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The influence of surfactants on drug release from acrylic matrices

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Summary

Hydrophobic matrices were prepared using Eudragit RS 100, flurbiprofen (as a model drug), with sorbitol as a diluent and magnesium stearate as a lubricant. The effect of adding each of five surface active agents (sodium lauryl sulphate, sodium taurocholate, cetylpyridinium chloride, cocamidopropyl betaine and cetrimide) individually to the matrix was investigated. To explore 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. The results were also compared to those which have been reported previously for Eudragit RL based matrix formulations.

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 disruptions in the matrix.

Only sodium taurocholate and sodium lauryl sulphate showed any significant increase in dissolution rate. From contact angle measurements, these were found to be the only two surfactants which increased the wettability of the tablets. Thus it was concluded that increased wettability is a prerequisite to an increase in dissolution rate. The increase in dissolution rates in the presence of surfactant solutions was, however, very small compared to the increase observed when the surfactant was incorporated within the matrix itself. By comparison with data for release from RL matrices, it is likely that the increase in dissolution rate when the surfactant is present in the matrix is related to the solubility of the surfactant. Thus it is necessary for the surfactant to increase the wettability of the tablet surface, to allow the fluid to gain access to the hydrophobic matrix, and then to dissolve. The increased dissolution rate is probably due to either the formation of pores due to the dissolution of the surfactant, or more likely, because of the influence of high local concentrations of surfactant solution, perhaps affecting adhesion within the matrix, leading to disintegration and thus dissolution.

The charge of the surfactant also produced a significant effect. The anionic surfactants resulted in lowering of contact angles and increased dissolution rates; the cationic surfactants did not result in changes in contact angle and caused smaller changes in dissolution. It is probable that there is an interaction between the cationic surfactants and the anionic model drug, resulting in an inactivation of these surfactants. Anionic/cationic interactions are not unexpected, but the presence of such an observation for this system (based on Eudragit RS) is surprising because no such interactions were observed for similar formulations based on Eudragit RL (published previously) (Eudragit RL and RS differ only in the extent of the quaternary ammonium substitution; RS being much greater than RL).

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Introduction

In a recent publication (Efentakis et al., 1991) the effects of five different surfactants (sodium lauryl sulphate (SLS), sodium taurocholate (ST), cetylpyridinium chloride (CPC), cocamidopropyl betaine (CDB) and cetrimide (Cet)) on the release of a model drug (flurbiprofen) from a hydrophobic matrix (a mixture of Eudragit RL 100 and sorbitol) were investigated. Three mechanisms were proposed by which drug release could be increased following the addition of surfactants (Efentakis et al., 1991); these were: improved wetting, solubilisation of the drug and the dissolution of the soluble surfactants to cause disruptions in the matrix. These three mechanisms were studied by comparing dissolution results of tablets with no added surfactant, to those in which surfactants had been added, and finally to monitor dissolution of tablets with no added surfactant in dissolution fluids to which different concentrations of surfactant had been added. If increased dissolution rate was noted when sub-micellar concentrations of surfactant were added to the dissolution fluid, then improved wetting was implicated, if further increases were noted in micellar surfactant solutions, then solubilisation could be a significant factor, and if the results for products with surfactant included in the matrix revealed even faster dissolution, then the local disruption of the matrix was also important. The most significant increase in drug release rate was observed when the most soluble surfactants (ST and Cet) were incorporated within the matrix, thus as these increases were greater than could be explained by wetting or solubilisation alone, the results (Efentakis et al., 1991) indicated that for the Eudragit RL/sorbitol matrices, the major mechanism by which surfactant increased the dissolution rate was by disruption of the matrix. This disruption could be due to the surfactant dissolving, or due to the dissolved surfactant solution reducing interparticulate adhesion within the wetted tablet (thus further speeding disintegration).

The current study reports similar experiments which differ only in one respect, this being that the Eudragit RL 100 has been replaced by Eudragit RS 100. It will be shown below, that the switch from RL to RS alters the rank order of dissolution rates of drug from the matrices containing different surfactants. Eudragit RS and RL are both biocompatible, non-degradable acrylate-methacrylate copolymers. Their permeability to water is unaffected by pH, but water can permeate more freely into Eudragit RL 100 than RS 100, due to the relative hydrophilicity of the RL polymer.

Materials and Methods

Materials were exactly as used before (Efentakis et al., 1991), except for the substitution of Eudragit RS 100 (a gift of Rohm-Pharma).

Tablets were prepared exactly as before (Efentakis et al., 1991) having the specifications: 500 mg weight, flat faced, diameter to thickness ratio between 0.7 and 0.9, and of sufficient strength such that a force of between 9 and 10 kg was required to break them. The composition was: powdered Eudragit RS 100 (25%), flurbiprofen (49%), sorbitol (25%) and magnesium stearate (1%). Six different batches of tablets were produced, one with no added surfactant, and the others with each of the five surfactants incorporated individually.

Contact angles were measured, on thin rectangular compacts of each of the six formulations, using a Wilhelmy plate method (see Zajic and Buckton, 1990, and Efentakis et al., 1991, for details).

Dissolution testing was undertaken using a USP paddle method (pH 7.4 phosphate buffer, 100 rpm, 37.0 °C) as before (Efentakis et al., 1991). Dissolution tests were performed on tablets with and without added surfactant (1% w/w in each case). Also the tablets without added surfactant were studied using dissolution fluids with added surfactant at concentrations of 0.25 and 1.25% w/v, which were judged to correspond to sub-micellar and micellar concentrations (Efentakis et al., 1991). All experiments were undertaken in triplicate.

Results

The results of the dissolution experiments are presented in Table 1. The data of Efentakis et al. (1991) for Eudragit RL matrices are reproduced for comparison in Table 2. These results are expressed as % drug released. The values quoted (expressed as % drug release as a function of time) are means of the three replicate determinations, which were of such reproducibility that spread of data around the mean was typically accurate to ± 1 (i.e., if a figure of 45 is quoted, that was the mean result, with all data typically being in the range 44–46% released).

The contact angle values for water on the Eudragit RS based compacts are presented in Table 3. The values quoted are accurate to $\pm 3°$.

It is outside the scope of this work to consider methods of assessing contact angle, however, it should be highlighted that the contact angle measurements on such complex systems as the formulations that are used here, are likely to be fraught with difficulties. It has been assumed that none of the components dissolve in the time scale of the experiment; this is not a reasonable assumption, but as the alternative is to saturate the water with the components of the product (including the surfactant!), this must constitute the best available alternative. The reproducibility of the results are not in question, but rather the significance of the value that was obtained. The contact angle results obtained in the current study seem to be more consistent than those reported previously, presumably due to the slower dissolution from the RS products.

Discussion

The ranking of the dissolution rates for the Eudragit RL based matrices (Efentakis et al., 1991) was, from fastest to slowest, ST, Cet, SLS, CPC, CDB /no added surfactant. Efentakis et al. (1991) observed that for Eudragit RL based matrices, all but one of the surfactants (CDB) improved the wetting of the product by the dissolution fluid, and that ultimately the increase in dissolution rate was proportional to the solubility of the surfactant. In the current work, the ranking is different, i.e., from fastest to slowest: ST,

TABLE 1

The % release of drug from the Eudragit RS matrices

	Time (h)							
	1	2	3	4	5	6	7	8
No surfactant	10	12	16	20	23	25	27	30
SLS [a]	12	16	22	26	31	35	39	44
SLS [b]	10	13	17	20	23	26	28	31
SLS [c]	11	14	17	21	24	27	30	33
ST [a]	14	19	24	29	34	38	42	46
ST [b]	10	14	17	21	24	26	29	32
ST [c]	11	15	18	22	26	29	32	35
Cet [a]	9	14	18	22	25	28	31	33
Cet [b]	9	12	15	18	20	23	26	29
Cet [c]	10	13	16	19	21	24	27	30
CPC [a]	8	12	15	19	22	25	27	29
CPC [b]	9	12	15	18	20	23	26	29
CPC [c]	10	13	16	19	21	24	27	30
CDB [a]	8	13	16	19	22	25	28	31
CDB [b]	10	13	16	19	22	24	27	30
CDB [c]	12	16	19	22	25	27	30	32

[a] Surfactant incorporated in tablet (1% w/w).

[b] 0.25% w/v surfactant in dissolution fluid, no surfactant in tablet.

[c] 1.25% w/v surfactant in dissolution fluid, no surfactant in tablet.

TABLE 2

The % release of drug from the Eudragit RL matrices

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

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

SLS, Cet, CPC/CDB/no added surfactant, thus there are notable differences between the effects of surfactants on release from Eudragit RS and Eudragit RL based matrices. These differences can be summarised thus: (1) all the formulations which contained RS had slower release rates than the equivalent RL formulations (Tables 1 and 2); (2) surfactants generally had a less significant effect on the release rates from RS formulations (compared to the RL tablets) (Tables 1 and 2); (3) the release rates from the RS tablets are not proportional to the solubility of the surfactant (which is the case for RL), i.e., there is a change in the rank order of the release rates; and (4) the presence of surfactants in the dissolution fluid has comparatively little effect on drug release from the RS products (Table 1), unlike the case for RL where significant increases in rate have been observed (Table 2).

TABLE 3

The contact angles formed by water on compacts of the formulations

Formulation	Contact angle (degrees)
No surfactant	63
SLS	54
ST	49
Cet	62
CPC	63
CDB	65

The dissolution data (Table 1) reveal that when surfactant is added to the dissolution fluid, the only significant increase in drug release rate is observed with high concentrations of ST and possibly SLS. The contact angles (Table 3) of water on the different formulations show that ST (49°) and SLS (54°) are the only two products for which there is any significant improvement of wettability following surfactant addition; all other formulations have contact angles that are unchanged following incorporation of surfactant in the compact (although the contact angle value obtained for cetrimide is slightly lower than that for the compact with no added surfactant, the difference is within the limits of experimental error; the apparent increase in contact angle for the CDB compacts may also be largely due to error, or may be a true effect due to a changed

orientation of molecules at the surface of the compact). Thus it follows that only in the cases in which wetting is improved is there any significant increase in dissolution rate following surfactant addition to the product. However, although improved wetting appears to be a prerequisite of increased dissolution rate, the results obtained when the surfactants which improved wettability were added to the dissolution fluid were only very slightly increased. Much larger increases in dissolution rate were observed when these surfactants (ST and SLS) are incorporated in the product. Thus apparently it is necessary (at least for these RS based matrices) to have the surfactant both improving wetting and dissolving within the matrix. The effect of the surfactant dissolving in the matrix may be to form pores which allow dissolution fluid to gain access to the matrix; or to cause some other type of disruption, perhaps to the adhesive bonds within the product. This effect cannot be reproduced by a 1.25% w/v solution in the dissolution fluid, either due to its inability to penetrate (despite having wetted) the matrix, or due to the fact that the surfactant within the tablet may have dissolved to form local concentrations that are substantially greater than 1.25%.

The fact that tablets with ST incorporated in them have faster release than those with SLS, has probably more to do with the higher solubility of ST, as both products will be adequately wetted by the dissolution fluid; this hypothesis is proposed because for the RL formulations the SLS had a lower contact angle than the ST product, but the dissolution rate was strongly linked to the surfactants' solubility, thus the ST had the faster dissolution rate. However, the fact that SLS produces faster dissolution than Cet when present inside the tablets, is probably due to the fact that the SLS product will be more completely wetted, and even though Cet is more soluble, the fluid cannot gain adequate access to the matrix due to its restricted wettability. It is, of course, logical that the wettability will have this dominant effect in such circumstances, as the tablet already contains a significant quantity of soluble material (sorbitol and drug); the high content of non-surfactant soluble material also adds support to the view that the dissolved surfactant has some disruptive role over and above simple dissolution and pore formation (e.g., forming high concentration solutions which may affect adhesion), as if pore formation were the reason for increased dissolution rate, it might be expected that this would be achieved by sorbitol or the drug dissolving. It is interesting to note that, presumably due to the high content of drug and sorbitol, the contact angle value for the RS and RL based formulations are similar in magnitude.

The essential difference between the two sets of formulations is that for the RL based systems most of the surfactants increased the wettability, but in this study on the RS systems only SLS and ST have resulted in improved wetting. Furthermore, for the RS formulations, it was the two anionic surfactants that resulted in the increased dissolution rates. The cationic and ampholytic (CDB) surfactants had no significant effect on the dissolution rate (with the possible exception of Cet, which resulted in a very slight rise when incorporated in the tablet). It has been reported that dissolution rates can in fact be slowed by the additon of, for example, an anionic surfactant with a cationic drug (Feely and Davis, 1988). Despite the conclusion of the previous publication (Efentakis et al., 1991), which stated that there was no correlation between the charge of the surfactant and the release rates, the data presented here for the Eudragit RS formulations seem to demonstrate an interaction between the anionic model drug (flurbiprofen) and the cationic surfactants (i.e., the cationic surfactants are inactivated by the anionic drug, such that they result in wettabilities, and hence dissolution rates, that are similar to control values). Formulations of Eudragit RL 100 with the same drug and excipients do not exhibit such interactions, as evidenced by the reduction in contact angles and improved dissolution (Efentakis et al., 1991). As Eudragit RS 100 and RL 100 differ only in the extent of the quaternary ammonium substitution (RS being much lower than RL), it is hard to provide an explanation for the importance of charge in RS formulations, but the lack of correlation with charge in equivalent RL tablets. It is, however, clear that all other factors remain the same with only the polymer being changed, thus

it is reasonable to assume that the greater content of ammonium substitution of the RL polymer (probably resulting in a slightly more cationic polymer, compared to the uncharged RS) in some way prevents the anionic drug from interacting with the cationic surfactant. It is inappropriate to attempt to develop a mechanism to explain such behaviour on the basis of the results to date.

Conclusion

The results obtained in this study assist in developing the explanation of the influence of surfactants on the release of drugs from hydrophobic matrices. There are certain apparent contradictions between these results and those reported previously for RL based matrices (e.g., changes in rank order of dissolution rates). Certain aspects of the effect of surfactants are the same in both situations; these can be summarised thus: firstly, it is necessary for the surfactant to improve wettability if any increase in dissolution rate is to be observed (this point was not observed with the RL results, as the dissolution experiments in the surfactant solutions indicated that wetting was improved by adding surfactant (except for CDB)); secondly, once wetting has been improved sufficiently to allow the dissolution fluid to gain access to the hydrophobic matrix, then the solubility of the surfactants will become significant. It is most likely that the effect of increased release rate will be due to the formation of high concentrations of surfactants in local positions in the tablet, which will adversely affect adhesion, and thus aid disintegration and dissolution. However, there is an essential difference between the RS and RL formulations, the RS based systems exhibit anionic/cationic (drug/surfactant) interactions, whilst there is no evidence of such behaviour in the RL formulations. This difference must be related to the only difference between the two sets of formulations (i.e., the extent of quaternary ammonium substitution of the polymer), but no mechanism for the effect has been proposed.

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