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Drug-excipient interactions resulting from powder mixing. VI. Role of various surfactants

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Summary

The role of various surfactants on the drug-excipient interactions resulting from prolonged powder mixing with magnesium stearate was investigated. Drug-excipient formulations containing 0.5% magnesium stearate and 0.1–0.5% surfactants were compared with the same formulations without the surfactant under identical mixing conditions to study the effect of prolonged mixing on the in vitro dissolution of ketorolac tromethamine from hand-filled, uncompacted capsules. The results indicate that some surfactants in a concentration as little as 0.1% (1:5 w/w ratio to magnesium stearate) can alleviate the deleterious effect of magnesium stearate on the prolonged mixing of powder, i.e., the decrease in the dissolution rate of the drug. The effectiveness of the surfactants is determined by their hydrophilic-lipophilic balance (HLB) value and solubility, and increases with increasing concentration or decreasing particle size. The hydrophilic anionic surfactants (sodium *N*-lauroyl sarcosinate, sodium stearoyl-2-lactylate, and sodium stearate), non-ionic surfactant (poloxamer 188), and cationic surfactant (cetylpyridinium chloride) are as effective as sodium lauryl sulfate reported in a previous study. Conversely, the lipophilic surfactant, glyceryl monostearate, failed to offset the deleterious effect of magnesium stearate. The results suggest that surfactant alone does not affect drug dissolution, but that it interacts with magnesium stearate during powder mixing. This interaction would reduce the net surface coverage of the drug-excipients by magnesium stearate. Furthermore, the water-soluble hydrophilic surfactant would help to detach any magnesium stearate film covering the drug-excipients, thus alleviating the decrease in drug dissolution caused by magnesium stearate. On the other hand, lipophilic surfactant is not soluble and ineffective despite its interaction with magnesium stearate.

Introduction

Magnesium stearate is widely used as a lubricant in the development of tablet dosage forms. Its function is to reduce the intergranular friction and the friction between granules and the die wall during tablet compression and ejection. The effect of physical interactions occurred during the mixing of drug-excipients and magnesium stearate has been the subject of many investigations (Levy and Gumtow, 1963; Bolhuis et al., 1975, 1987; Chowhan and Chi, 1985a,b, 1986a,b; Wang and Chowhan, 1990). This is in light of the findings that, with prolonged mixing time, magnesium stearate can cause a decrease in tablet crushing

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strength and an increase in disintegration time of the tablet with concurrent decrease in drug dissolution rate. The magnitude of this deleterious effect of magnesium stearate is dependent on the magnesium stearate concentration (Bolhuis et al., 1975), the other excipients in the formulation (Bolhuis et al., 1981; Chowhan and Chi, 1985a, 1986a), the drug particle size (Chowhan and Chi, 1985b), the mixing time (Shah and Mlodozeniec, 1977; Lerk et al., 1982), and the type, size and rotation speed of the mixer (Bolhuis et al., 1987). By minimizing or eliminating these interactions, adverse effects on the final product performance can often be avoided.

The mechanism by which magnesium stearate exerts its effect has been proposed by several investigators (Bolhuis et al., 1975; Shah and Mlodozeniec, 1977; Chowhan and Chi, 1985a,b, 1986a,b). During the mixing process, magnesium stearate flakes are mechanically sheared to form film layers which could adhere to the drug-excipient particles (Bolhuis et al., 1975; Chowhan and Chi, 1985a,b, 1986a,b). This film layer would interfere with the inter-particle bonding during tablet compression and inhibit the penetration of water during disintegration and dissolution processes. Obviously, the adherence or physical interaction between magnesium stearate and drug-excipients is a critical prerequisite for the apparent adverse effects. In this regard, mixing of magnesium stearate with various tablet excipients has been the subject of several investigations. Bolhuis et al. (1981) reported that magnesium stearate caused a greater increase in disintegration time for a tablet containing potato starch, a slightly swelling disintegrant, than a tablet containing sodium starch glycolate which is a strongly swelling disintegrant. More important is the specific physical interaction between magnesium stearate and the disintegrant/excipient as reported by Chowhan and Chi (1985a, 1986a). They found that the disintegration time and dissolution rate of ketorolac tromethamine or prednisolone capsules containing pregelatinized starch, although a slowly swelling disintegrant, was not affected by prolonged mixing with magnesium stearate. But adverse effects were observed when a mixture of lactose and corn starch was used in the ketorolac tromethamine capsules, and when a combination of dibasic calcium phosphate dihydrate with potato starch or with sodium starch glycolate was used in the prednisolone capsule formulation. For a mixture of lactose, microcrystalline cellulose and magnesium stearate, Bolhuis et al. (1987) reported that the effect of lubricant mixing on tablet crushing strength depended heavily on the type, size and rotation speed of the mixer. The decrease in crushing strength occurred after a shorter mixing time in production-scale mixers than in lab-scale mixers when they were operated at the same speed. Thus, lab-scale mixers must be operated at high rotation speed in order to predict the deleterious effect of lubricant admixing in production-scale mixers.

Most recently, Wang and Chowhan (1990) reported that sodium lauryl sulfate could prevent the increase in disintegration time and the decrease in dissolution rate of ketorolac tromethamine capsules in which the drug-excipient mixture has been mixed with magnesium stearate over a prolonged period of time. Based on scanning electron microscope examination, the authors suggested that magnesium stearate interacts strongly with sodium lauryl sulfate, freeing the magnesium stearate film from the drug-excipient agglomerates.

The present study was undertaken to correlate the properties of surface active agents and their role in alleviating the deleterious effects of magnesium stearate on prolonged mixing with drug-excipient powder mixtures.

Materials and Methods

Materials

The drug, ketorolac tromethamine (tromethamine salt of (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid), was obtained from the Institute of Organic Chemistry (Syntex Research, Palo Alto, CA). All other materials used in the formulations were obtained commercially without further purification: Crospovidone, NF (GAF Corp., New York, NY), spray dried lactose, USP (Foremost, San Francisco, CA), magnesium stearate, NF (Mallinckrodt, St. Louis, MO),

TABLE 1

Two formulations of ketorolac tromethamine capsule

Ingredients	Content (mg per capsule)	
	I	II
Ketorolac tromethamine	10.00	10.00
Crospovidone, NF	9.00	9.00
Magnesium stearate, NF	2.25	2.25
Surfactant [a]	0.45–2.25	–
Lactose, spray dried, USP q.s. to	450.00	450.00

[a] Sodium lauryl sulfate, sodium *N*-lauroyl sarcosinate, sodium stearoyl-2-lactylate, sodium stearate, poloxamer 188, glyceryl monostearate, or cetylpyridinium chloride.

sodium lauryl sulfate, USP (DuPont Chemical and Pigment, Wilmington, DE), sodium *N*-lauroyl sarcosinate, sodium stearate and cetylpyridinium chloride (Sigma Chemical Co., St. Louis, MO), sodium stearoyl-2-lactylate (Pationic SSL) (R.I.T.A. Corp., Woodstock, IL), poloxamer 188 (Pluronic F-68 prill) (BASF Wyandotte Corp., Parsippany, NJ), and concentrated powdered glyceryl monostearate (Myvaplex 600P) (Eastman Chemical Products, Inc., Kingsport, TN).

Capsule preparation

When necessary, the surfactants were milled through a no. 80, 200 or 325 mesh sieve to obtain a mean particle size of 100 μm or less. The capsule formulations are listed in Table 1. The concentrations of ketorolac tromethamine, crospovidone, and magnesium stearate remained constant in formulation I (with surfactant) and formulation II (without surfactant). Lactose was used as a filler for both formulations. The preparation of the capsules has been previously described (Wang and Chowhan, 1990). Briefly, ketorolac tromethamine, crospovidone and lactose were blended in a small planetary mixer (Kitchen Aid, Model K5-A, Hobart Manufacturing, Troy, OH) at 35 rpm for 25 min. Magnesium stearate, with or without surfactant, was then added and mixed for additional 2, 5, 10, 20 and 28 min. At each time point, 10 samples were withdrawn from different locations and reserved for drug homogeneity assay. The sample size was approx. 1 g, except the last sample of 10 g for filling into size zero hard gelatin capsules.

In addition to the above general procedure, the order of mixing was investigated in which the drug-excipients were first mixed with magnesium stearate and then with surfactant, or vice versa, i.e., drug-excipients were first mixed with surfactant and then with magnesium stearate.

Experimental methods

The experimental methods have been fully described by Wang and Chowhan (1990) and are briefly repeated here for convenience. Drug homogeneity was determined by dissolving and extracting the drug in purified water, and the ketorolac was assayed by measuring its ultraviolet absorbance at 322 nm using a system similar to that of the following dissolution method. The USP Method II was used to determine the in vitro dissolution rate of ketorolac tromethamine. Each of the six capsules of a particular formulation was secured at the bottom of a 1 l round-bottom flask containing 500 ml of deaerated water equilibrated at 37°C and stirred at 50 rpm. The dissolved drug was analyzed by recording its ultraviolet absorbance at 322 nm using an automated monitoring system previously described (Wang and Chowhan, 1990).

Binary mixtures of each surfactant and magnesium stearate in a 1:5 w/w ratio were prepared by blending 50 g of the mixture in a small V-shaped blender for 30 min. These powder mixtures were coated with gold-palladium and examined under a scanning electron microscope and photographs were taken as reported in the above reference.

The aqueous solubilities of the surfactants were estimated by dispersing 1 g of each surfactant in 5 ml of water and then adding an incremental volume of water until the surfactant was completely dissolved. Since the surfactant would form micellar solutions, only minimum solubilities were determined.

Particle size analyses were performed using a Droplet and Particle Sizer (Malvern Instruments, Series 2600C, Malvern, U.K.). Light mineral oil was used to disperse the hydrophilic surfactant, and water for the lipophilic surfactant.

Results and Discussion

Drug homogeneity

To assess the homogeneity of the powder mixture, 10 samples of each of formulation I containing sodium lauryl sulfate and formulation II taken from different locations in the mixer after 2 and 28 min additional mixing were assayed for the drug. The drug contents of the four powder mixtures ranged from 91 to 95% of theoretical values, with standard deviations ranging from 3.6 to 5.5%. There was no change in the drug homogeneity between the 2 and 28 min additional mixing times.

Drug dissolution rate

The relative standard deviation (RSD) of the six replicate dissolution runs for each formulation ranged from 15 to 18% at the 10 min dissolution time, then decreased to 7.5–9.3% and 4.5–6.1% at the 20 and 30 min dissolution times, respectively.

The dissolution profiles of uncompacted capsules containing formulation II showing the effect of mixing time on in vitro dissolution after the addition of magnesium stearate are shown in Fig. 1. The results indicate that mixing the formulation with 0.5% magnesium stearate for more than 5 min dramatically decreased the dissolution rate of ketorolac tromethamine. Following 28 min of mixing, only approx. 45% of the drug dissolved after 30 min. In contrast, formulation I containing 0.1% hydrophilic surfactants afforded dissolution rates that were not adversely affected by the prolonged mixing with magnesium stearate. Following 28 min mixing, the percentages of drug dissolved of the theoretical values after 30 min were 100% for milled sodium stearate (Fig. 2), 90% for milled sodium *N*-lauroyl sarcosinate, milled sodium stearoyl-2-lactylate, and cetylpyridinium chloride (Figs 3–5, respectively), and 80% for sodium lauryl sulfate and milled poloxamer

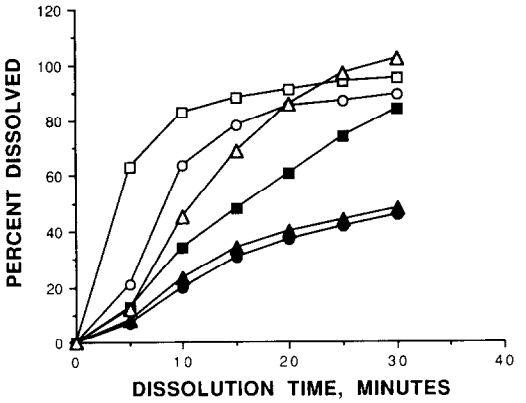

Fig. 2. Dissolution profiles for capsules containing formulation I with 0.1% milled sodium stearate (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

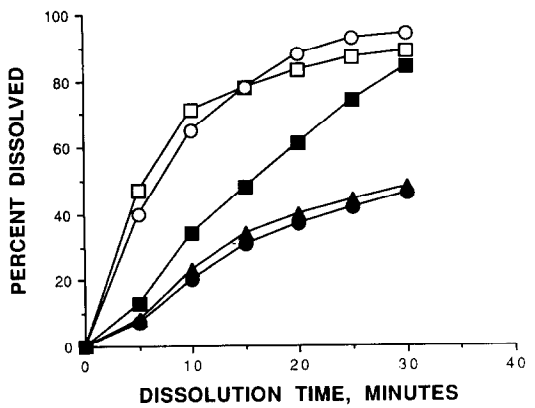

Fig. 1. Dissolution profiles for hand-filled, uncompacted, capsules containing formulation II, showing the effect of mixing time on in vitro dissolution after the addition of magnesium stearate. (□) 2, (○) 5, (■) 10, (●) 20 and (▲) 28 min.

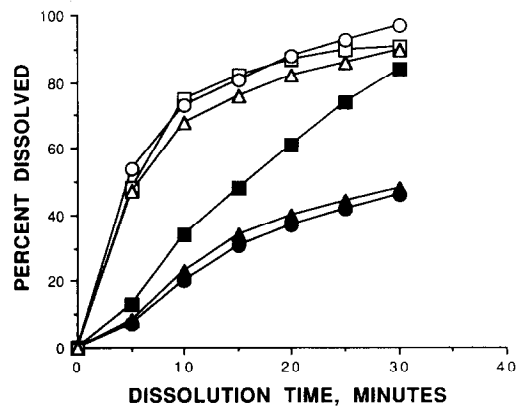

Fig. 3. Dissolution profiles for capsules containing formulation I with 0.1% milled sodium *N*-lauroyl sarcosinate (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

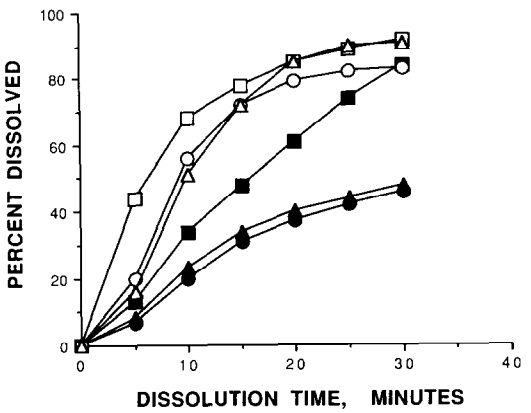

Fig. 4. Dissolution profiles for capsules containing formulation I with 0.1% milled sodium stearoyl-2-lactylate (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

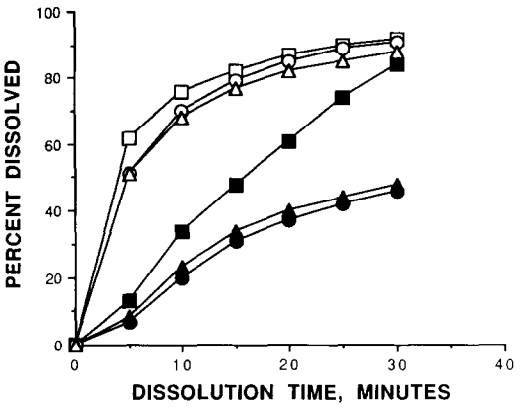

Fig. 5. Dissolution profiles for capsules containing formulation I with 0.1% cetylpyridinium chloride (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

188 (Figs 6 and 7, respectively). These surfactants were effective regardless of their charges, i.e., they are anionic, nonionic, or cationic surfactants. Sodium lauryl sulfate, of which the effect was reported previously (Wang and Chowhan, 1990), was included in this study to serve as a positive control to which the other surfactants were compared for their effectiveness. The results show that the above hydrophilic surfactants are as effective as sodium lauryl sulfate, provided their particle sizes are not largely different (see below). It should be noted that not all hydrophilic surfactants are suitable for inclusion in the formulation due to their physical characteristics and toxicity. The hydrophilic surfactants reported here are deemed suitable for oral solid dosage forms because they are free-flowing powders and used in oral preparation as additives for food, toothpaste or oral antiseptics.

With the exception of sodium stearoyl-2-lactylate, all of the above surfactants have high hydrophilic-lipophilic balance (HLB) values (Table 2), and therefore, are hydrophilic. The aqueous solubilities of the surfactants (Table 2) can be used to estimate their HLB values by comparison

TABLE 2

HLB values and approximate aqueous solubilities of the surfactants

Surfactant		HLB value	Solubility (mg/ml)
Anionic	sodium lauryl sulfate	40 [a]	at least 180
	sodium *N*-lauroyl sarcosinate	29 [b]	at least 125
	sodium stearate	17.6 [c,d]	approx. 1
	sodium stearoyl-2-lactylate (Pationic SSL)	6.5 [a,c]	approx. 1 [e]
Non-ionic	poloxamer 188 (Pluronic F-68 Prill)	29 [a]	at least 100
	glyceryl monostearate (Myvaplex 600P)	3.8–4.0 [a]	insoluble
Cationic	cetylpyridinium chloride	24–29 [b]	at least 180

[a] McCutcheon (1988).
[b] See text.
[c] Bernardi and Lavazza (1983).
[d] Lin and Somasundaran (1971).
[e] Patco, Bulletin no. 101.

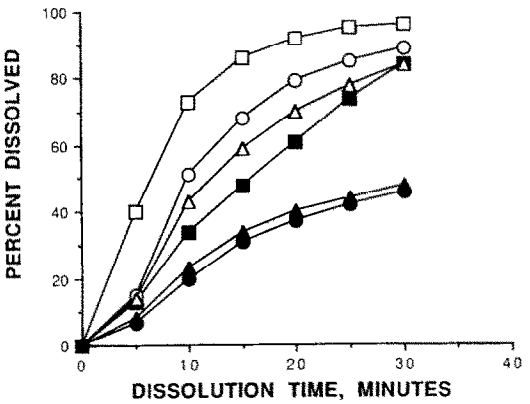

Fig. 6. Dissolution profiles for capsules containing formulation I with 0.1% sodium lauryl sulfate (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

with sodium lauryl sulfate. Thus, the HLB values of sodium *N*-lauroyl sarcosinate and cetylpyridinium chloride can be expected to be as high as sodium lauryl sulfate, because they have high aqueous solubilities.

The HLB values of sodium *N*-lauroyl sarcosinate and cetylpyridinium chloride have been calculated from the following equation (Davies, 1957; Lin and Marszall, 1976), which has been found to be consistent with experimental values:

$$\text{HLB} = \Sigma(\text{hydrophilic group numbers}) - \Sigma(\text{lipophilic group numbers}) + 7 \quad (1)$$

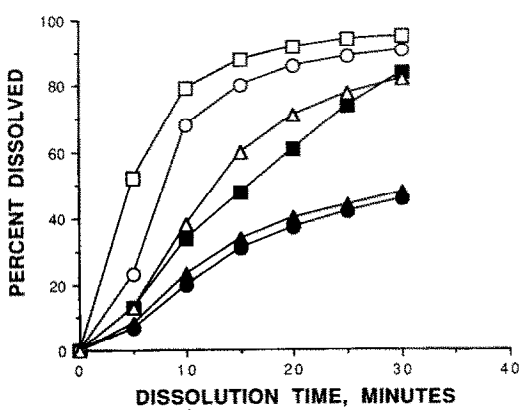

Fig. 7. Dissolution profiles for capsules containing formulation I with 0.1% milled poloxamer 188 (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

For surfactants containing the lipophilic groups CH_3-, $-CH_2-$, or $=CH-$,

$$\Sigma(\text{lipophilic group numbers}) = n \times 0.475 \quad (2)$$

where n is the number of $-CH_2-$ groups in the surfactant molecule. Thus, Eqns 1 and 2 yield the following equation:

$$\text{HLB} = \Sigma(\text{hydrophilic group numbers}) - n \times 0.475 + 7 \quad (3)$$

For sodium *N*-lauroyl sarcosinate, the hydrophilic group numbers are 19.1 for -COONa and 9.4 for the tertiary amine, and $n = 13$. The HLB value is 29 calculated from Eqn 3.

The HLB value of cetylpyridinium chloride has been estimated from the HLB value (25–30) of an analogous cationic surfactant *N*-cetyl-*N*-ethyl morpholinium ethosulfate (ICI, 1967). This HLB value of 25–30 must be corrected for the hydrophilic group -O- (group number +1.3) and lipophilic group $-CH_2-$ (group number −0.475) contributions. Thus, the HLB value of cetylpyridinium chloride is estimated to be 24–29.

Sodium stearoyl-2-lactylate has an HLB value of 6.5 and a solubility of at least 1 mg/ml. Since the concentration of sodium stearoyl-2-lactylate in the capsule formulation is 0.45 mg/capsule, it would completely dissolve in the 500 ml dissolution medium to afford a similar effect to that of the more hydrophilic surfactants investigated in this study.

The mechanism of action by which a hydrophilic surfactant alleviates the deleterious effect of prolonged mixing with magnesium stearate is not simply by lowering the surface tension and effective wetting. This is evident from the data (Wang and Chowhan, 1990) showing that an equivalent amount of the hydrophilic surfactant dissolved in the dissolution medium was not effective.

Fig. 8 shows that the non-ionic lipophilic surfactant, i.e., glyceryl monostearate, failed to alleviate the deleterious effect of magnesium stearate. Glyceryl monostearate has a particle size distribution (mean of 103 μm) comparable to that of

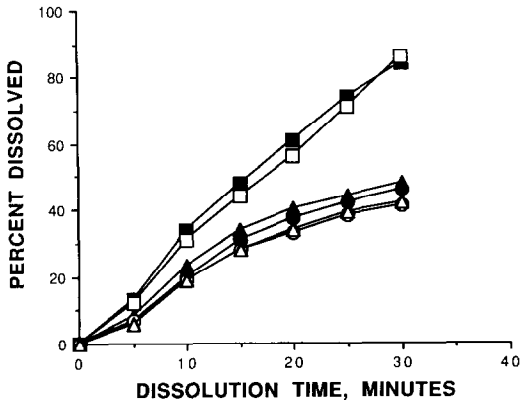

Fig. 8. Dissolution profiles for capsules containing formulation I with 0.1% glyceryl monostearate (open symbols) as compared with formulation II without surfactant (solid symbols), mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min.

the effective hydrophilic surfactants, but has a very low HLB value of 3.8–4.0 and is insoluble in water. The results suggest that hydrophilicity is a very important property contributing to the effectiveness of the surfactants.

Effect of particle size

Table 3 lists the particle size distribution of the surfactants used in this study. Surfactants with large particle sizes were milled to obtain a range comparable to sodium lauryl sulfate. The effect of particle size of the hydrophilic surfactants was studied for sodium *N*-lauroyl sarcosinate, sodium stearoyl-2-lactylate, sodium stearate, and poloxamer 188. These four surfactants have mean particle sizes ranging from 135 to 325 μm as received. After milling, their mean particle sizes ranged from 20 to 94 μm. The results are represented in Fig. 9 for sodium *N*-lauroyl sarcosinate which showed markedly improved effectiveness when the particle size was reduced from a mean of 325 to 33 μm. Reducing the particle size of the hydrophilic surfactants increased their surface area and dissolution rate, and conse-

TABLE 3

Particle size distribution of the surfactants

Surfactant	Percent (by volume) of particles at stated ranges				Mean (μm)
	< 50 μm	50–150 μm	150–300 μm	> 300 μm	
Sodium lauryl sulfate	40	53	6	1	70
Sodium *N*-lauroyl sarcosinate					
As received	6	14	10	70	325
Milled [a]	77	22	1	0	33
Sodium stearoyl-2-lactylate					
As received	16	27	28	29	211
Milled [a]	100	0	0	0	21
Sodium stearate					
As received	11	46	41	2	135
Milled [b]	29	53	15	3	94
Poloxamer 188					
As received	3	31	61	5	179
Milled [c]	100	0	0	0	20
Glyceryl monostearate	29	46	20	5	103
Cetylpyridinium chloride	18	53	29	0	113

[a] Passed through no. 200 mesh sieve.
[b] Passed through no. 80 mesh sieve.
[c] Passed through no. 325 mesh sieve.

quently, their effectiveness in preventing the decrease in the drug dissolution rate which would otherwise occur after prolonged mixing with magnesium stearate. The effect of particle size is very pronounced for hydrophilic surfactants with low solubility such as sodium stearate and sodium stearoyl-2-lactylate, or those which dissolve slowly such as poloxamer 188, as they were effective only after their particle sizes were reduced by milling (Figs 2, 4 and 7).

Effect of concentration

Increasing the concentration of the unmilled sodium *N*-lauroyl sarcosinate, with a mean particle size of 325 μm, from 0.1 to 0.5% increased its effectiveness in preventing the decrease in the drug dissolution rate after 10, 20 and 28 min mixing with magnesium stearate. Fig. 10 shows the results for 28 min mixing with magnesium stearate as a representative example. At an equal concentration of 0.1%, the unmilled sodium *N*-lauroyl sarcosinate used in this particular study (mean particle size of 325 μm) was less effective than sodium lauryl sulfate (mean particle size of 70 μm). However, when the concentration of sodium *N*-lauroyl sarcosinate was increased to 0.2 or 0.5% (up to 1 : 1 w/w ratio to magnesium stearate), it performed equal to or even better

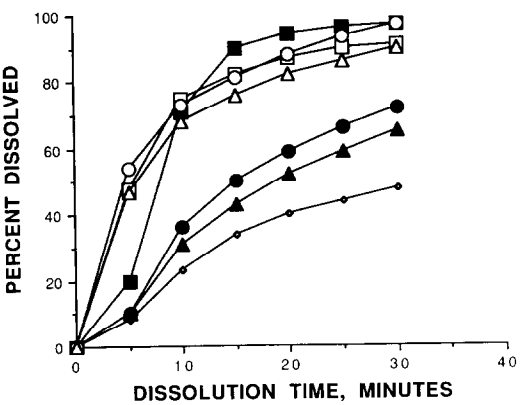

Fig. 9. Dissolution profiles for capsules containing formulation I with 0.1% sodium *N*-lauroyl sarcosinate comparing milled (open symbols) and unmilled (solid symbols) surfactants, mixed for (□,■) 10, (○,●) 20 and (△,▲) 28 min. Profile for formulation II without surfactant after 28 min mixing is shown for comparison (◇).

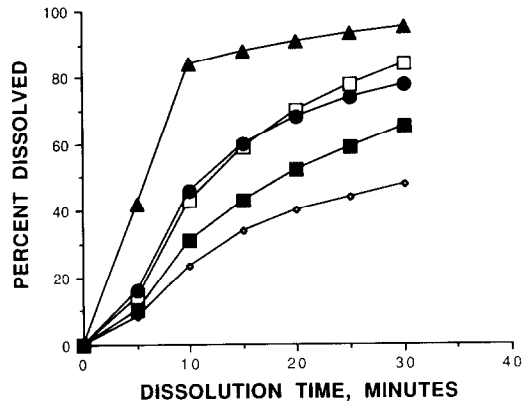

Fig. 10. Dissolution profiles for capsules containing formulation I with (■) 0.1%, (●) 0.2% and (▲) 0.5% unmilled sodium *N*-lauroyl sarcosinate, mixed for 28 min. Profiles for formulation I with 0.1% sodium lauryl sulfate (□) and formulation II without surfactant (◇) are shown for comparison.

than sodium lauryl sulfate. Since the solubility, and therefore, the HLB value of sodium *N*-lauroyl sarcosinate are high (Table 2), it dissolved rapidly and completely even at the highest concentration to exert a greater degree of effectiveness. The concentration effect was, interestingly enough, not observed with the unmilled sodium stearate with a mean particle size of 135 μm. Practically no improvement of the effectiveness was apparent after 10 or 28 min mixing with magnesium stearate, when the concentration of sodium stearate was increased from 0.1 to 0.5%. Sodium stearate, with an HLB value of 17.6 which is relatively low for an anionic surfactant, dissolves very slowly in water. Thus, the dissolution rate, instead of concentration, was the limiting factor for its effectiveness. This is proven by the fact that milled sodium stearate with a mean particle size of 94 μm showed a high degree of effectiveness (Fig. 2).

Order of mixing

In all of the studies with surfactant (formulation I), the surfactant and magnesium stearate were added to the drug-excipient mixture and then mixed for the intended period of time. To investigate further the role of surfactant in powder mixing, the effects of surfactant alone upon mixing with drug-excipients and of changing the

order of mixing of surfactant and magnesium stearate were studied. As shown in Fig. 11, hydrophilic or lipophilic surfactant did not significantly affect the dissolution of drug after mixing for 28 min. When magnesium stearate was subsequently added and mixed for an additional 28 min, the hydrophilic surfactant sodium *N*-lauroyl sarcosinate, but not the lipophilic surfactant glyceryl monostearate, prevented the decrease in drug dissolution caused by prolonged mixing with magnesium stearate. In this order of mixing, the surfactant was homogeneously mixed with the drug-excipients before coverage by magnesium stearate. Thus, the water-soluble hydrophilic surfactant would dissolve and detach the magnesium stearate film such that the decrease in drug dissolution was alleviated. This effect was not observed with lipophilic surfactant since it was not soluble. In Fig. 12, the order of mixing was reversed, i.e., the drug-excipients was first mixed with magnesium stearate for 28 min, followed by additional mixing for 28 min with surfactant. The results confirmed that hydrophilic, but not lipophilic, surfactant prevented the decrease in drug dissolution. In this order of mixing, the effectiveness of hydrophilic surfactant was not as high as when it was first mixed with the drug-excipients, apparently because the magnesium

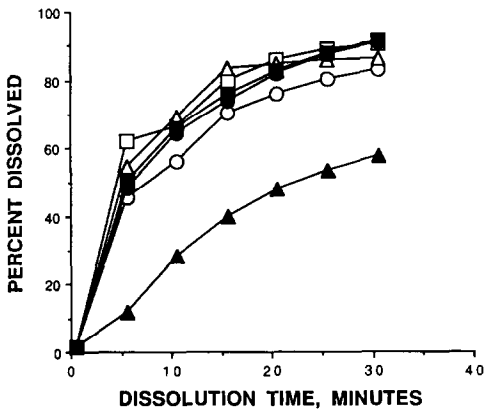

Fig. 11. Dissolution profiles for capsules containing formulation I with 0.1% milled sodium *N*-lauroyl sarcosinate (open symbols) or glyceryl monostearate (solid symbols). Drug and excipients were mixed for 25 min (□,■), followed by mixing with surfactant for 28 min (○,●) and then with magnesium stearate for an additional 28 min (△,▲).

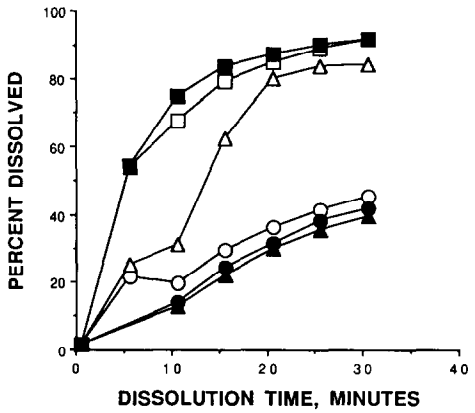

Fig. 12. Dissolution profiles for capsules containing formulation I with 0.1% milled sodium *N*-lauroyl sarcosinate (open symbols) or glyceryl monostearate (solid symbols). Drug and excipients were mixed for 25 min (□,■), followed by mixing with magnesium stearate for 28 min (○,●) and then with surfactant for an additional 28 min (△,▲).

stearate film has covered the drug-excipient mixture.

The results tend to suggest an interaction between surfactant and magnesium stearate, that would reduce the net surface coverage of the drug-excipients by magnesium stearate. They further suggest that the solubility of surfactant played a major role in eliminating the magnesium stearate film from the drug-excipients such that the decrease in drug dissolution can be alleviated.

Scanning electron micrographs

The scanning electron micrographs (SEMs) of ketorolac tromethamine, crospovidone, spray dried lactose, magnesium stearate and sodium lauryl sulfate, as well as of the powder mixture of sodium lauryl sulfate and magnesium stearate in a ratio of 1:5 w/w have been clearly depicted in a previous publication (Wang and Chowhan, 1990). A strong interaction between sodium lauryl sulfate and magnesium stearate is believed to inhibit the interactions between magnesium stearate and the drug-excipient particles. This would allow the drug and excipients to dissolve freely without being impeded by the magnesium stearate film layers.

The present study indicates that other hydrophilic surfactants, whether anionic, non-ionic

or cationic, are as effective as sodium lauryl sulfate, provided they have approximately equivalent particle size distributions. On the other hand, lipophilic surfactant such as glyceryl monostearate failed to show the effectiveness of its hydrophilic counterparts. Since all surfactants contain hydrophilic as well as lipophilic functional groups, it is reasonable to believe that a strong hydrophobic interactions would occur between the lipophilic functional group and the magnesium stearate. Scanning electron microscopy examination revealed that in fact all of the surfactants used in this study show strong interactions with magnesium stearate, each in a binary mixture of 1:5 (w/w) ratio as used in formulation I (Table 1). Fig. 13A and B depicts the SEMs of neat sodium *N*-lauroyl sarcosinate and its binary mixture of 1:5 (w/w) ratio with magnesium stearate, respectively, as representative evidence for the hydrophilic surfactants that were effective in this study. Fig. 14A and B depicts the SEMs of neat glyceryl monostearate and its binary mixture of 1:5 (w/w) ratio with magnesium stearate, respectively, as an example for the non-effective lipophilic surfactant. As can be seen in Figs 13B and 14B, both surfactants interact strongly and are covered by magnesium stearate film layers.

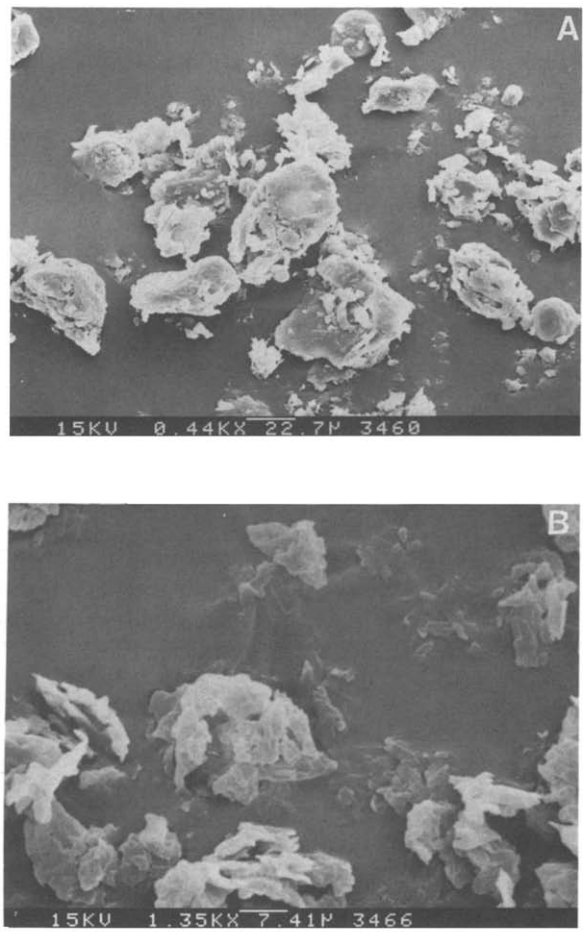

Fig. 13. Scanning electron micrographs of: (A) milled sodium *N*-lauroyl sarcosinate (×440), and (B) binary powder mixture of milled sodium *N*-lauroyl sarcosinate and magnesium stearate in a ratio of 1:5 (w/w) (×1350).

The overall results tend to suggest that surfactant alone does not affect the drug dissolution from drug-excipient mixture without magnesium stearate. When magnesium stearate was added and mixed, the surfactant would interact with and attach to the magnesium stearate flakes. This interaction would reduce the net surface coverage of the drug-excipients by magnesium stearate. But more importantly it is the solubility of the hydrophilic surfactant which would dissolve and detach the magnesium stearate film from the drug-excipients such that the decrease in drug dissolution can be alleviated. This capability is not shown by lipophilic surfactant despite its interaction with magnesium stearate. Thus, the effectiveness of the surfactants is determined by their HLB value and solubility, and increases with increasing concentration or decreasing particle size.

Conclusion

The results of the present study indicate that hydrophilic anionic, non-ionic or cationic surfactants, when added with the lubricant magnesium stearate in a ratio as low as 1:5 (w/w), can alleviate the decrease of in vitro drug dissolution caused by prolonged mixing with magnesium stearate. Factors influencing the effectiveness of the surfactants include their HLB value, solubility, particle size, and concentration. Conversely, lipophilic surfactants such as glyceryl monostearate do not show the effectiveness of their

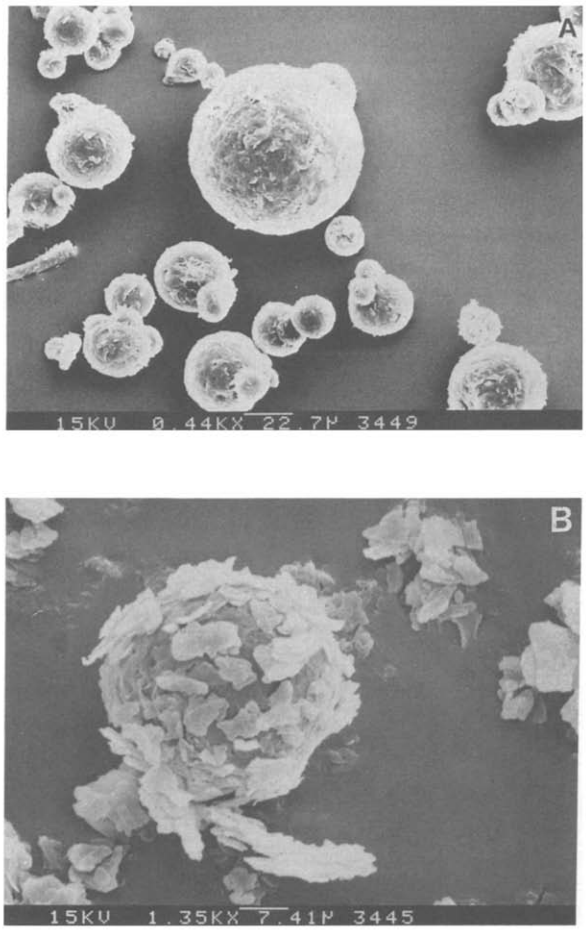

Fig. 14. Scanning electron micrographs of: (A) glyceryl monostearate (×440), and (B) binary powder mixture of glyceryl monostearate and magnesium stearate in a ratio of 1:5 (w/w) (×1350).

hydrophilic counterparts. The examination of surfactant-magnesium stearate binary mixture of a 1:5 (w/w) ratio demonstrated a strong interaction between the two components, regardless of whether the surfactant is hydrophilic or lipophilic. Therefore, it can be suggested that at least two factors serve as the prerequisites for the effectiveness of a surfactant in alleviating the deleterious effect of prolonged mixing with magnesium stearate: a strong particle-particle interaction with magnesium stearate during powder mixing, and a sufficiently high HLB value and solubility to be able to dissolve rapidly in aqueous media.

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