The influence of surfactants on drug release from a hydrophobic matrix

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Summary

Hydrophobic matrices were prepared using Eudragit RL 100. Flurbiprofen was used as a model drug, with sorbitol as a diluent. The effect of adding each of five surfactants (sodium lauryl sulphate, sodium taurocholate, cetylpyridinium chloride, cocamidopropyl betaine (CDB) and cetrimide) individually to the matrix was investigated. To investigate the mechanism by which the rate of drug release was increased following the incorporation of surfactants, experiments were undertaken to assess the wettability of the different formulations, and to measure drug release in the presence of submicellar and micellar concentrations of the surfactants. Three mechanisms were proposed by which drug release could be increased following the addition of surfactants: improved wetting, solubilisation, and the dissolution of the soluble surfactants to form pores in the matrix. When the surfactant was added to the dissolution fluid, only one surfactant (CDB) did not result in an increase in drug release; for the other surfactants a minor increase in drug release was observed. Therefore, in most cases, wetting plays a small role in aiding dissolution. There was no significant change in release rate when the experiment was performed in the presence of either sub-micellar or micellar concentrations of the surfactants, thus solubilisation of the drug does not seem to be implicated in the drug release mechanism. The most significant increase in drug release rate was caused by incorporating the most soluble surfactants (sodium taurcholate and cetrimide) within the matrix. As the increase was significantly greater than could be explained by wetting alone, it must be concluded that for these matrix systems the major mechanism by which surfactants increase the dissolution rate is by the formation of pores to aid the access of the dissolution fluid and egress of the dissolved drug. It is also possible that the presence of the relatively concentrated surfactant solution in the wetted tablet would reduce interparticle adhesion and thereby speed drug release rate as a result of an increased disintegration.

Introduction

In a recent publication (Efentakis et al., 1990), the influence of incorporating either sodium lauryl

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sulphate or sodium taurocholate into hydrophobic matrices was investigated. Different matrix systems were studied, consisting of either Eudragit RS 100 or RL 100, a diluent (lactose, dextrose, sorbitol or Avicel PH-l0l) and a model drug (flurbiprofen). The Eudragit polymers are biocompatible, non-degradable acrylic resins, consisting of copolymers of acrylic and methacrylic resins. In all combinations of polymer and diluent, the ad-

dition of either of the two surfactants resulted in a significant increase in the dissolution rate, the explanation for this effect was described as being either due to a change in wetting of the tablet formulation by the dissolution fluid, or due to the production of channels within the product, causing a wicking effect and thus increasing the access of the dissolution fluid (Efentakis et al., 1990). The purpose of this study is to investigate the two proposed mechanisms and to identify which is of greatest significance.

A number of factors could influence the drug release profile from a hydrophobic matrix. Firstly, the wetting of the dosage form may be improved if a surfactant is present, to study this, products with each of five surfactants incorporated individually were compared with results in which the surfactant was omitted from the tablet. Secondly, when surfactant is present in the tablet (1% w/w) it may dissolve to form a solution of indeterminate concentration in the micro-environment around the preparation; it is, therefore, necessary to investigate the effect of surfactant concentrations of less than, and greater than the CMC. The use of dissolution media containing sub-micellar and micellar surfactant solutions and tablets with no added surfactant will achieve this objective. Thirdly, it is possible that it is the solubility of the surfactant that is important, and that as it is dissolved it forms pores (or other disruptions) in the matrix, thus facilitating drug release. Finally, it is possible that a number of these mechanisms may occur simultaneously for different products.

Materials and Methods

Materials

One diluent (sorbitol) and one polymer (Eudragit RL 100) were selected for study, with the same model drug as used before (flurbiprofen) (Efentakis et al., 1990). Five different surfactants were used, two were anionic (sodium salts), two were cationic and one ampholytic (cocamidopropyl betaine).

Matrices were prepared using flurbiprofen (a gift of The Boots Co. Ltd), Eudragit (a gift of Rohm-Pharma), sorbitol (Merck), magnesium stearate (BDH), sodium taurocholate (ST) (Fluka), sodium lauryl sulphate (SLS) (BDH), cetylpyridinium chloride (CP) (Fluka), cocamidopropyl betaine (CDB)(a gift of Goldsmith) and cetrimide (CET)(Serva). All chemicals used were reagent grade. Water was double distilled (for surface tension experiments) or reverse osmosis (for wetting experiments). Ethanediol (BDH) was used as a probe liquid for the wetting experiments.

Methods

Preparation of the tablets

The Eudragit RL 100 was powdered in a ball mill and sieved through a 300 μm sieve. The tablets were formed from a mix of the powdered polymer (25%), drug (49%), sorbitol (25%) and magnesium stearate (1%). Six different batches of tablets were produced, one without surfactant, and the others with each of the five surfactants incorporated individually.

The powders were compressed to prepare 500 mg tablets on a single punch tablet machine (Korch-Erweka). The ratio between the diameter and thickness of the cylindrical flat faced tablets was between 0.7 and 0.9. The hardness of the tablets was controlled such that a breaking force of between 9 and 10 kg was required (Schleuniger-2 hardness tester).

Wettability

Powder mixtures of the same composition as those used to produce the tablets were prepared and compacted into rectangular beams of nominal dimensions 4 cm $\times$ 1 cm $\times$ 1 mm. These beams were attached to a microbalance system, and used as a Wilhelmy plate to measure the contact angle of water and ethanediol on the formulation. The method was exactly as previously described (Zajic and Buckton, 1990).

By measuring the contact angle formed by two liquids of known surface tension and polarity, it is possible to calculate the surface energy and polarity of the test solid (see for example, Zajic and Buckton, 1990). Having obtained the surface energy (γ) and the polar (p) and dispersion (d) components for a solid, it is possible to calculate

TABLE 1

Percentage release of drug from the tablets

	Time (h)							
	1	2	3	4	5	6	7	8
No surf.	10	15	20	26	30	35	39	43
SLS (a)	14	21	28	35	40	44	48	52
(b)	11	17	24	31	36	40	43	46
(c)	12	18	25	32	37	41	45	48
ST (a)	19	29	36	46	56	60	63	67
(b)	12	18	24	32	37	40	43	47
(c)	13	19	25	33	38	42	46	50
CET (a)	16	22	30	38	45	51	56	61
(b)	10	15	22	29	34	38	41	44
(c)	10	16	24	30	35	39	41	44
CP (a)	9	17	28	34	38	42	45	48
(b)	9	14	19	24	29	33	37	41
(c)	9	15	20	25	29	33	38	43
CDB (a)	9	16	22	30	35	39	42	45
(b)	11	17	23	29	35	39	42	44
(c)	12	18	24	30	35	39	42	45

(a) Surfactant incorporated in tablet (1% w/w of tablet).
(b) Surfactant 0.25% w/v in dissolution fluid, no surfactant in tablet.
(c) Surfactant 1.25% w/v in dissolution fluid, no surfactant in tablet.

The contact angles, the surface energies and dispersion and polar components of surface energy, of the tablets with added surfactants are presented in Table 2, as are the spreading coeffi-

TABLE 2

Contact angles measured on the formulations containing the surfactants, the surface energies calculated for the formulations, and the spreading coefficients of water over the different formulations

	θ_W	θ_E	γ	γ^p	γ^d	λ_{12}
	($\degree$)			(mN/m)		
SLS (a)	48	40	52.3	36.6	15.7	17.0
ST (a)	54	39	48.2	30.7	17.5	19.4
CET (a)	59	35	45.7	25.3	20.4	19.4
CDB (a)	68	35	41.8	18.0	23.8	16.9
CP (a)	74	38	39.8	13.7	26.1	13.2

Reproducibility of the contact angle data was at worst $\pm 3\degree$.
(a) Results for formulation with 1.0% w/w surfactant added.
W, water; E, ethanediol.

cients for water over the surface of these formulations.

Discussion

The drug release profiles obtained with all of these formulations follow a pseudo zero order release profile for about 5 h, and then deviate to form another near linear release profile which is of a slower rate than the initial release. For the formulations that have been investigated here, the release profiles remain parallel (Fig. 2) throughout the 8 h experiment. The experimental error associated with the dissolution results was extremely small, such that the replicate determinations where almost superimposable.

Two possible mechanisms have been postulated as to why surfactants increase the rate of drug release from matrix formulations (e.g. Desai et al., 1965; Dakkuri et al., 1978). Firstly, it is possible that the surfactant lowers the interfacial tension between the product and the dissolution fluid, secondly, it is possible that the surfactant acts as a wicking agent, causing the fluid to enter the dosage form, the surfactant may then dissolve and form pores (or other disruptions) from which the drug release may be effected (Dakkuri et al., 1978). In a previous study, dissolution profiles of flurbiprofen release from matrix systems containing Eudragit polymers demonstrated that surfactants increase drug release, but the mechanism(s) for this was/were not investigated (Efentakis et al., 1990). In the introduction, four possibilities have been postulated as mechanisms by which drug release from matrix systems can be increased due to the presence of a surfactant.

In this study we have investigated the effect of five surfactants, as expected the anionic/cationic nature of these excipients does not seem to have a major effect on the release data (e.g. ST (anionic) and CET (cationic) have the fastest release rates, and CP (cationic) and SLS (anionic) have slower release rates). In circumstances where anionic/cationic interactions are expected it is possible to achieve a reduction in the dissolution rate by the addition of a charged surfactant (e.g. anionic surfactant/cationic drug (Feely and Davis, 1988)).

The incorporation of the individual surfactants into the formulation results in a range of drug release profiles (Fig. 2 and Table 1). As mentioned above, there is a change in rate of release at ~ 5 h for each formulation. The ranking of the release rates can be made from Fig. 1 and going from the fastest to slowest release is: ST, CET, SLS, CP, CDB/no surfactant.

It is generally regarded that the surfactants will result in improved wettability of the surface of the preparation, and that this is the major factor causing the increased release rate. If wetting of the surface was of greatest significance, then a tablet without added surfactant, which was allowed to release drug in the presence of a surfactant solution, should have a very similar release rate to a tablet in which that surfactant was incorporated into the matrix. The results in Table 1 allow a comparison of the dissolution data for tablets in which the different surfactants have been incorporated, with those tablets which have been dissoluted in the presence of surfactant solutions. For CDB there was no difference between the data for tablets with incorporated surfactant, and those in which the surfactant was added to the dissolution fluid. The data for CDB are all slightly higher than the product without surfactant added (hereafter termed the 'blank') up to 5 h, after which the dissolution rate fell significantly and at 8 h was indistinguishable from the blank. These data indicate that the increased dissolution rate caused by CDB (either incorporated in the product, or in the dissolution fluid) is due to increased wetting of the tablet surface. The increase in rate over the initial period is probably entirely due to improved wettability, after about 5 h, the slower release rate is probably due to the dissolution front receding from the surface of the tablet, into the body of the matrix. Drug release in the later stages will be linked to the diffusion of the dissolved drug away from the dissolution front. The addition of CDB does not aid this diffusion process. Dissolution experiments that were performed in the presence of surfactants other than CDB, showed similar responses, that is the amount dissolved was higher than the blank at 5 h, and rather more similar to the blank at 8 h.

The addition of CP to the dissolution fluid did not result in any increase in the drug release from the blank tablets, however, when CP was incorporated there was a slight increase in release. For this surfactant it can be concluded that wetting does not play a significant role in the dissolution process, and the minor acceleration with the incorporated CP must be due to the surfactant dissolving and forming pores/channels, thus increasing the effective surface area by a method other than wetting. The results in Table 2 confirm these findings, the formulation with incorporated CP has the highest contact angle with water, and the lowest spreading coefficient (i.e. is the most hydrophobic of the surfaces studied).

When the other surfactants (SLS, ST, CET) were incorporated in the matrices, they produced different dissolution profiles to those obtained when the blank was studied in the corresponding surfactant solutions. Furthermore, the results obtained in the surfactant solutions were different to the results for the blank in buffer alone. There was no significant difference between the drug release following dissolution in sub-micellar or micellar concentrations of either SLS, ST, CET or CDB. This leads to the conclusion that improved wetting of the tablet surface is achieved with these four surfactants (but not CP), and that the potential resultant increase in drug release due to improved wetting is finite. After adequate wetting of the surface has been achieved, there must be further mechanisms which facilitate more rapid dissolution i.e. there must be a soluble component in the matrix which will dissolve easily to form pores, or to disrupt the matrix in some other fashion. The similarity between results obtained in sub-micellar and micellar surfactant solutions provides further evidence to support this hypothesis: the drug release is controlled by the permeation through the matrix, and is not, after a certain point, affected by the wetting of the surface, and is not affected by the solubility of the drug, i.e. the potential for solubilisation does not increase the dissolution rate to any serious extent. The data presented in Table 2 demonstrate that the spreading coefficients of water over the tablets with incorporated surfactant fall in a rank order that correlates with the rank order of drug release from these formulations. As has been explained above, this is of

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