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Dry adsorbed emulsion: 2. Dissolution behaviour of an intricate formulation

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Abstract

The behaviour of a pharmaceutical form, called dry adsorbed emulsion (DAE), containing a sparingly soluble drug (i.e. theophylline) was studied for dissolution drug release kinetic, in relation with DAE structure characterisation. In vitro dissolution testings were performed under different experimental conditions (medium at pH 1.2 and 7.4, medium with or without surfactant addition, different particle sizes, discrete or densified particles). Discrete DAE particles showed an extended release, in comparison with the native drug powder, depending on both drug solubility in the medium and particle size. The relevance of dissolution data was not improved by surfactant addition (0.1% sodium lauryl sulfate: SLS). After an initial release due to theophylline of the DAE superficial layer, the dissolution followed the Higuchi model. This suggested that DAE behaved as an inert matrix, which controlled drug release by diffusion through the hydrophobic part of the DAE. Densified DAE particles showed a slower dissolution rate than discrete DAE particles, because of their weak wettability and their poor disintegrant properties due to the particulate rearrangement under pressure. Lastly in a technological point of view, DAE could be considered as a potential drug delivery system in capsules or tablets to better control bioavailability of drugs.

Keywords: Dry emulsion; Dissolution; Particle; Sustained release

1. Introduction

Dry adsorbed emulsion (DAE) is an intricate system initiated by a water in oil (W/O) emulsion which is changed into a free-flowing powder by using two adsorbents with suitable polarities (Farah and Rollet, 1986). It can be of interest, because of its manufacturing process (without organic solvent) and its stability (in comparison with usual emulsion Farah et al., 1987). Also, many authors have studied this recent pharmaceutical form for its sustained release effects with hydrophilic drugs, i.e. sodium salicylate (Berthod et al., 1988) and chlorpheniramine maleate (Meshali et al., 1996). Nevertheless, no result has been yet published with less soluble drugs.

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In a previous part of this work (Chambin et al., 2000), a DAE containing theophylline as a sparingly soluble drug model, was manufactured and investigated in morphological and structural fields with regard to the organisation of aqueous and oily phases. The present study aimed to follow the release kinetic of theophylline to characterise the drug dissolution profile, from such a formulation.

In vitro dissolution testing provides useful information about the drug release, at several stages of development process (Dressman et al., 1998), selection of a candidate formulation, influence of critical manufacturing variables, in vitro/in vivo correlations, quality assurance. Therefore, these tests must be performed under appropriate conditions for the data interpretation. In this work, were investigated different experimental conditions such as chosen dissolution medium (pH 1.2 and 7.4; surfactant addition or not), different DAE particle sizes, discrete as well as densified particles. Particular attention was given to the influence of these parameters upon the relevance of dissolution data.

Finally, the introduction of DAE in a pharmaceutical dosage form, such as capsules or tablets, was discussed to forecast its use as a potential drug delivery system for oral administration.

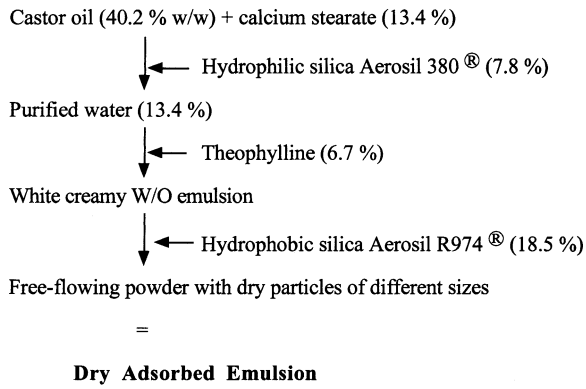
2. Materials and methods

2.1. Materials

Theophylline (Sigma Chemical Company) was chosen as drug due to its solubilities (1 g per 120 ml in water, 1 g per 110 ml in chloroform, soluble in alkali hydroxides and in diluted acids) (Windholz and Budavari, 1976).

2.2. Dry adsorbed emulsion (DAE) preparation

DAE described a solid form that appeared after an emulsified state. It was obtained by the following process (Chambin et al., 2000). First, hydrophilic silica (Aerosil 380®-Degussa) was blended with the lipid phase (castor oil + calcium stearate). Secondly, purified water was added under a high stirring rate, which produced a creamy W/O emulsion where the drug (theophylline) was dispersed. Finally, hydrophobic silica (Aerosil R974®-Degussa) was added bit-by-bit: the cream changed into a paste and then into a free-flowing powder made of dry particles with various diameter sizes .



This pulverulent preparation was sieved with a Tamisor® and two particle classes—the most important quantitatively—(i.e. 125–355 and 355–710 μm particle sizes) were retained and were named the discrete particles. Then, densified particles so-called 'compacts' were obtained from these same size classes of particles in a single punch tabletting machine (Korsh EK0). Die height and die diameter were fixed at 12 and 10 mm, respectively, and stroke of the upper punch was constant (pressure = 140 MPa), so the powder volume reduction was constant.

DAE structure was investigated by solid state characterisation (size, shape, specific surface area) and by electron spin resonance (ESR) studies to follow the behaviour of both liquid phases during manufacturing process (Chambin et al., 2000). DAE can be described as a free-flowing powder with non-porous particles of size from 125 to 710 μm, with small specific surface are a (0.26–0.40 $m^2 g^{-1}$) and spherical shape. DAE particles appear to be made up of a random pack of hydrophilic and hydrophobic components including liquid phases (aqueous and oily) adsorbed on the silica of same polarity by weak bonds.

2.3. Dissolution method

In vitro dissolution studies of DAE were performed (in triplicate) using the rotating paddle

method (Erweka DT 6 apparatus) at 37 ± 0.5 °C and 60 rpm, up to 6 h. The reference was native drug (i.e. theophylline powder from Sigma Chemical Company).

Five hundred milligram of DAE was introduced into each vessel, corresponding to 100 mg of theophylline, which is an usual therapeutic dose for this drug. The dissolution media (1000 ml) were simulated gastric (pH 1.2) or intestinal (pH 7.4) buffered solutions with or without surfactant (0.1% sodium lauryl sulfate (SLS)). Samples (3 ml) were withdrawn from the dissolution vessels at predetermined time intervals, and the amounts of dissolved theophylline were measured by spectrophotometry at 274 nm (Uvikon K 930, Kontron).

Cumulated released amounts (in percentage of the initial amounts calculated after experimental total extraction) were plotted versus time. Times corresponding to 20, 50 and 90% theophylline release (T 20, T 50 and T 90) were also calculated as dissolution specifications (Pillay and Fassihi, 1998).

Since, the DAE particles were undamaged during the experiments, dissolution data were tested according to the Higuchi law (O'Connor and Schwartz, 1993) which predicts a linear relationship between the amount of drug release (Q) and the square root of time (t).

$$Q = kt^{1/2}$$

where k is the Higuchi release rate constant.

The percent of released theophylline was plotted versus the square root of time and linear regression analysis was performed.

3. Results

3.1. Dissolution results obtained with discrete DAE particles

Fig. 1 shows the dissolution profiles of theophylline powder (native drug) at pH 1.2 and 7.4, while Fig. 2 gives drug profiles obtained at the same pH from the two DAE classes. T 20, T 50 and T 90 corresponding to these curves are stated in Table 1.

An extended release effect was obtained with discrete DAE particles in comparison with theophylline native, whatever, the particle size tested. Nevertheless, the release rate was faster for the 125–355 μm DAE class than for the 355–710 μm DAE class.

The pH influence was not marked: there was no significant difference between discrete DAE particles dissolution at pH 1.2 or 7.4 and it was the same phenomenon for the drug itself.

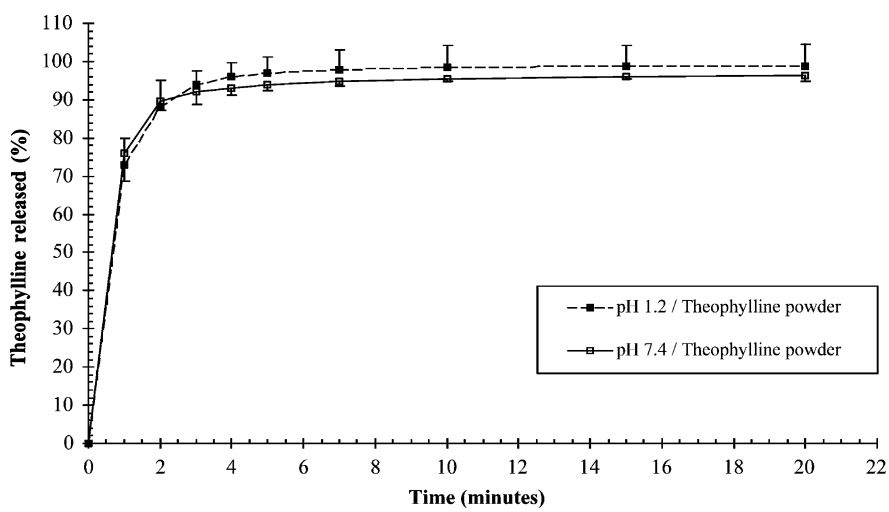


Fig. 1. Dissolution profiles of theophylline—native drug—(mean and 95% confidence interval, $n = 3$) at pH 1.2 and 7.4.

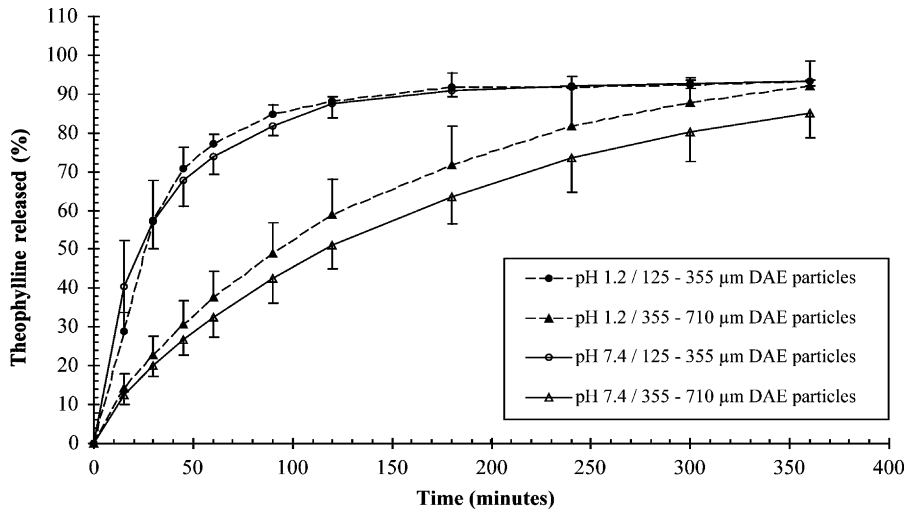


Fig. 2. Release profiles of theophylline (mean and 95% confidence interval, $n = 3$) from the two discrete DAE particle size classes at pH 1.2 and 7.4 without surfactant addition.

Table 1
Kinetic data obtained for two discrete DAE particle size classes without surfactant in the dissolution medium ($n = 3$)

Dissolution time (min)	Medium at pH 1.2		Medium at pH 7.4	
	DAE particles (125–355 μm)	DAE particles (355–710 μm)	DAE particles (125–355 μm)	DAE particles (355–710 μm)
T 20	<15	25	<15	30
T 50	27	92	25	118
T 90	160	340	210	>360

As DAE wettability was poor (DAE particles formed aggregates on the surface medium), dissolution tests were also performed by adding a surfactant in the medium (0.1% SLS) (Crison et al., 1997). The profiles obtained are represented in Fig. 3 and the kinetic data in Table 2. In all the cases, theophylline release was increased when using surfactant and the same trends were found whatever the tested parameters (particle size and pH). After the Higuchi regression analysis of dis- solution data, the correlation coefficients are presented in Table 3.

3.2. Dissolution results obtained with densified DAE particles

DAE was able to produce a cohesive mass under compaction pressure which led to wax- like 'compacts' characterised by their weights (mean = 463.8 ± 21.8 mg for the 125–355 μm densified DAE particles and 470.9 ± 26.3 mg for the 355–710 μm densified DAE particles; $n = 20$) and their diameter (9.99 ± 0.31 mm for the 125–355 μm DAE 'compacts' and 10.02 ± 0.38 mm for the 355–710 μm DAE 'compacts'; $n = 20$).

Dissolution profiles from these densified DAE particles at pH 1.2 and 7.4, without or with surfactant (0.1% SLS) are presented in Figs. 4 and 5. After densification, theophylline release slowed down extensively and the drug dissolved reached only 18 and 28% (in 360 min) without and with surfactant. Consequently T 20, T 50 and T 90 could not be determinated since, they were not achieved after 6 h.

There was no difference between the two DAE particle size classes: the theophylline was released at the same extent with 'compacts' made of 125–355 μm DAE particles as well as with 'compacts' of 355–710 μm DAE particles. Furthermore, as for the discrete DAE particles, pH was not found to influence release of theophylline.

The correlation coefficients obtained with the Higuchi equation for the densified DAE particles experiments are also presented in Table 3.

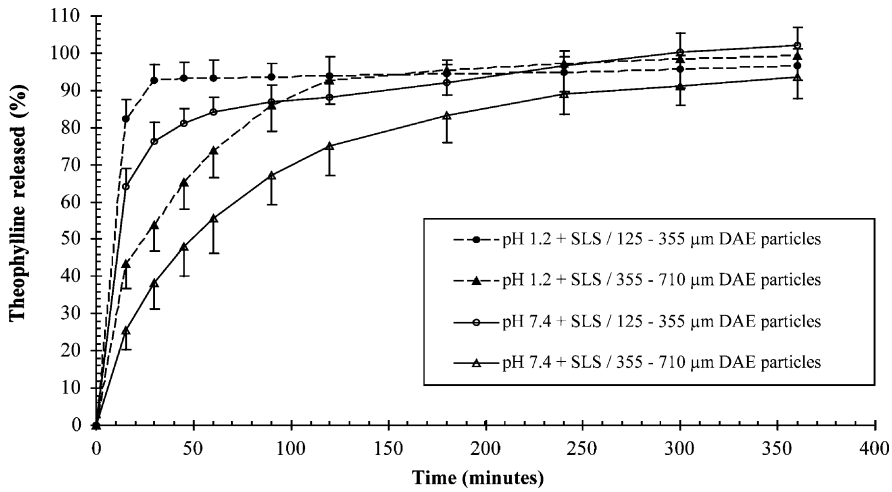


Fig. 3. Release profiles of theophylline (mean and 95% confidence interval, $n = 3$) from the two discrete DAE particle size classes at pH 1.2 and 7.4 with surfactant (0.1% SLS).

Table 2
Kinetic data obtained for two discrete DAE particle size classes with surfactant (0.1% SLS) in the dissolution medium ($n = 3$)

Dissolution time (min)	Medium at pH 1.2		Medium at pH 7.4	
	DAE particles (125–355 μm)	DAE particles (355–710 μm)	DAE particles (125–355 μm)	DAE particles (355–710 μm)
T 20	<15	<15	<15	<15
T 50	<15	25	<15	48
T 90	25	110	150	270

Table 3
Correlation coefficients after Higuchi linearisation

Experimental conditions	pH 1.2		pH 7.4	
	Without SLS	With SLS	Without SLS	With SLS
Discrete DAE particles (125–355 μm)	0.8223	0.7202	0.8886	0.8571
Discrete DAE particles (355–710 μm)	0.9936	0.8685	0.9974	0.8638
Densified DAE particles (125–355 μm)	0.9993	0.9993	0.9979	0.9971
Densified DAE particles (355–710 μm)	0.9995	0.9988	0.9974	0.9971

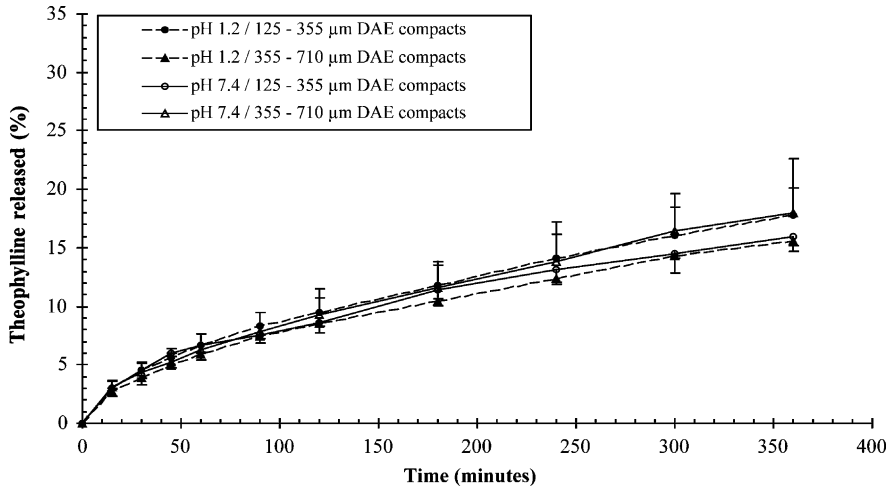


Fig. 4. Release profiles of theophylline (mean and 95% confidence interval, $n = 3$) from the two densified DAE particle size classes at pH 1.2 and 7.4 without surfactant addition.

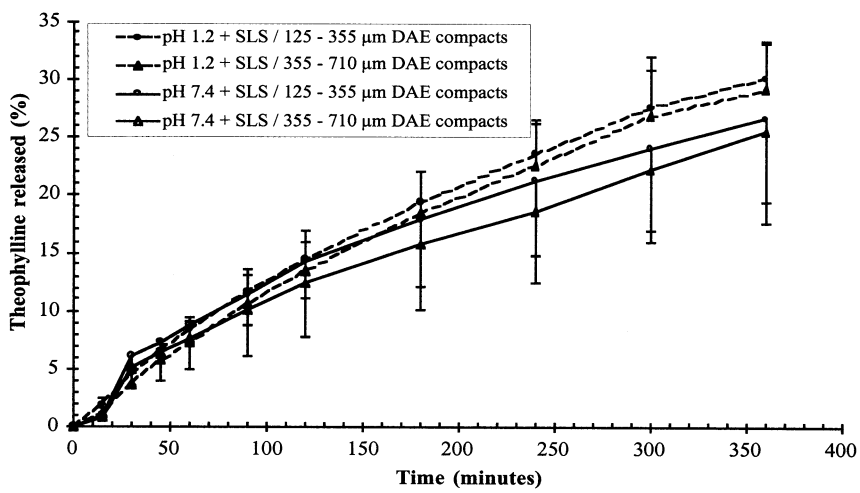


Fig. 5. Release profiles of theophylline (mean and 95% confidence interval, $n = 3$) from the two densified DAE particle size classes at pH 1.2 and 7.4 with surfactant (0.1% SLS).

4. Discussion

Theophylline powder (Fig. 1) was dissolved in a few minutes in experimental conditions (100 mg of drug in 1000 ml of medium). When included in DAE, the theophylline dissolution was much slower in all cases (Fig. 2). Thus, the DAE could be considered as an extended release pharmaceutical form particularly with the 355–710 µm particles since, the theophylline release lasted several hours. This point has already been shown with very hydrophilic drugs, i.e. sodium salicylate (Berthod et al., 1988) and chlorpheniramine maleate (Meshali et al., 1996) where the DAE structure was described as a hydrophilic nucleus with the drug coated by a lipidic phase (Farah et al., 1987). In this study with a poorly water soluble drug, an extended release was also ob-

served which is explained by the joint use of a hydrophilic silica and a hydrophobic silica. The latter modified the physico-chemical properties of particles (Chambin et al., 2000) which did not wet easily in dissolution medium and reduced the theophylline release rate. As shown in ESR studies, DAE particles were made up of a random pack of a few hydrophilic and many hydrophobic elements. Each part included liquid phases (aqueous and oily) trapped in the silica of the same polarity by weak bonds (hydrogen or hydrophobic bonds). The drug was dispersed in each of them. Dissolution results strengthened this model structure: a part of theophylline was immediately released from superficial layer, and the remaining drug was slowly delivered from hydrophobic parts.

When T 20, T 50 and T 90 were calculated (Table 1), no significant difference could be observed between pH 1.2 and 7.4. DAE particles were undamaged by the pH and the solubility was the only factor which seemed to control drug release. Theophylline solubility was not influenced by buffer composition (Kader and Jalil, 1998a) as shown by saturated concentrations at 37 °C: 12.7 g l^{-1} at pH 1.2 and 14.6 g l^{-1} at pH 7.4.

On the contrary, the theophylline release depended on the particle size: T 50 increased from 25 min for the 125–355 μm DAE class to 105 min for the 355–710 μm DAE class (Table 1). The same phenomenon was found with DAE of sodium salicylate (Berthod et al., 1988) and with theophylline microtablets (Rey et al., 1998). The theory of solid drug dissolution and Noyes Whitney equation (Buckton and Beezer, 1992) explains this fact: a reduction of particle size increases the surface area which results in a more rapid dissolution process by enhancing the solid–liquid interface (Hintz and Johnson, 1989).

For in vitro dissolution studies, the addition of a surfactant to the dissolution medium is proposed to simulate gastric or intestinal fluid with low surface tension (Luner, 2000), to ensure sink conditions for sparingly water-soluble drugs and to improve wettability of the dosage forms. SLS is commonly used for this purpose (Crison et al., 1997). Due to poor wettability of the DAE particles, experiments were performed with this surfactant in medium at pH 1.2 and 7.4. SLS was introduced at low concentration (0.1%) just above the critical micellar concentration (0.03% in buffer) to minimise the effect on drug release (Knop and Matthée, 1997). As expected, theophylline dissolution rate was always quicker with media at 0.1% SLS (Fig. 3 and Table 2) and same trends were found in dissolution data.

Finally, the drug release mechanism from the discrete DAE particles was investigated. The theophylline dissolution showed an initial fast release followed by a much slower phase (Fig. 2) which was a first order release profile. With 125–355 μm DAE particles, the Higuchi equation could not be applied on all the kinetic duration but only on the first points, because the dissolution was too fast (70% dissolved within 45 min) which disturbed the diffusion gradient. On the other hand, the 355–710 μm DAE particles without SLS presented a good linearity ($r > 0.99$) showing that the release followed Higuchi model and could be classified as a sustained release formulation. Extrapolation of the linear portion gave negative value on the time axis, indicating the presence of an initial rapid release (Kader and Jalil, 1998b) due to dissolution of surface theophylline rather than a lag phase often observed with delayed formulation. The Higuchian release of theophylline meant that the 355–710 μm DAE particles behaved as non erodible inert matrices in which drug release occurred by drug diffusion throughout porous network created by the medium (Brossard and Wouessidjewe, 1990) into important hydrophobic part of DAE. This finding could also be explained by outer structure of DAE particles. With scanning electron microscopy (SEM) studies (JEOL JSM-6400F electron microscope), needle crystals were found all over the surface of the particles (Fig. 6a). These crystals had the same shape of those observed on an electron micrograph of theophylline at the same magnification (Fig. 6b). It suggested that theophylline was presented, in the DAE particle, as a crystalline dispersion surrounded by hydrophobic silica. Such a drug dispersion is expected to give Higuchian dissolution profiles.

With densified DAE particles, the theophylline release (Fig. 4) was much slower than with discrete DAE particles (percentage of drug dissolved was always below 30% by the end of the experiment)

even if the media were added with 0.1% SLS (Fig. 5). But the difference between the two DAE particle size classes disappeared: during densification, a high pressure was applied to the discrete particles producing a particulate rearrangement with a reduction of the spaces between the particles leading to closer packing (Doelker, 1994). Then particle–particle interactions happened which induced a cohesive mass. The dissolution media could hardly wet the 'compacts' made of an important amount of hydrophobic silica which kept the theophylline inside the DAE structure: the dissolution rate was reduced. In addition, the cohesive mass had poor disintegrant properties and remained undamaged during the entire dissolution experiments, which did not allow the partition of 'compacts' into discrete particles.

The 'compacts' obtained from both DAE particles were produced in the same compaction die and offered the same surface to the medium contact and thus, presented the same dissolution profiles.

Futhermore, the kinetic release followed the Higuchi law (Table 3) with a linearity expressed by $r > 0.99$, confirming that the DAE is an inert matrix. The densification step did not damage the DAE behaviour as a sustained release formulation and on the contrary, intensified this phenomenon.

Thus, dry emulsions can be presented as a potential oral drug delivery system (Pedersen et al., 1998). Considering the physical and microbiological instability of usual emulsions, a dry emulsion (used as a powder) appears to be of interest for the formulator.

With regard to rheological properties, DAE discrete particles had a good flowability: Hausner index (ratio between tapped and bulk density measured with Stampfvolumenometer STAV 2003) were close to 1 (i.e. 1.12 ± 0.03 for the 125–355 μm DAE particles and 1.06 ± 0.01 for the 355–710 μm DAE particles). A dry emulsion (containing coconut fat, milk-protein, phospholipids, maltodextrin and water) has already been compressed into oral dosage forms, with a standard tabletting process (Steffens and Schroeder, 2000). Another recent study (Christensen et al., 2001) showed that preparation of dry emulsions could be optimised for tablet manufacturing with preservation of their different properties.

These results allowed to foresee their use in pharmaceutical forms as capsules and tablets with industrial equipment.

5. Conclusions

The dissolution behaviour of an intricate formulation-DAE-including a poorly water soluble drug (i.e. theophylline) was investigated under different experimental conditions.

DAE could be considered as a sustained release form for sparingly soluble drugs as well as for hydrophilic drugs. Drug release depended on drug solubility in the medium, on drug distribution in

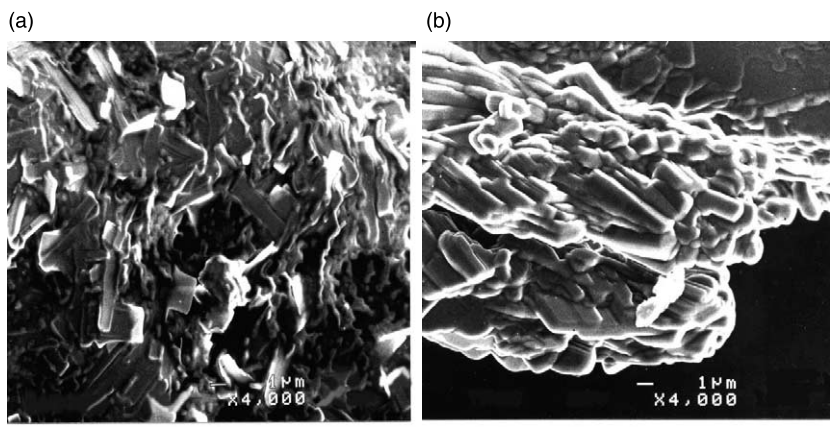


Fig. 6. Scanning electron micrographs (× 4000) of DAE particles (a) and theophylline (b).

the DAE particles (crystalline dispersion) and on the tested particle size. Thus for theophylline, medium pH did not influence drug release and the dissolution rate was faster with a smaller particle size. The surfactant (SLS) addition in the medium increased the dissolved amounts, but did not improve the relevance of data (similar influence of various parameters). After an initial release due to theophylline of superficial layer, the drug release from DAE particles followed the Higuchi model. This dissolution profile suggested that DAE behaved as an inert hydrophobic matrix in which the drug release occurred by diffusion throughout porous network created by the medium into the DAE structure.

With DAE densified particles, the dissolution rate slowed down extensively, because of their weak wettability and their poor disintegrant properties. The influence of particle size disappeared since, the surface of the cohesive mass laid to medium was the same whatever DAE classes. Furthermore, the Higuchi model fitted well theophylline release, confirming that DAE could be classified as a matrix with a delivery mechanism controlled by drug diffusion.

Finally, DAE could be useful to produce capsules and tablets (good flowability, cohesiveness) as a potential drug delivery system to improve bioavailability in adjusting the drug dissolution rate at a biopharmaceutical level.

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References

Berthod, A., Rollet, M., Farah, N., 1988. Dry adsorbed emulsions: an oral sustained drug delivery system. J. Pharm. Sci. 77, 216–221.

Brossard, C., Wouessidjewe, D., 1990. Contrôle de dissolution des formes pharmaceutiques orales solides à libération ralentie. STP Pharm. Sci. 6, 728–741.

Buckton, G., Beezer, A.E., 1992. The relationship between particle size and solubility. Int. J. Pharm. 82, R7–R10.

Chambin, O., Bellone, C., Champion, D., Rochat-Gonthier, M.H., Pourcelot, Y., 2000. Dry adsorbed emulsion: 1. Characterization of an intricate physicochemical structure. J. Pharm. Sci. 89, 991–999.

Christensen, K.L., Pedersen, G.L., Kristensen, H.G., 2001. Technical optimisation of redispersible dry emulsions. Int. J. Pharm. 212, 195–202.

Crison, J.R., Weiner, N.D., Amidon, G.L., 1997. Dissolution media for in vitro testing of water-insoluble drugs: effect of surfactant purity and electrolyte on in vitro dissolution of carbamazepine in aqueous solutions of sodium lauryl sulfate. J. Pharm. Sci. 86, 384–388.

Doelker, E., 1994. Assessment of powder compaction. In: Chulia, D., Deleuil, M., Pourcelot, Y. (Eds.), Powder Technology and Pharmaceutical Processes. Elsevier, Amsterdam, pp. 403–471.

Dressman, J.B., Amidon, G.L., Reppas, C., Shah, V.P., 1998. Dissolution testing as a pronostic tool for oral drug absorption: immediate release dosage forms. Pharm. Res. 15, 11–22.

Farah, N., Rollet, M., 1986. Nouveaux procédés de préparation à partir d'émulsions sèches de formes orales solides à libération modifiée et retardée de leur principes actifs. French Patent 86 02694, 24 Fev.

Farah, N., Bouzon, J., Rollet, M., Taverdet, J.L., Vergnaud, J.M., 1987. 'Dry emulsion'—a sustained release form: modelling of drug transfers in liquids. Int. J. Pharm. 36, 81–88.

Hintz, R., Johnson, K.C., 1989. The effect of particle size distribution on dissolution rate and oral absorption. Int. J. Pharm. 51, 9–17.

Kader, A., Jalil, R., 1998a. Effect of physicochemical factors on the release kinetics of hydrophilic drugs from poly(L-lactic acid) (L-PLA) pellets. Drug Dev. Ind. Pharm. 24, 535–539.

Kader, A., Jalil, R., 1998b. In vitro release of theophylline from poly(lactic acid) sustained-release pellets prepared by direct compression. Drug Dev. Ind. Pharm. 24, 527–534.

Knop, K., Matthée, K., 1997. Influence of surfactants of different charge and concentration on drug release from pellets coated with an aqueous dispersion of quaternary acrylic polymers. STP Pharm. Sci. 6, 507–512.

Luner, P.E., 2000. Wetting properties of bile salt solutions and dissolution media. J. Pharm. Sci. 89, 382–395.

Meshali, M.M., Gabr, K.E., El-Fattah, E.A., 1996. Preparation and evaluation of different polymers based on dry adsorbed emulsions of chlorpheniramine maleate as a sustained drug delivery system. STP Pharma 6, 370–375.

O'Connor, R.E., Schwartz, J.B., 1993. Drug release mechanism from a microcrystalline cellulose pellet system. Pharm. Res. 10, 356–361.

Pedersen, G.P., Fäldt, P., Bergenstahl, B., Kristensen, H.G., 1998. Solid state characterisation of a dry emulsion: a potential drug delivery system. Int. J. Pharm. 171, 257–270.

Pillay, V., Fassihi, R., 1998. Evaluation and comparison of dissolution data derived from different modified release

dosage forms: an alternative method. J. Contr. Release 55, 45–55.

Rey, H., Wagner, K.G., Wehrle, P., Schmidt, P.C., 1998. Development of theophylline sustained-release micro tablets. In: Proceeding of the Second World Meeting on Pharmaceutics Biopharmaceutics Pharmaceutical Technology, Paris, APV/APGI, pp. 303–304.

Steffens, K.J., Schroeder, M., 2000. Development of a fast disintegrating tablet from a dry emulsion. In: Proceeding of the Third World Meeting on Pharmaceutics Biopharmaceutics Pharmaceutical Technology, APV/APGI, Berlin, pp. 101–102.

Windholz, M., Budavari, S., 1976. The Merck Index, ninth ed. Merck, Rahway, p. 8997.