In vitro release studies on drugs suspended in non-polar media

The release of sodium chloride, paracetamol and chloramphenicol from suspensions in liquid paraffin

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Release of drug substances suspended in non-aqueous media includes the following steps:

a. transport of the solid to the oil/water interface;
b. transport through this interface;
c. dissolution in the aqueous phase.

In the under-mentioned study the mechanisms involved in the release process were investigated in a model system, following a systematic approach. Sodium chloride, paracetamol and chloramphenicol, all almost insoluble in the non-polar medium (liquid paraffin), were chosen as model substances covering a wide range of water solubilities: 360, 13 and 3.6 mg/ml respectively. Other parameters studied were particle size (5-60 μm), concentration of the solid (up to 10% m/m) and the presence of additives in the liquid paraffin: DOSS-Na [di-(2-ethyl-hexyl) sodium sulphosuccinate], Span 85 (sorbitan trioleate) and water. The release rate was determined by putting a suspension on top of a stirred aqueous layer. The interfacial area and the layer thickness were kept constant.

For the sodium chloride suspensions the release was controlled by transport to the interface, which means essentially sedimentation in the model system used. As agglomeration occurred during settling not only the primary particle size, but also the formation of agglomerates and therefore the concentration of the solid was important. Additives like DOSS-Na and water influenced the release by changing the degree of agglomeration, Span 85 by decreasing the degree of wettability of the particles. For paracetamol and chloramphenicol suspensions the particles stayed at the interface during dissolution. Sedimentation controlled the release only as long as the rate of transport to the interface did not exceed a certain value. After reaching this limiting rate the process became dissolution controlled. Then the release rate was constant and independent of particle size, concentration and degree of agglomeration. With the additives present in the non-polar phase the release mechanism could change, resulting in dramatic alterations in release profiles.

The observed phenomena could be predicted to a large extent by analysing the different steps and applying existing theories on the stability of particles against agglomeration (DLVO-theory), the rate of agglomeration, the behaviour of particles at interfaces and the dissolution of solid particles. For these predictions only basic physico-chemical properties of the system involved – which are available in the literature or can be measured rather easily – have to be known.

The results obtained in the model system used are of importance to pharmacy as this system simulates in part the release of drugs from fatty suspension suppositories *in vivo*. But

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as melting and spreading of the suppository are not taken into account these *in vitro* results cannot directly be extrapolated to the *in vivo* situation.

First-pass elimination of some high-clearance drugs following rectal administration to humans and rats

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A frequently encountered speculation with regard to rectal absorption of drugs is that drugs will enter the general circulation without first passing through the liver. This assumption is based on the fact that in man the inferior, and probably also the middle rectal veins pass directly into the inferior *vena cava*. However this anatomical situation is complicated by the fact that the rectal veins are connected with each other by anastomoses. In the literature experimental evidence concerning the bypass of the liver after rectal administration in humans and rats is scarce. Therefore investigations were performed in male rats and healthy male volunteers with three high-clearance drugs (lidocaine, propranolol and salicylamide) to compare their rectal systemic availability with oral availability. From the literature it is known that these drugs show a substantial 'first-pass' effect in humans and rats.

Because excipients used in the preparation of solid dosage forms can influence the systemic availability and absorption rate of drugs considerably, these influences were excluded as much as possible by administering the test drugs in aqueous solution. The assays of drugs in blood and plasma were carried out according to newly developed procedures applying gas chromatography with capillary and micropacked columns, nitrogen selective detection and a solid injection system.

The lidocaine experiments with humans showed that the mean rectal systemic availability was significantly higher than orally: 63% versus 31% (whole blood) and 71% versus 34% (plasma). An equation was derived for the calculation of the fraction of the dose given rectally that bypasses the liver after absorption. This mean fraction is slightly more than half of the dose administered, assuming that the total dose is absorbed. Repeating the oral and rectal experiments in the same panel of volunteers showed that the mean rectal systemic availability based on plasma concentrations was now 67% versus 27% orally. Intra-individual variability was rather small, indicating that oral and rectal bioavailability of lidocaine is quite reproducible in a certain individual.

The systemic availability of two different rectal dosage forms (suppository and capsule) was determined also in human volunteers. The mean systemic availability of the suppository (Witepsol H15, lidocaine-HCl) was 49% and 54% was found for the capsule (containing slow-release granules, lidocaine-HCl), when compared to the results obtained in the previous investigation after intravenous administration. Although early defaecation occasionally caused a loss of still unabsorbed drug the results confirm the previous findings that rectal administration of lidocaine results in a higher systemic availability than oral administration.

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