

Dissolution of Lithium and Magnesium from Lithium Carbonate Capsules Containing Magnesium Stearate

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Abstract □ A lithium carbonate capsule mix designed for an automatic capsule-filling machine used about 0.25% magnesium stearate as a lubricant. While the formulation ran well, it had an undesirably long disintegration time and a slow dissolution rate due to the waterproofing effect of the lubricant. Studies on the addition of sodium lauryl sulfate separately to both the formulation and the dissolution medium showed that 2 mg (0.002%) added to the capsule (12 mg/600 ml of 0.3% HCl) was more effective in improving lithium dissolution than 6 g (1%) added directly to 600 ml of medium. Furthermore, while the addition of 0.02% sodium lauryl sulfate to the dissolution medium reduced the surface tension of the medium by more than 50%, it had no effect on dissolution rate; increasing the amount of sodium lauryl sulfate from 0.03 to 0.5% in the dissolution medium had a pronounced effect on dissolution rate. Magnesium dissolution from magnesium stearate and lithium dissolution from lithium carbonate were directly related.

Keyphrases □ Lithium carbonate capsules formulated with magnesium stearate—direct relationship between dissolution of magnesium and lithium □ Magnesium stearate as lubricant in lithium carbonate capsules—direct relationship between dissolution of magnesium and lithium □ Dissolution, lithium carbonate capsules formulated with magnesium stearate—direct relationship between dissolution of magnesium and lithium

Surface effects should be considered in the design of solid dosage forms, especially powder-filled capsules because they usually float. When the gelatin shell dissolves, liquid must displace air and spread over the powder surface before it can be immersed, dispersed, and dissolved. If wetting does not occur rapidly, the powder will float on the surface and agglomerate to minimize air-liquid contact and impede dissolution (1-5). Therefore, the practice of including surfactants in capsule and tablet formulations to ensure wetting and subsequent rapid disintegration and dissolution is widely followed (6-20). The lack of wetting properties of many formulations is not caused by the active material but by the widely used lubricant magnesium stearate, an excellent waterproofing agent (21-23). This does not imply that wetting is the only important consideration in capsule disintegration and dissolution. Packing, porosity, filling method, type and concentration of diluents, lubricants, and surfactants have effects (18, 24-28). Other variables also have been cited (29).

Surfactants have also been added to dissolution fluids in attempts to study wetting, disintegration, and dissolution. A direct correlation for phenacetin powder dissolution rate and surface tension of 0.1 N HCl solution with different amounts of polysorbate

Table I—Capsules with Different Lubricants

Lubricant, mg/Capsule	Number of Dissolution Runs	Minutes for 50% Lithium Dissolution in 0.3% HCl by NF Method II ($\pm \sigma$)	Coefficient of Variation of Capsule Weight, %
None	3	3.4 (0.3)	3.9
1.0 Magnesium stearate	6	44.8 (4.3)	2.2
1.0 Magnesium stearate and 2.0 sodium lauryl sulfate	6	3.1 (0.3)	1.9
1.0 Magnesium lauryl sulfate	3	2.7 (0.03)	2.4
1.0 Stearic acid	3	3.0 (0.3)	1.3
1.0 Sodium stearate	3	2.7 (0.5)	1.2

80 was found (3). Phenobarbital powder and aspirin powder dissolution rates in 0.1 N HCl solution were also found to increase with increasing content of polysorbate 80 (30). Dilute aqueous lysolecithin solutions exhibited micellar solubilizing properties on powdered griseofulvin, glutethimide, and a diuretic compound. This solution dissolved these relatively water-insoluble drugs faster and more completely than water did (31). Benzoic acid pellets with large pores dissolved faster in a dilute sodium lauryl sulfate solution than in water (32). Hydrochlorothiazide tablets dissolved at equivalent rates in distilled water, 0.1 N HCl, and simulated intestinal fluid. The addition of 0.03% polysorbate 80 to these media did not change these rates (33).

The purposes of this study were to: (a) compare the relative effectiveness of surfactant in a formulation and in the dissolution fluid, (b) determine the effect of surface tension on the dissolution of slowly wettable capsules, and (c) compare dissolution rates of lithium and magnesium from lithium carbonate capsules containing magnesium stearate.

EXPERIMENTAL

Preparation of Capsules—Lithium carbonate (0.9 kg), spray-dried lactose (0.27 kg), and magnesium stearate (3.0 g) were mixed on a small paddle mixer¹ for 10 min, passed through a No. 8 screen on a hammer mill² at high speed with impact forward, remixed for 10 min, and filled into No. 1 capsules on an automatic capsule-filling machine³. Theoretical fill for each capsule was

¹ Kitchen Aid.

² Fitzpatrick comminuting.

³ Zanasi model LZ 164.

Table II—Effect of External Surfactant on Dissolution Rate of Lithium Carbonate from Capsules with Magnesium Stearate

Percent Sodium Lauryl Sulfate in 0.3% HCl	Number of Dissolution Runs	Minutes for 50% Dissolution in 0.3% HCl by NF Method II ($\pm \sigma$)	Student's <i>t</i> Test on T_{50} Values ^a	Dissolution Fluid Surface Tension, dynes/cm ($\pm \sigma$)
0	6	44.8 (4.3)	Control	71.9 (0.1)
0.0054	6	41.3 (3.2)	NS	36.6 (0.4)
0.02	9	44.8 (5.1)	NS	31.1 (0.2)
0.0316	6	23.4 (3.8)	S ^b	29.2 (0.2)
0.04325	3	16.8 (0.8)	S	28.9 (0.3)
0.115	3	10.2 (2.5)	S	25.8 (0.1)
0.173	3	10.1 (1.8)	S	26.4 (0.2)
0.5	3	5.9 (0.9)	S	30.9 (0.3)
1.0	3	5.9 (0.4)	S	30.7 (0.2)

^a NS = not significant. S = significant at $p < 0.05$ level. ^b $p < 0.05$.

391 mg, equivalent to 300 mg of lithium carbonate, 90 mg of spray-dried lactose, and 1 mg of magnesium stearate. Other capsules were prepared as indicated in Table I.

Magnesium and Lithium Dissolution Rates—Dissolution testing was done using NF XIII dissolution method II in 600 ml of fluid (34). All glassware was washed with dilute acid and rinsed with distilled water to remove magnesium salts. Six capsules were used in each test, and tests were repeated at least three times. Samples (20 ml) were removed at some or all of the following intervals: 2, 4, 5, 6, 8, 10, 15, 20, 25, 30, 35, and 60 min. Fresh fluid was added at each interval to replace the withdrawn volume. Samples were immediately filtered⁴. Undiluted samples were analyzed for magnesium on an atomic absorption spectrophotometer⁵ equipped with a magnesium lamp. Magnesium content of gelatin capsules and capsule contents with no magnesium stearate were subtracted from these assays to give magnesium dissolution from magnesium stearate. Samples were diluted 2 to 200 and analyzed for lithium by atomic absorption with a lithium lamp. Corrections were made for removed samples, and the data were plotted on logarithmic normal probability paper to obtain T_{50} values.

Surface Tension—A tensiometer⁶ was used to determine surface tension of dissolution fluids. Parenteral water run as a control had a typical surface tension of 72.5 (± 0.2) dynes/cm.

Lubricant Particle Size—Lubricant particle size was determined on a particle analyzer⁷ as described previously (35). Mass median diameter values for magnesium stearate, sodium lauryl sulfate, and magnesium lauryl sulfate particles were between 11.1 and 18.2 μm . Stearic acid particles were slightly larger, with a mass median diameter of 37.7 (9.7–145.5) μm .

RESULTS AND DISCUSSION

Several batches of capsules were made with the same amounts of lithium carbonate and spray-dried lactose but with different lubricants (Table I). Capsules with no lubricant dissolved rapidly by NF XIII method II in 600 ml of 0.3% HCl, with effervescence, but they did not have satisfactory weight control; a lubricant was needed. In contrast, capsules with magnesium stearate (1 mg) had satisfactory weight control but dissolved slowly ($T_{50} = 44.8$ min); the capsules floated and when the gelatin shell dissolved, the powder continued to float. These results clearly show the dramatic effects of magnesium stearate as a lubricant and as a waterproofing agent.

Capsules with both magnesium stearate (1 mg) and the surfactant sodium lauryl sulfate (2 mg) dissolved rapidly and had satisfactory weight control. Thus, sodium lauryl sulfate counteracted the waterproofing effect without counteracting the lubricant effect of magnesium stearate. Capsules with sodium lauryl sulfate (2.5 mg) alone added as surfactant-lubricant dissolved rapidly

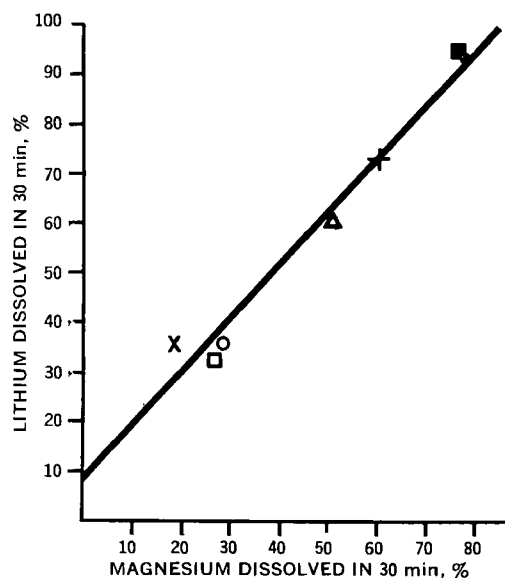


Figure 1—Dissolution of magnesium from magnesium stearate and lithium from lithium carbonate in 0.3% HCl with added sodium lauryl sulfate in percent indicated. Key: ○, 0%; ×, 0.0054%; □, 0.02%; △, 0.0316%; +, 0.04325%; ●, 0.115%; and ■, 0.173%.

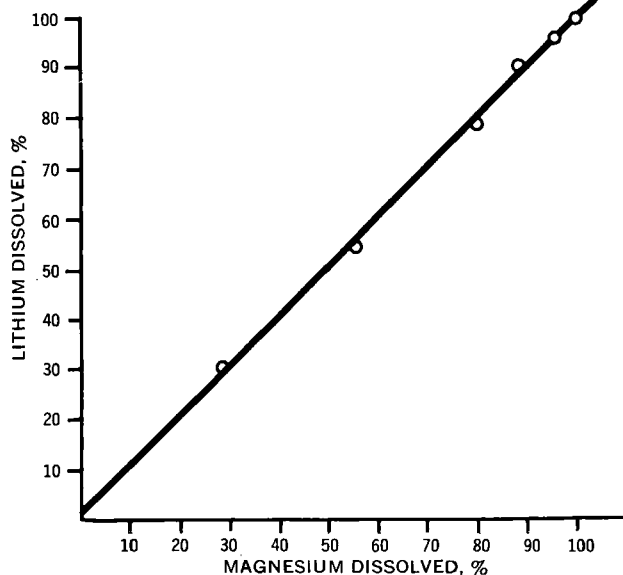


Figure 2—Dissolution of magnesium from magnesium stearate and lithium from lithium carbonate in 3% HCl.

⁴ Through a 0.45- μm Millipore pad in a Swinnex 25 filter.

⁵ Techtron type AA4.

⁶ Du Nouy.

⁷ Coulter counter, model B.

Table III—Dissolution of Lithium and Magnesium from Lithium Carbonate Capsules Containing Magnesium Stearate

Solvent	Time for 50% Dissolution ($\pm \sigma$)		Slope	Intercept	<i>r</i>
	Li	Mg			
3.0% HCl	13.4 \pm 0.9 ^a	13.6 \pm 1.18 ^a	0.968	2.132	0.998
0.5% Sodium lauryl sulfate	14.4 \pm 0.8 ^b	13.8 \pm 0.7 ^b	1.014	-6.252	0.998

^a Not significant by *t* test. ^b Not significant by *t* test.

but did not have satisfactory weight control. Finally, capsules with the surfactant-lubricant magnesium lauryl sulfate dissolved rapidly and had satisfactory weight control. These studies show that a lubricant is necessary in these lithium carbonate capsules and that 2 mg of sodium lauryl sulfate added to the capsule formulation is able to counteract the waterproofing effect of 1 mg of magnesium stearate.

The capsules with 1 mg of magnesium stearate were studied further in an attempt to explain why they dissolved so slowly in 0.3% HCl. Low concentrations (0.0054 and 0.02%) of sodium lauryl sulfate in the 0.3% HCl dissolution fluid sharply reduced surface tension, from 72 to 37 and 31 dynes/cm, respectively, but had no effect on dissolution rate. Higher sodium lauryl sulfate concentrations, from 0.03 to 0.5%, had a pronounced effect on dissolution rates but did not further reduce surface tension (Table II). Thus, 12 mg of sodium lauryl sulfate in six capsules was more effective in increasing lithium carbonate dissolution than was 6 g (1%) of sodium lauryl sulfate added directly to 600 ml of media⁸.

The ability of higher sodium lauryl sulfate concentrations to accelerate dissolution is not easily explained in view of the observation of Levy and Gumtow (20), who reported that the dissolution rate-enhancing effect of sodium lauryl sulfate is not due to any modification of microenvironmental pH or solubilization by micelles but rather to the better penetration of solvent into tablets and their component granules and the resulting greater avail-

ability of drug surface (20). The critical micelle concentration (CMC) for sodium lauryl sulfate in 0.3% HCl is about 0.009% when measured by the surface tension method. The apparent lack of dissolution rate and surface tension correlation was unexpected in view of the excellent correlation reported by Finholt and Solvang (3) for phenacetin powder and polysorbate 80.

The studies with sodium lauryl sulfate added to the 0.3% HCl solution were repeated with samples collected at 30 min. Lithium dissolution from lithium carbonate and magnesium dissolution from magnesium stearate were determined. Regression analysis of these data gave a slope of 1.076, an intercept of 8.326, and *r* of 0.991, which show that magnesium and lithium dissolutions are directly related (Fig. 1).

Dissolutions were also run in distilled water and 0.3, 1.0, 3.0, and 10.0% HCl. Again magnesium and lithium dissolutions were directly related. These data gave a slope of 1.053, an intercept of 5.216, and *r* of 0.992.

Dissolution rates were determined in 3% HCl and in 0.5% sodium lauryl sulfate. Samples were removed at 10, 15, 20, 25, 30, and 35 min. In both cases, magnesium and lithium dissolutions were directly related (Figs. 2 and 3 and Table III).

Thus in this formulation, which floats even after the gelatin shell dissolves, dissolution of magnesium from magnesium stearate is the rate-determining step in the dissolution of lithium from lithium carbonate in hydrochloric (3%) acid solution, dilute hydrochloric acid (0.3%) plus sodium lauryl sulfate solution, and sodium lauryl sulfate solution. Postulated mechanisms for magnesium dissolution are double-decomposition chemical reactions: (a) magnesium stearate + excess HCl \rightarrow magnesium chloride + stearic acid, and (b) magnesium stearate + excess sodium lauryl sulfate \rightarrow magnesium lauryl sulfate + sodium stearate.

To test these postulated mechanisms, additional batches of lithium carbonate capsules with stearic acid and sodium stearate as lubricants were prepared; magnesium lauryl sulfate has already been shown to give a rapidly dissolving formulation. Both stearic acid and sodium stearate gave formulations that ran well and had rapid dissolution rates (Table I). These results are in agreement with the postulated mechanisms.

Note that some of the surface tension values in Table II are below 30 dynes/cm. These lower values are due to the presence of impurities formed when sodium lauryl sulfate hydrolyzed in the acid solution to lauryl alcohol and sulfate (36). Motsavage and Kostenbauder (37) studied this hydrolysis in detail and found that sodium lauryl sulfate was hydrolyzed about 30 times faster above than below the CMC. Table IV shows that two solutions give lower surface tension values upon aging.

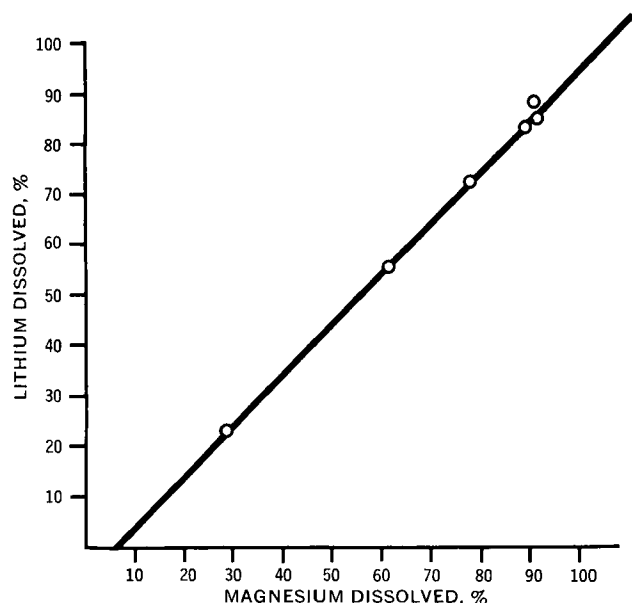
SUMMARY

Dissolution of magnesium from magnesium stearate is the rate-

Table IV—Surface Tension Changes of 0.3% HCl Solutions with Sodium Lauryl Sulfate

Sodium Lauryl Sulfate Concentration, %	Time	Surface Tension, dynes/cm ($\pm \sigma$)
0.115	Original	31.3 (0.2)
	3 days ^a	28.6 (0.2)
	8 days	25.3 (0.2)
	9 days	25.8 (0.1)
	43 days	25.4 (0.2)
0.173	Original	31.5 (0.2)
	18 days	27.8 (0.3)
	40 days	26.4 (0.3)

^a Stored 3 days at 37°; the rest was stored at room temperature, 24°.

**Figure 3**—Dissolution of magnesium from magnesium stearate and lithium from lithium carbonate in 0.5% sodium lauryl sulfate.

⁸ The referee says this, in his experience, is a common observation which, based on the following arguments, appears to be reasonable. The volume of a No. 1 capsule is approximately 0.48 cm³; and the volume occupied by the 391 mg of lithium carbonate-lactose, etc., assuming a weighed average density of 1.97 g/cm³, is 0.20 cm³. Therefore, the void space within the capsule is 0.28 cm³. This void space is also equal to the maximum volume of water, which will theoretically first mix with the powder blend. If the 2 mg (concentration of sodium lauryl sulfate per capsule) is considered to dissolve in this volume of water (0.28 cm³), the effective surfactant concentration, 2 mg/0.28 cm³, is approximately 7 mg/ml or 0.7%. Note from Table II that this is in the range, 0.5-1%, where greatly improved dissolution occurs.

determining step in the dissolution of lithium from slow-dissolving lithium carbonate capsules in three solvent systems. Postulated mechanisms for magnesium dissolution are double-decomposition reactions of magnesium stearate with hydrochloric acid to yield stearic acid and with sodium lauryl sulfate to yield sodium stearate and magnesium lauryl sulfate. These three suggested products were formulated into lithium carbonate capsules that exhibited rapid dissolution rates.

Sodium lauryl sulfate was much more efficient in aiding lithium dissolution when added to the formulation than when added to the dissolution medium.

Low concentrations of sodium lauryl sulfate in the dissolution fluid sharply reduced surface tension but had no effect on dissolution rate.

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