kakemi et al. (1972a and b) measured the distribution coefficients of acetanilide, salicylamide, sulphanilamide and sulphapyridine between diethyl phthalate, ethyl laurate and isopropyl palmitate, and water, and compared them with the degree of absorption from oil in water emulsions through isolated rat intestine. Their results fell into two groups according to the variation of absorption with volume fraction of oil, those in which the oil–water distribution coefficient was less than one, and those in which it exceeded one. The results for systems in which the distribution coefficient was less than one were considered to suggest that absorption involved prior release from the oil to the luminal fluid. Noguchi et al. (1977) examined lipid-soluble dyes and vitamin A acetate in triolein, monolein and oleic acid emulsions, using the isolated intestinal loop technique, and considered that absorption of lipid-soluble materials first involved absorption of solute and lipid into membrane lipids.

If it is accepted that any of the absorption processes described above can operate, we can list principal factors which will influence the choice of route and method of absorption. These are briefly discussed below.

(a) The solubility of the drug in the lipid vehicle. The release of a drug from a solution is an inverse function of its solubility in the solvent. Ferguson (1939) used the parameter chemical potential (concentration/solubility), which was a more accurate indicator of biological activity than concentration alone. Thus a less efficient solvent will release the drug more readily, but the advantage is limited by the amount of drug which the solvent can dissolve.

(b) The aqueous solubility of the drug. The higher the aqueous solubility, the greater the quantity that will dissolve in the gastrointestinal fluid, and hence be available for absorption. The less hydrophobic drugs would be expected to follow this route. Experimental results indicate that the solubility need not be very great, since even ethynyloestradiol (Steinetz et al., 1966), progesterone (Bruni and Galletti, 1970) and prednisolone (Alibrandi et al., 1960) appear to favour a process of solution in the gastrointestinal fluid, followed by absorption. If the oily solution which was administered and the gastrointestinal fluid are in equilibrium, the distribution coefficient will become the controlling factor. The failure of pharmacodynamic parameters to correlate with distribution coefficients suggests that the process is dynamic, and controlled by the rate of transfer from one solvent to the other (Armstrong et al., 1979; Davies, 1977).

(c) The nature of the solvent. Bloedow (1974) has suggested that digestible lipids influence drug absorption in a different way from non-digestible lipids. The former were claimed to function as drug carriers, so that the nature of the solvent could be an important factor influencing rate of migration and rate of metabolism. Non-digestible solvents

were considered to retard the absorption of lipid-soluble drugs.

The solvents discussed so far have all been hydrophobic. Hydrophilic, non-aqueous liquids, such as propylene glycol, polyethylene glycol and polysorbate 80, are increasing in importance as solvents for water-insoluble drugs, for use in soft gelatin capsules. Bioavailability is usually greater and more rapid from these solvents than from either powdered drug or aqueous suspension. Indoxole, an anti-inflammatory agent with low water solubility, was administered in soft gelatin capsules containing a solution in polysorbate 80, and produced a higher, more rapid plasma level than an aqueous suspension or hard gelatin capsules containing the powder (Wagner et al., 1966). The serum level response was approximately equivalent to that obtained with indoxole dissolved in the oily phase of an emulsion. Temazepam was given to healthy subjects as a single 20 mg dose, either as a powder in hard gelatin capsules or as a solution in polyethylene glycol in soft gelatin capsules. Absorption from the soft gelatin capsules produced earlier and higher peak plasma levels, but there was no significant difference between total availabilities (Fuccella et al., 1977). The absorption and elimination of ethosuximide from a solution in polyethylene glycol in soft gelatin capsules has been compared in 5 children with that from an aqueous solution. Plasma levels followed similar time courses with the two preparations (Buchanan et al., 1969). Digoxin, dissolved in a water-soluble mixture consisting of N,N-dimethylacetamide and polyethylene glycol, and packed in soft gelatin capsules, has been compared with tablets in vitro, and found to dissolve more readily (Ghirardi et al., 1977; Astorri et al., 1979). Higher bioavailability from the capsules was observed in dogs (Ghirardi et al., 1977) and humans (Ghirardi et al., 1977; Astorri et al., 1979; Alvisi et al., 1979). Similar results have been obtained using capsules containing a solution of digoxin in a mixture of polyethylene glycol and propylene glycol (Mallis et al., 1975) and also in a mixture of polyethylene glycol 400, ethanol, propylene glycol and 1% water (Marcus et al., 1976; Johnson et al., 1976). Griseofulvin gave 88% absorption in dogs from soft gelatin capsules containing a dispersion in polyethylene glycol 6000, in comparison with 100% from polyethylene glycol 400 solution. Commercial tablets and hard capsules containing micronized drug gave 45% and 33% absorption respectively (Chiou and Riegelman, 1970).

Hom and Miskel (1970) compared the dissolution rates from capsules and tablets in vitro, examining 10 drugs in all. They were either dissolved in polyethylene glycol 400 or suspended in polyols or non-ionic surfactants. In all cases, the maximum quantity of drug was dissolved from the capsule in 4 min, while the corresponding concentration was not reached from tablets in less than half an hour. Biological results shed little light on the mechanism of absorption from these solvents in vivo, but the most probable route begins with dilution of the capsule contents with the luminal fluid, the drug either remaining in solution, or that in excess of solubility separating out as a fine precipitate.

(d) The nature of the drug. The indications are that highly lipophilic drugs are absorbed by a lipid transport process, and that less lipophilic drugs are first dissolved in the luminal fluid. Lipid solvents favour the first group, and the more hydrophilic solvents, the second.

MECHANISMS OF DRUG RELEASE FROM A LIPOPHILIC MEDIUM IN THE GASTROINTESTINAL TRACT

Kakemi et al. (1966) considered that two absorptive mechanisms are available when drugs are administered rectally in a water-immiscible solution. One involves the transfer of drug from the lipid phase into the rectal contents, absorption taking place from aqueous solution, and the second mechanism is by direct absorption from the oily solution, through the rectal membrane. It was later shown (Kakemi et al., 1972b) that the major route was that involving preliminary transfer to an aqueous phase. Evidence was presented that not only is direct absorption from the oil phase negligible, but that the oil can significantly reduce absorption, if present as a coating on the absorbing membrane. This factor will be of greatest significance when the volume of oil is great in comparison with that of the aqueous phase, such as may apply in the rectum. The process could also account for the interference by liquid paraffin with the gastrointestinal absorption of fat-soluble vitamins after oral administration, since though the area of the gastrointestinal mucosa is high, so is the quantity of lipid involved.

At equilibrium, the quantity of drug in aqueous solution (M_w) is given by Eqn. 1. M_0 is the quantity dissolved in the lipid phase, K the lipid–water partition coefficient, and ϕ the volume ratio of lipid to aqueous phase. ϕ must therefore be taken into account when considering the effect of an oily vehicle on drug release.

$$M_0 = K\phi M_w \tag{1}$$

For example, in the oral administration of an oil-in-water emulsion or a soft gelatin capsule, the volume of oil in relation to the amount of aqueous liquid present will be small, and ϕ has a low value. The converse applies to the administration of a lipophilic suppository, when in the relatively dry conditions of the rectum, a much larger value of ϕ is appropriate. A further factor which must be considered is the rate at which the partition of the drug between the two phases is achieved. In situations where this is slow in comparison with absorption from the aqueous phase, equilibrium may not be reached, and the transfer from oil to water becomes the rate-determining process.

In the above treatment, the interfacial area between lipid and aqueous phases has been assumed to be a constant, but this assumption will not be valid in most in vivo situations, except possibly that of the intramuscular injection. Rectally administered solid lipid will melt, and the resulting liquid will be distributed through the rectum, though the degree of subdivision of the lipid will depend on a number of factors, such as viscosity of the liquid, the rectal pressure and possibly the posture of the patient. Orally administered lipid will almost certainly be subdivided in the gastrointestinal tract with a corresponding increase in interfacial area. This will be aided by emulsifiers present in the formulation, and also by bile. Whilst any degree of subdivision may be expected to increase the rate at which drug is released from the lipid phase, redissolution of the drug by the oil will also be facilitated.

Drug absorption from aqueous solution and an oil-in-water emulsion have been compared by Kakemi et al. (1972a) with respect to partition coefficient and phase volume ratio. Their conclusions are summarized in Fig. 1, but this study neglects the effect that

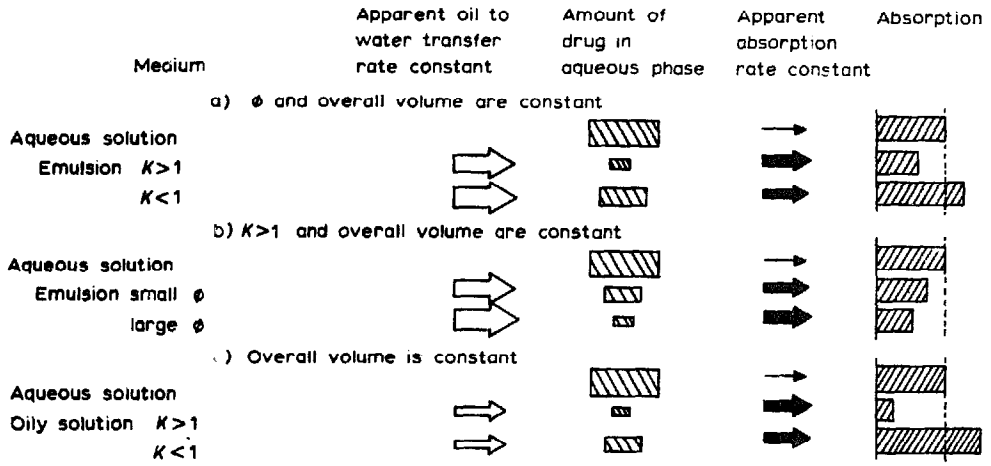

Fig. 1. Schematic relation between absorption and various factors affecting the absorption from aqueous solution, emulsion, and from oily solutions. The width of arrows, the area of squares and the length of bars represent the relative rate constant, the relative amount of drugs in aqueous phase, and the relative magnitude of absorption, respectively. (Kakemi et al., 1972b, reprinted with permission).

an interfacial film between the two phases may have on release rate from the oily phase. Ghanem et al. (1969) have shown that the presence of a gelatin film slows solute release from a lipophilic vehicle by a factor of 10^4, compared to release from a diffusion-controlled system, and have drawn attention to the implications of their findings to the effect of protein and polymeric substances in drug absorption. The influence of the gelatin shell in soft gelatin capsules, for example, does not appear to have been studied from this standpoint.

THE USE OF IN VITRO MODELS TO PREDICT DRUG RELEASE FROM LIPOPHILIC SOLVENTS

The crucial test of any in vitro technique is whether the results correlate with in vivo data. Few model systems appear to have been devised to study drug release from lipophilic solutions. The major requirement of such a model is that it must take into account the partition of the drug between the lipid and the aqueous biophase. Additional features would be the means of varying the phase–volume ratio, and a form of sink in the aqueous phase to prevent build up of released solute. Whether a simulated biomembrane is required depends on the dosage form being examined. Drugs administered orally or rectally are required to cross the membrane of the gastrointestinal tract before drug action can occur, and hence in the study of these dosage forms, a simulated luminal membrane is desirable. On the other hand this would not be required in the simulation of release from oily injections.

A number of in vitro studies on drug release from suppository bases has been reported. The method used by Muhlemann is typical (Muhlemann and Neuenschwander, 1956). A mixture of drug and base was placed in a tube, the end of which was closed with a semipermeable membrane. The tube was then immersed in an aqueous fluid, and the appear-

ance of the drug in the latter monitored. A similar technique has been used by Voight and Falk (1968). Whilst this technique may be suitable for suppositories in which the drug is in a completely dissolved state, the presence of the semipermeable membrane will constitute a physical barrier to any undissolved drug particles, and hence an important mechanism for the release of suspended particles will be nullified.

Doluisio and Swintosky (1964) devised an apparatus shaped like an inverted 'Y'. The two arms of the 'Y' represented a simulated gastrointestinal phase and simulated plasma respectively, joined by a lipid barrier representing the gastrointestinal membrane (in this case, cyclohexane was used). Under the influence of a gentle rocking motion, drug dissolved in the gastrointestinal compartment was extracted by cyclohexane, which in turn was extracted by the plasma phase. Whilst the volume of lipid phase seems to be excessive as a simulated lipid membrane, the mathematical treatment associated with the technique (Doluisio et al., 1970) has proved applicable to the method described by Armstrong et al. (1979). Their partition–permeation device consisted of two perspex blocks, each bored out to form a cylindrical cell. When the blocks were clamped together, they were joined by a circular hole, across which was placed a cellulose nitrate membrane filter impregnated with a simulated gastrointestinal lipoid barrier (Stricker, 1971). One cylinder contained a solution of the drug in lipid plus an aqueous solution representing the contents of the gut, whilst across the barrier was an aqueous liquid representing the plasma, which acted as a sink. Armstrong et al. (1979) obtained rank order agreement with in vivo behaviour using this apparatus. They showed that the non-aqueous solution was not in equilibrium with simulated gut contents, and that the release from the lipid depended on the transfer rates from one solvent to another.

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