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RESEARCH PAPERS

EFFECTS OF LUBRICANT LEVEL, METHOD OF MIXING, AND DURATION OF MIXING ON A CONTROLLED-RELEASE MATRIX TABLET CONTAINING HYDROXYPROPYL METHYLCELLULOSE

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ABSTRACT

The effects of the lubricant magnesium stearate at different concentrations, mixing shear rates, and mixing times on the tablet properties and drug dissolution from controlled-release matrix tablets containing hydroxypropyl methylcellulose 2208, USP (METHOCEL® K4M Premium) have been studied. Diphenhydramine HCl and hydrochlorothiazide were chosen as the model drugs. Spray-dried hydrous lactose (Fast Flo Lactose-316®) and anhydrous dibasic calcium phosphate (A-TAB®) were chosen as the model excipient/fillers. The impact of magnesium stearate on the mechanical strength of tablets appeared to be dependent on the bonding mechanism of the components of the powder mix. Tablets containing A-TAB, which compacts via a brittle fracture mechanism, were harder and had significantly better friability patterns than those prepared using Fast Flo Lactose-316. The compaction of Fast Flo Lactose-316 appears to be a combination of brittle fracture and plastic deformation. Mixes containing lower levels of lubricant (0.2%) generated tablets that had higher crushing strengths than those with higher lubricant levels (2.0%). Drug release was impacted to the greatest extent by the solubility of the drug and excipient/filler but was only slightly affected by the level of magnesium stearate and duration of mixing.

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INTRODUCTION

Hydroxypropyl methylcellulose (HPMC) is a water-soluble cellulose ether that has been evaluated extensively as a polymer in controlled-release (CR) matrix applications (1-4). Prior authors have investigated various aspects involving the manufacturing of matrix tablets such as direct compression, wet granulation, and roller compaction (5-9). As with any tabletted dosage form, CR matrix tablets require the addition of a lubricant to help ease tablet ejection from the die cavities. Magnesium stearate is one of the most efficient and commonly used lubricants in the pharmaceutical industry. Its mechanism of action is to cover the particles in a powder-mix with a thin film during the mixing stage (10-12). It has been well documented in the literature that this hydrophobic boundary-type lubricant may have negative effects on tablet properties such as disintegration, dissolution, and hardness (13-19).

The purpose of the present investigation was to evaluate the behavior and effect of the lubricant magnesium stearate when added to a direct compression CR formulation at different concentrations, shear rates, and mixing times. Diphenhydramine HCl and hydrochlorthiazide (HCTZ) were chosen as the model drugs. Spray-dried hydrous lactose (Fast Flo Lactose-316) and unmilled anhydrous calcium phosphate, dibasic (A-TAB) were chosen as the model excipient/fillers.

MATERIALS

The following materials were used as received: hydrochorothiazide, USP, (Abbott Laboratories, North Chicago, IL); diphenhydramine hydrochloride, USP, (Wyckoff Chemical Company, Inc., South Haven, MI); Methocel K4M Premium, hydroxypropyl methylcellulose 2208, USP, (The Dow Chemical Company, Midland, MI); spray-dried hydrous lactose NF, Fast Flo Lactose-316, (Foremost Whey Products, Baraboo, WI); unmilled anhydrous calcium phosphate, dibasic, USP, A-TAB, (Rhone-Poulenc, Inc., Cranbury, NJ); and magnesium stearate, NF, (Mallinckrodt, Inc., St. Louis, MO). All reagents were analytical grade or better.

METHODS

Tablet formulation: This study used four formulations (A-D), which are listed below. The two excipient/fillers were unmilled anhydrous calcium phosphate,

dibasic (A-TAB) and spray-dried hydrous lactose (Fast Flo Lactose-316). Figure 1 illustrates the particle size characteristics of the two excipients. These two excipients were chosen because they are commonly used in direct compression tablet formulations. They were also chosen because of their compaction characteristics. A-TAB compacts via a brittle fracture mechanism (20-22) and Fast Flo Lactose-316 appears to be combination of brittle fracture and plastic deformation (19,23).

Low lubricant (0.2%) formulas

(A)	(%w/w)	(B)
Hydrochlorothiazide	6.25	Diphenhydramine HCl
HPMC 2208, USP	20.0	HPMC 2208, USP
A-TAB or Fast Flo Lactose	73.55	A-TAB or Fast FloLactose
Magnesium stearate	0.2	Magnesium stearate

High lubricant (2.0%) formulas

(C)	(%w/w)	(D)
Hydrochlorothiazide	6.25	Diphenhydramine HCl
HPMC 2208, USP	20.0	HPMC 2208, USP
A-TAB or Fast Flo Lactose	71.75	A-TAB or Fast Flo Lactose
Magnesium stearate	2.0	Magnesium stearate

Powder mixing (twin-shell blender): Drug (hydrochlorothiazide or diphenhydramine HCl), excipient/filler (A-TAB or Fast Flo Lactose-316), and polymer (HPMC) were charged into the twin-shell blender and mixed for 10 minutes. Magnesium stearate was added and mixed for either two minutes (62 revolutions) or 30 minutes (930 revolutions).

Powder mixing (high shear mixer): Drug (hydrochlorothiazide or diphenhydramine HCl), excipient/filler (A-TAB or Fast Flo Lactose-316), and polymer (HPMC) were charged into the high shear mixer and mixed for 1 minute at a 200 rpm main blade speed and 1000 rpm chopper speed to help ensure homogeneity. After this pre-mix step, magnesium stearate was added and

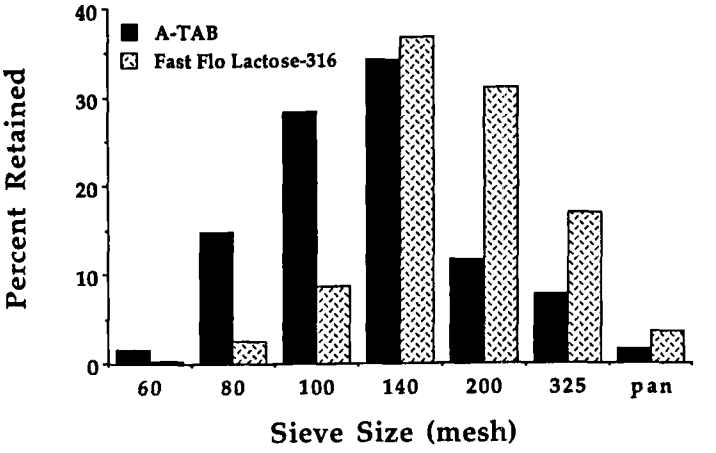

FIGURE 1.

Particle size distribution of the two filler excipients (average of three sieve tests).

mixed at the same rates. A portion of the mix was removed after 2 minutes (approximately 400 revolutions-main blade and 2,000 revolutions-chopper) and after 30 minutes (approximately 6,000 revolutions-main blade and 30,000 revolutions-chopper) of mixing.

Tablet preparation: Mixes were tabletted using an instrumented 16-station Stokes RD-3 rotary tablet press (J.J. Stokes Machine Co., Philadelphia, PA) equipped with 13/32-inch (10.3-mm) round, flat-faced, bevel-edged tooling. The applied compression force was 6000 lb (26.6 kN). To help normalize the tablet hardness values, tablet weights were adjusted to maintain a tablet thickness of 0.180 +/- 0.005 inches. This tablet thickness produced an average tablet weight of 606 mg (± 5 mg) for tablets containing A-TAB and 497 mg (± 4 mg) for those containing Fast Flo Lactose-316.

Tablet property testing: Tablets were tested for friability, thickness, hardness, and rate of dissolution. Tablet friability testing used a Vanderkamp friabilator (model 10801, VanKel Industries, Chatham, NJ). After 20 tablet samples were tumbled for 6 minutes, the percent weight loss was measured. Tablet thickness

was measured using an Ames thickness gauge (model 27, B. C. Ames, Co., Waltham, MA) on 20 tablets. Tablet hardness testing was completed using a Key hardness tester (model HT300, Key International, Englishtown, NJ). Twenty randomly chosen tablets were tested from each set.

Drug dissolution: Dissolution testing of six tablet samples from each group was performed using a Distek dissolution system (model 2100, Distek, Monmouth Junction, NJ). The USP Apparatus 1 (basket) method was used at an agitation rate of 50 rpm. Data were acquired using a spectrophotometer (Hewlett-Packard Co., Valley Forge, PA). Dissolution profiles were generated at 37.5 °C, with detection at 228 nm for hydrochlorothiazide and 230 nm for diphenhydramine hydrochloride. Tablets were introduced into 900 mL of solution that consisted of 0.1 N HCl for hydrochlorothiazide and pH 7.0, 0.1M phosphate buffer for diphenhydramine HCl.

RESULTS AND DISCUSSION

Table 1 shows the crushing strength values of tablets prepared with both model drug compounds and both excipient fillers using low-shear and high-shear agitation along with 0.2% and 2.0% magnesium stearate levels and 2 minute and 30 minute mixing times. Tablets prepared in the high-shear mixer, for either drug tested, had lower crushing strength values than those prepared in the twin-shell blender. Previous authors (11, 15) suggested that based on the layer structure of the magnesium stearate crystal, it behaves by shearing off during mixing and is adsorbed onto the surface of other particles in the mix, forming a barrier which interferes with bonding between particles. The high level of mechanical activity of a high-shear mixer may remove a greater percentage of the lubricant from its crystal surface per unit of time versus the low shear twin-shell blender. This difference may create a greater degree of distribution of the lubricant within the powder mix, which results in lowered tablet hardness values.

Tablets containing unmilled anhydrous calcium phosphate, dibasic (A-TAB) were harder than those prepared using spray-dried hydrous lactose (Fast Flo Lactose-316) regardless of drug type or mixing condition. It was reported in past studies that the impact of magnesium stearate on the mechanical strength of tablets is dependent on the bonding mechanism of the

TABLE 1

The Effect of Mixing Time and Magnesium Stearate Level on the Crushing Strength Values of Tablets (kp)

Lubricant Level and Mixing Time	Hydrochlorothiazide				Diphenhydramine HCl			
	A-Tab		Fast Flo-316		A-Tab		Fast Flo-316	
	TSB*	HS**	TSB	HS	TSB	HS	TSB	HS
0.2% mag. st., 2 min. mix	>32.1	27.9	17.2	11.5	>32.1	25.1	17.4	10.9
0.2% mag. st., 30 min. mix	>32.1	26.1	7.1	7.0	27.8	23.1	10.4	10.1
2.0% mag. st., 2 min. mix	24.9	15.0	18.2	8.1	23.8	14.3	12.1	7.8
2.0% mag. st., 30 min. mix	16.7	13.5	12.4	10.1	22.4	14.2	6.8	6.9

TABLE 2

The Effect of Mixing Time and Magnesium Stearate Level on the Friability Values of Tablets (Percent Weight Loss After Six Minutes of Testing)

Lubricant Level and Mixing Time	Hydrochlorothiazide				Diphenhydramine HCl			
	A-Tab		Fast Flo-316		A-Tab		Fast Flo-316	
	TSB	HS	TSB	HS	TSB	HS	TSB	HS
0.2% mag. st., 2 min. mix	0.1	0.05	0.04	3 caps	0.02	0.05	0.1	2 caps
0.2% mag. st., 30 min. mix	0.1	0.04	0.02	3 caps	0.1	0.08	0.12	6 caps
2.0% mag. st., 2 min. mix	0.1	0.05	0.07	6 caps	0.1	0.1	0.02	6 caps
2.0% mag. st., 30 min. mix	0.8	0.05	0.14	6 caps	0.8	0.06	0.24	6 caps

* (TSB = Twin-shell blender)
** (HS = High shear mixer)

components of the powder mix (11, 19). A-TAB fragments during compaction, which creates clean, lubricant-free surfaces with which to bond and establish tablet strength. There were slight differences in tablet hardness as a result of mixing time when using mixes that contained 0.2% magnesium stearate and A-TAB. The 2.0% lubricant level samples showed a similar trend. The exception was observed in tablets containing hydrochlorothiazide and A-TAB, which were mixed for 30 minutes in a twin-shell blender. These tablets had the greatest difference in hardness values (32.9%).

Fast Flo Lactose-316 appears to compact via a combination of brittle fracture and plastic deformation, which does not create as many new surfaces. The implication is that this type of compaction behavior is more susceptible to the interference of bonding sites by magnesium stearate, resulting in lower tablet crushing strength values as observed in Table 1. The most significant difference in tablet hardness was seen in tablets containing diphenhydramine HCl or hydrochlorothiazide, and Fast Flo Lactose-316 and mixed in the twin-shell blender.

Mixes containing 0.2% magnesium stearate generated tablets that had higher crushing strengths than those with 2.0% lubricant. This was observed for both excipients. This is a logical result of more magnesium stearate available for creation of its characteristic film which interferes with tablet bonding properties.

Table 2 shows the effect of mixing time and magnesium stearate level on the friability values of tablets. Only tablets containing Fast Flo Lactose-316 and mixed in the high shear mixer exhibited capping tendencies in the friabilator. This was observed for both model drug compounds. Capping is usually associated with poor bonding within a compressed tablet. The tablets generated with Fast Flo Lactose-316 using the twin-shell blender and all tablets containing A-TAB had friability values of less than 1% weight loss after 6 minutes of testing. Friability values of less than 1% weight loss are considered acceptable in the pharmaceutical industry. Friability testing is a determination of the ability of a tablet to withstand the mechanical activity associated with packaging and handling during manufacturing.

Table 3 shows the effect of mixing time and magnesium stearate level on the tablet ejection forces from a rotary press. Lubricants like magnesium stearate ease tablet ejection by reducing the coefficient of friction between the compressed tablet and the die wall of the tablet tooling (15). The ejection forces of tablets

TABLE 3

Effect of Mixing Time and Magnesium Stearate Level on the Tablet Ejection Forces From a Rotary Press (kg)

Lubricant Level and Mixing Time	Hydrochlorothiazide				Diphenhydramine HCl			
	A-Tab		Fast Flo-316		A-Tab		Fast Flo-316	
	TSB*	HS**	TSB	HS	TSB	HS	TSB	HS
0.2% mag. st., 2 min. mix	54.4	67.1	37.2	44.4	96.6	160.5	44.9	41.7
0.2% mag. st., 30 min. mix	56.2	69.8	41.7	48.1	146.5	183.2	39.9	46.3
2.0% mag. st., 2 min. mix	40.8	45.4	34.5	38.1	44.9	46.7	38.5	37.6
2.0% mag. st., 30 min. mix	42.2	49.0	37.6	45.4	43.1	57.6	37.2	41.3

* (TSB = Twin-shell blender)

** (HS = High shear mixer)

containing A-TAB were higher than the corresponding Fast Flo Lactose-316 samples. This may be due to the brittle fracture compaction behavior of A-TAB, which when compressed within the die cavity, creates new uncontaminated surfaces free of lubricant. These clean surfaces would then have a high coefficient of friction and would produce elevated ejection force values. It is interesting to note that when reviewing tablets with 0.2% lubricant, those containing diphenhydramine HCl and A-TAB had ejection forces 2 to 3 times higher than those containing hydrochlorothiazide and A-TAB, regardless of which mixing equipment or mixing times were used. Tablets containing Fast Flo Lactose-316 had similar ejection force values regardless of the type of drug, magnesium stearate level, or method of mixing. All tablets containing 2.0% magnesium stearate had similar ejection force values regardless of the type of drug, excipient, or mixing method used.

Figures 2-5 represent drug release profiles from tablets containing diphenhydramine HCl. Figures 6-9 represent drug release from tablets containing hydrochlorothiazide. To assist the reader in making comparisons between dissolution profiles, dotted lines were placed at the 80% drug release and ninth hour positions. Generally, drug release was impacted to the greatest extent by the solubility of the model drug, followed by the type and solubility of the excipient/filler, and to a lesser extent by the type of mixer used. Hydrochlorothiazide, which has poor aqueous solubility, was released over a longer period of time than was the highly water soluble diphenhydramine HCl. Drug release from tablets within the same model drug and excipient type was faster for those mixed in a high shear mixer versus those mixed in a twin-shell blender. It was also observed that within a specific model drug, those tablets containing A-TAB (water insoluble) released the drug over a longer period of time than those containing Fast Flo Lactose-316 (water soluble). Overall, the level of magnesium stearate had minimal impact on the drug release profiles from the controlled-release tablets used in this study. This is not the case for conventional immediate-release dosage forms, which have been shown to be susceptible to the hydrophobic effects of magnesium stearate, which results in the lengthening of drug disintegration and dissolution times (13, 15, 16, 18, 24, 25).

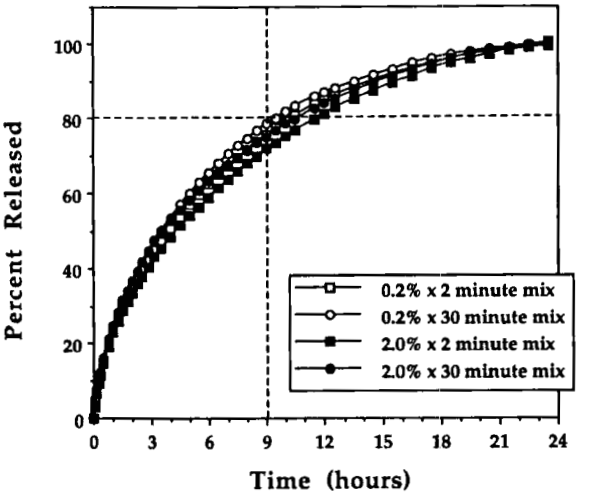

FIGURE 2.

Diphenhydramine HCl release from tablets containing A-TAB and mixed in a twin-shell blender.

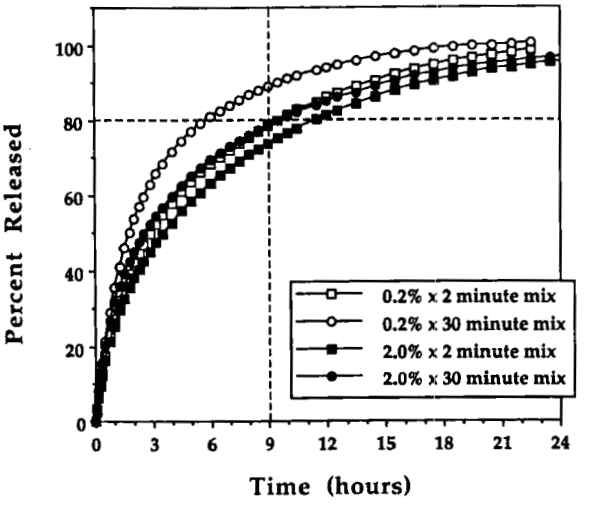

FIGURE 3.

Diphenhydramine HCl release from tablets containing A-TAB and mixed in a high shear mixer.

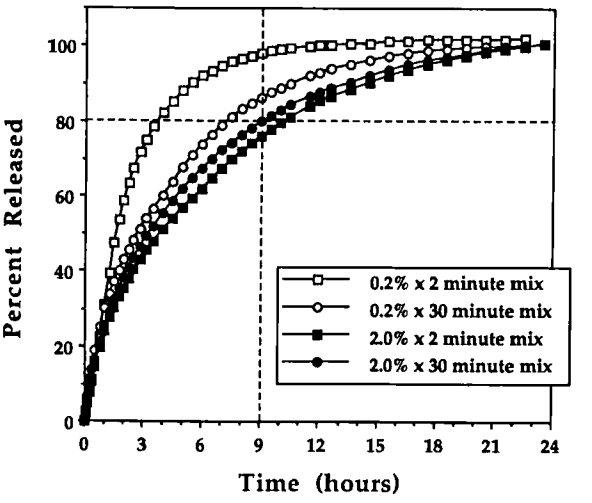

FIGURE 4.

Diphenhydramine HCl release from tablets containing Fast Flo Lactose-316 and mixed in a twin-shell blender.

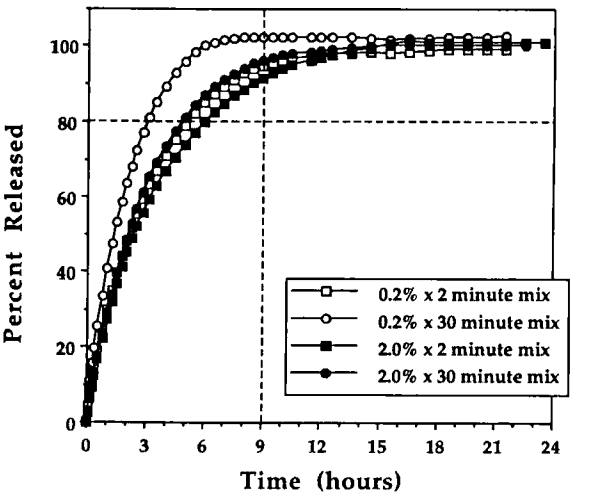

FIGURE 5.

Diphenhydramine HCl release from tablets containing Fast Flo Lactose-316 and mixed in a high shear mixer.

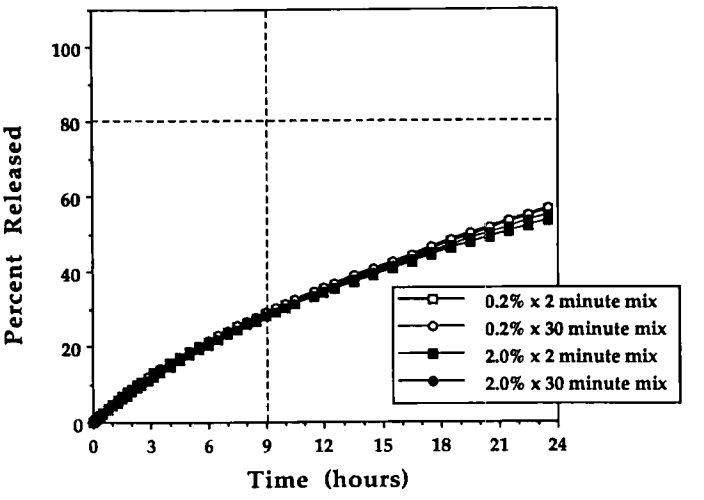

FIGURE 6.

Hydrochlorothiazide release from tablets containing A-TAB and mixed in a twin-shell blender.

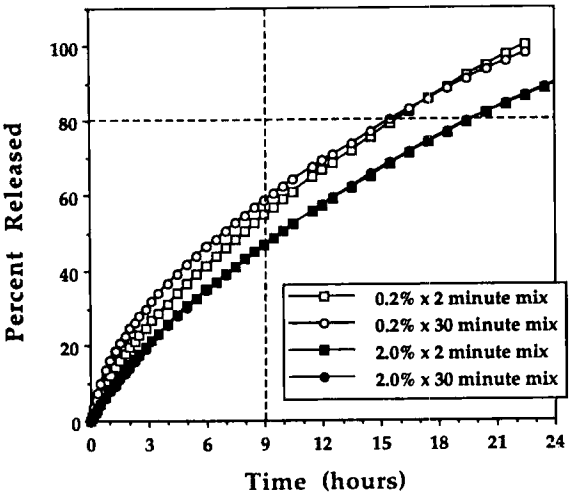

FIGURE 7.

Hydrochlorothiazide release from tablets containing A-TAB and mixed in a high shear mixer.

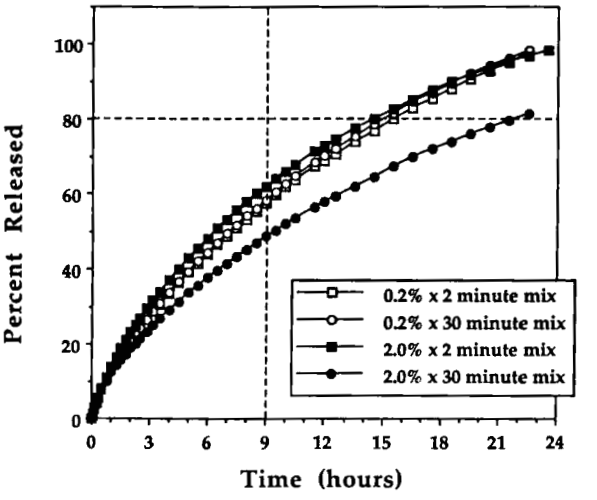

FIGURE 8.

Hydrochlorothiazide release from tablets containing Fast Flo Lactose-316 and mixed in a twin-shell blender.

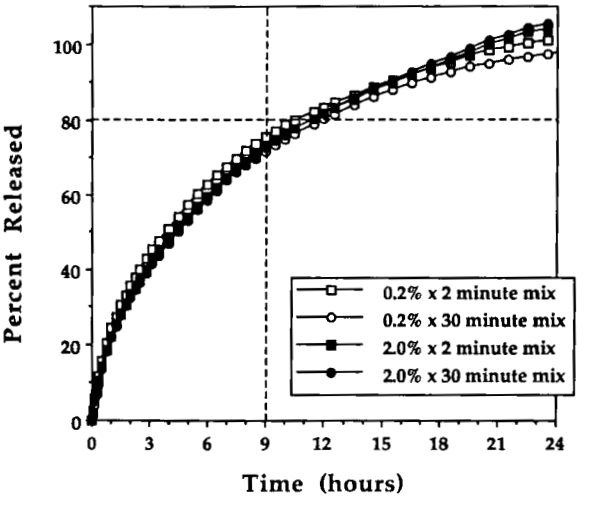

FIGURE 9.

Hydrochlorothiazide release from tablets containing Fast Flo Lactose-316 and mixed in a high shear mixer.

CONCLUSIONS

The following conclusions are based on the model drug compounds used in this study:

1. Drug release was impacted to the greatest extent by the solubility of the drug and excipient/filler but was only minimally affected by the level of magnesium stearate.

2. Tablets containing unmilled anhydrous calcium phosphate, dibasic (A-TAB) were harder and had significantly better friability patterns than those prepared using spray-dried hydrous lactose (Fast Flo Lactose-316), regardless of drug type or mixing condition.

3. Mixes containing 0.2% magnesium stearate generated tablets that had higher crushing strengths than those with 2.0% of the lubricant.

4. The impact of magnesium stearate on the mechanical strength of tablets appears to be dependent on the bonding mechanism of the components of the powder mix.

5. Tablet ejection forces were influenced to the greatest extent by the level of lubricant in the formulation.

6. The effects of magnesium stearate on controlled-release matrix tablets appears to be similar to any tabletted dosage form with regard to its interference with particle bonding. However, it also appears that drug release from these matrix systems is rather resistant to the hydrophobic effects of magnesium stearate. This is important because of all the excipients used in tabletted dosage forms, magnesium stearate is responsible for a majority of the formulation concerns and manufacturing problems.

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