Drug Development and Industrial Pharmacy, 22(7), 587-594 (1996)

Spray-Dried Rice Starch: Comparative Evaluation of Direct Compression Fillers

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ABSTRACT

Spray-dried rice starch (SDRS), microcrystalline cellulose (MCC), lactose (L), pregelatinized starch (PS), and dibasic calcium phosphate (DCP) were studied for their flow behaviors and tableting properties. Both flow rate and percent compressibility values indicated that SDRS exhibited excellent flowability. The increase in magnesium stearate content reduced the hardness of MCC and SDRS tablets; however, general tablet properties were still acceptable while the PS tablets were unsatisfactory at high lubricant concentrations. The hardness of L or DCP tablets was not affected by the lubricant. The disintegration of L tablets was prolonged with the increased lubricant concentration while that of PS tablets seemed to be decreased due to softened tablets. The disintegration times of MCC and SDRS tablets seemed to be independent of the lubricant added. With respect to the dissolution, SDRS-based tablets offered fast and complete release of the drug regardless of its solubility. SDRS, L, and DCP exhibited comparable carrying capacity for ascorbic acid. The best dilution potential was obtained with MCC while the worst was obtained with PS.

INTRODUCTION

The direct compression technique has been employed for tablet manufacture for several decades, but it is still not widely accepted for many reasons. The availability influences the approval of tablet manufacturers, especially when the fillers have to be imported. Most direct compression fillers are produced in the United States or Europe; therefore, cost of a filler in some areas may be relatively high. Thus the direct compression technique may not offer any economical advantage over the wet granulation process. Recently a new direct compression filler—i.e., spray-dried rice starch (SDRS)—was produced in Thailand and marketed under the trade name

of Era-Tab®. Mitrevej and Varavinit (1) had shown that SDRS was spherical and made up almost entirely of agglomerates of rice starch grains (Fig. 1). The compactibility of SDRS was second to that of microcrystalline cellulose (Avicel® PH102). The dissolution of the drugs, regardless of their solubilities, was excellent. The authors claimed that SDRS could be employed successfully in direct compression tableting. Bos et al. (2) had also reported the potential application of SDRS as a direct compression filler. It is known that flowability and compatibility as well as dilution potential are prime concerns in the application of direct compression fillers. The term "dilution potential" or "carrying capacity" is defined as the amount of active ingredients which the diluent can successfully carry in the direct compression technique (3). This study was designed to investigate the flow rate, packing characteristics, and the effects of magnesium stearate level on tablet strength, disintegration, and carrying capacity of SDRS in comparison with other direct compression fillers. Dissolution of active drugs from the directly compressed tablets was also studied.

MATERIALS

Five directly compressible fillers were employed throughout the study. These fillers were: spray-dried rice starch, SDRS (Era-Tab, Erawan Pharmaceutical Research and Laboratory, Thailand), microcrystalline cellulose, MCC (Avicel PH102, Asahi Chemical Industry, Japan), lactose, L (Tablettose®, Meggle, Germany), pregelatinized starch, PS (Starch® 1500, Colorcon, England), and dibasic calcium phosphate, DCP (Emcompress®, Edward Mendell, USA). Ascorbic acid, hydrochlorothiazide, and propranolol hydrochloride were employed as active drugs, and magnesium stearate was used as lubricant.

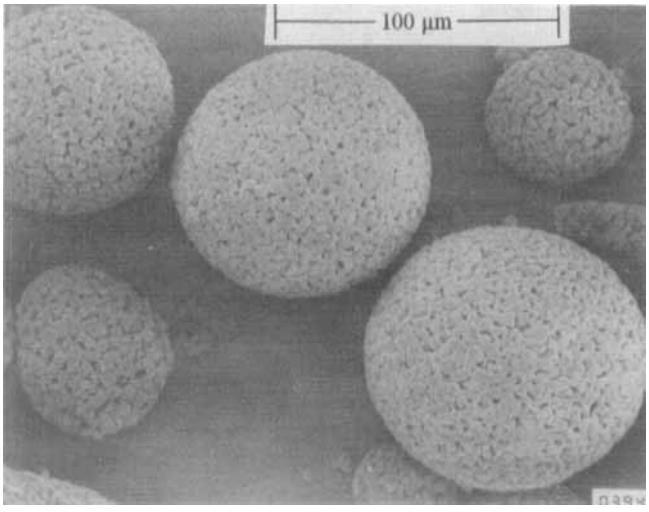

Figure 1. Photomicrograph of spray-dried rice starch.

METHODS

Densities and Percent Compressibility

Each previously weighed filler was gently poured into a 100-ml cylinder. The initial volume was determined and the bulk density was calculated. To determine the packed density, the cylinder was placed on a jolting volumeter (J. Engelmann, Germany) and then tapped for 1000 times. The % compressibility was calculated from the bulk and packed densities as follows (4):

$$\% \text{ compressibility} = \frac{\text{packed density} - \text{bulk density}}{\text{packed density}}$$

Each value reported is an average of three determinations.

Flowability Study

Flow property of each filler was evaluated using a strain gauged flow meter. The construction of the flow meter was similar to that described by Gold et al. (5). The signal was amplified and recorded via a dynamic strain amplifier (Kyowa DPM-612A, Japan) and an oscillographic recorded (Pantos U-631, Japan). The powder was allowed to flow through a funnel with the height of 6 cm, upper diameter of 6 cm, and orifice diameter of 1 cm. The average of three determinations is reported.

Effect of Lubricant Concentration

Each filler was lubricated with magnesium stearate at the 0.25%, 0.5%, 0.75%, and 1.0% levels; except DCP, which was lubricated at the 0.75%, 1.0%, 1.25%, and 1.5% levels. Each mixture was blended in a V-shaped blender for 5 min. The tablets were compressed on an instrumented single-punch tablet press (Fette type E1, Germany), fitted with 10-mm flat-faced punches. Both the upper and lower punch holders were bonded with metal foil resistance strain gauges (Micro-Measurements, USA). The bonding and wiring proce-

dure was similar to that described by Salpekar and Augsburger (6) for compression event. The Wheatstone bridge circuit was connected to a dynamic strain amplifier (Kyowa DPM 612A, Japan). The signals were amplified and recorded on a strip chart oscillographic recorder (Pantos U-631, Japan). The tablet weight was adjusted to 300 mg and compressed at various applied loads ranging from 12.5 to 125 MPa depending upon the fillers.

Dilution Potential Study

Ascorbic acid was added to each filler at various concentrations, i.e., 5%, 10%, 15%, 20%, 25%, and 30%. The filler and ascorbic acid were blended in the V-shaped blender for 10 min. Magnesium stearate was added at the level of 0.75% and mixed for an additional 5 min. The tablets were prepared as previously described.

Dissolution Study

Hydrochlorothiazide (HCTZ) tablets and propranolol hydrochloride (PPNL) tablets were prepared at 25 mg and 40 mg strength, respectively. Each formulation consisted of an active drug, a direct compression filler, and magnesium stearate. The active drug was blended with the filler for 10 min in the V-blender. Magnesium stearate was added at 0.5% level and blended for an additional 2.5 min. The powder mixtures were compressed using 8-mm tooling. The tablet weight and hardness were adjusted to 200 mg and 50 N, respectively.

Evaluation of Tablet Properties

Tablet properties were determined after the tablets were stored for 24 hr at 25°C and 45% RH. The hardness was measured with an electronic hardness tester (Scheuniger 4M, Switzerland). The average hardnesses of 10 tablets at each compaction load were compared. The disintegration time was determined using the USP XXII method; each value reported is the average reading of six tablets.

Dissolution test for each drug preparation was performed as described in USP XXII. The dissolution apparatus setup consisted of a dissolution station using rotation baskets (Hanson QC 72RB, USA) and an ultraviolet (UV)/visible spectrophotometer (Beckman DU65, USA) equipped with six 1-cm flow cells and a 6-channel peristaltic pump. An absorbance was determined every 5 min.

RESULTS AND DISCUSSION

Flow Characteristics

Packing Characteristics

The bulk and packed densities as well as Carr's compressibility index, or % compressibility, are reported in Table 1. Bulk densities of the fillers were comparable to those reported elsewhere (7). The term "compressibility" in this study refers to the packing characteristics of the materials, and it has been suggested that the lower the value, the better is the flow (8). In this case,

Table 1

Density and Carr's Compressibility Index

	Density, g/ml[a]		
	Bulk	Packed	% Compressibility
SDRS	0.527	0.623	15.42
	(0.006)	(0.003)	(0.88)
MCC	0.341	0.478	28.66
	(0.005)	(0.004)	(0.52)
L	0.549	0.772	28.45
	(0.006)	(0.004)	(1.39)
PS	0.599	0.760	21.14
	(0.004)	(0.004)	(0.95)
DCP	0.861	1.050	17.99
	(0.008)	(0.004)	(0.60)

[a]The numbers in parentheses are standard deviations.

the order of decreasing flowability was SDRS > DCP > PS > L ≈ MCC. Jones (9) had reported the compressibility of several excipients, and the values reported for Emcompress and Starch 1500 agreed very well with those found in this study.

Flow Rate

It can be seen that the compressibility index is not a direct method for the evaluation of flowability. To directly measure the flow characteristic, flow rate measurement should be considered. Flow rate of each filler in grams per second was calculated from the tracing on the recorded strip chart paper. Many filling processes are controlled by volume adjustment. Tablet and capsule weights, for example, are adjusted by controlling the volume of the powder in the cavity in which the tablets or capsules will be formed. Therefore, the flow rate by volume is meaningful as well. Since the powder is allowed to flow freely under the gravitational force through the funnel orifice, the volume of the powder can be calculated by dividing the powder weight by the bulk density of the powder. In this study the bulk density of each powder was obtained from Table 1. The volumetric flow rate was calculated and reported in milliliters per second. Table 2 shows the flow rates both by weight and by volume. The order of decreasing flow rate by weight was DCP > SDRS > PS > L > MCC, and by volume was SDRS > DCP > PS > L > MCC. The volumetric flow is governed by the volume of each particular powder; hence, the flow rate by volume should be better than that by weight in relation to the value of % compressibility. The choice of choosing either parameter—i.e., flow rate by volume or by weight—should depend on the application of the value. If the process of filling or handling of the material is carried out by weight, then flow rate by weight should be chosen, and vice versa.

Table 2

Flow Rate Through a Funnel of 1-cm Orifice

	Flow Rate[a]	
Filler	g/sec	ml/sec
SDRS	33.93	64.01
	(1.58)	(2.99)
DCP	47.62	52.33
	(–)	(–)
PS	29.83	48.11
	(2.66)	(3.00)
L	19.83	29.17
	(0.98)	(1.44)
MCC	No flow	No flow

[a]The numbers in parentheses are standard deviations.

It was reported that SDRS had spherical dimentions (1,2). Undoubtedly, SDRS would flow better than any directly compressible fillers used in this study. The bulk density of DCP, however, was higher than that of SDRS. The flow of DCP by weight was therefore better than that of SDRS. It was also found that the flow of DCP was so reproducible that variation among tests was not observed.

MCC was found to be the only filler which did not flow under the test conditions employed, i.e., the specified orifice diameter and dimensions of the funnel. This was not surprising since MCC had the lowest bulk density. Its flow governed by gravitational force without any stimulation or inducer might be difficult.

Effect of Lubricant Concentration

Hardness

The effect of magnesium stearate concentration on the tablet hardness at various compression forces is illustrated in Fig. 2. As expected, the hardness increased with compression force. The hardness decreased with increased lubricant level, except those of L and DCP. The hardnesses of both L and DCP tablets were unchanged regardless of lubricant level. DCP has been reported to be fragment material, and the hardness of the DCP tablets would unlikely to be affected by the degree of lubrication (10,11). L was believed to undergo either plastic or brittle fracture under compaction (12–14). The results showed that under the experimental conditions employed in this study, fragmentation was a prominent deformation of L.

Even though the reduction of the hardness of SDRS tablets with increased lubricant level was noticeable, the hardness of the tablets compressed at the force of 100 MPa or higher was acceptable in comparison with DCP, PS, and L. To the contrary, the hardness of PS tablets was markedly decreased with increased lubricant concentration, and the tablets were difficult to handle if the lubricant level was higher than 0.5%. It has been shown that starch-based fillers were sensitive to the alkali stearate lubricants (9,10). MCC was also affected by the presence of the lubricant; however, the decrease in the hardness was not significant. The results indicated that the overall order of decreasing compactibility was MCC > SDRS > DCP > L > PS. Since the hardness of PS depended greatly on the concentration of magnesium

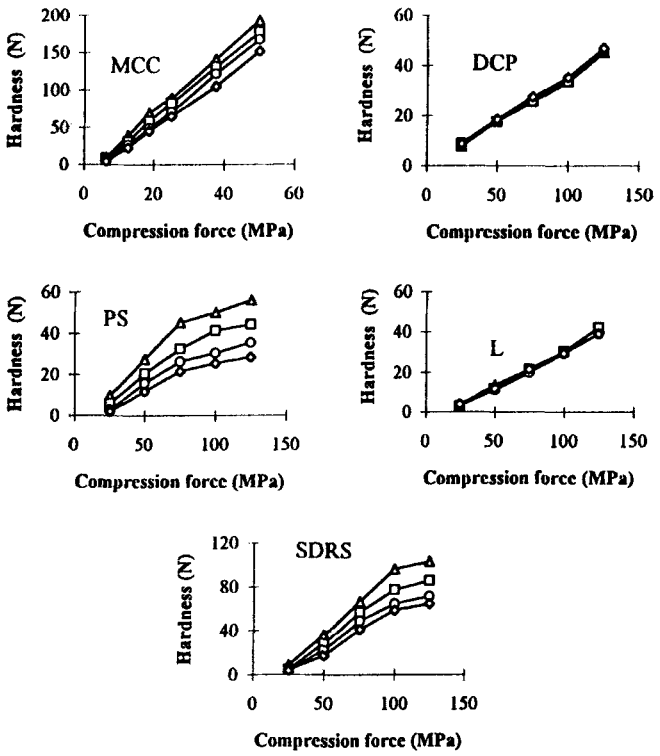

Figure 2. Effect of magnesium stearate concentration on tablet hardness. For MCC, PS, L, and SDRS: (Δ) 0.25%, (□) 0.5%, (○) 0.75%, (◇) 1.0%. For DCP: (Δ) 0.75%, (□) 1.0%, (○) 1.25%, (◇) 1.5%.

stearate, the compactibility in this case should be compared at the same magnesium stearate level.

Disintegration Time

Figure 3 demonstrates the effect of magnesium stearate on the disintegration time. With SDRS, the disintegration property seemed to be independent of the lubricant concentration and compression force. However, the tablets containing 1.0% lubricant and compressed at the pressure of 25 MPa were too friable for the test. Since SDRS mainly comprised the agglomeration of starch grains as shown in Fig. 1, the matrix probably fell apart easily when being immersed in the water. PS tablets became gel-like when wetted; the gelatinous layer impeded the penetration of water into the tablets and thus prolonged the disintegration. Since the increase in lubricant concentration substantially decreased the hardness, the faster disintegration time of PS tablets at higher lubricant levels could very well be due to the softer tablets. Bolhuis and Lerk (15) showed that the hardness of PS tablets decreased with the increased magnesium stearate concentration. They also suggested that magnesium stearate should not be used in concentrations greater than 0.5%. Moreover, they found that the disintegration time of PS tablets lubricated with 0.5% magnesium was shorter than those without magnesium stearate. Their findings agreed very well with those in the present study. MCC tablets disintegrated rapidly regardless of the magnesium stearate concentration. This finding could be due to the fact that MCC exhibited disintegration property (16–18). Since DCP was water insoluble and no disintegrating agent was added to the tablets, the DCP tablets did not disintegrate in 45 min except those compressed at 25 MPa of pressure, the hardness of which was less than 10 N.

The disintegration time of L tablets markedly increased with lubricant level while the hardness, as previously mentioned, was not significantly affected. The increased disintegration time could be due to the fact that L was water soluble; therefore, the L tablets would dissolve rather than disintegrate. The higher lubricant concentration undoubtedly imparted more hydrophobicity to the tablets (10,19). The wettability of the tablets would be reduced, thus resulting in prolonged disintegration or dissolution of the tablets. It should be mentioned again that the effect of magnesium stearate on the hardnesses of L and PS tablets were different, and that the behaviors of L and PS tablets in aqueous medium, as mentioned earlier, were not the same. Therefore the results of lubricant hydrophobicity on the disintegration of these two materials were not parallel.

In terms of comparison among various direct compression fillers, at any lubricant level, MCC tablets exhibited the fastest disintegration time, i.e., less than 1 minute whereas DCP tablets seemed to give the longest disintegration. L and SDRS tablets appeared to possess similar disintegration times; however, those of SDRS were not affected by the compression force. PS tablets disintegrated more slowly than did L and SDRS tablets. The decreasing order of disintegration property was MCC > SDRS ~ L > PS > DCP.

Dilution Potential Study

The ability of each directly compressible filler to carry ascorbic acid was studied. Since ascorbic acid itself is not compressible, it was an ideal excipient for the evaluation of carrying capacity of these fillers. Kanig (3) and Lamberson and Raynor (20) suggested that the dilution potential or carrying capacity was expressed in terms of the highest percentage of noncompressible material in the acceptable tablets or as optimum drug to

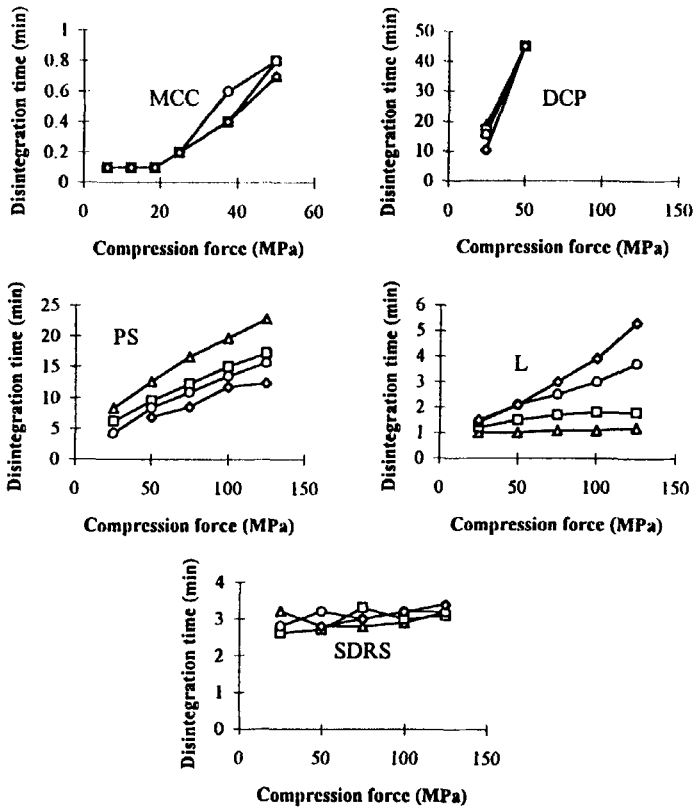

Figure 3. Effect of magnesium stearate concentration on disintegration time. For MCC, PS, L, and SDRS: (Δ) 0.25%, (□) 0.5%, (○) 0.75%, (◇) 1.0%. For DCP: (Δ) 0.75%, (□) 1.0%, (○) 1.25%, (◇) 1.5%.

carrier or filler ratio. This present study did not try to define the term "carrying capacity" as a single number but it should be pointed out that as the amount of non-compressible component was increased, the compactibility would be decreased, and the extent of decrease depended upon the carrying capacity of each filler. The results are shown in Fig. 4. The addition of ascorbic acid to any filler tested significantly decreased the tablet hardness. The results clearly demonstrated that MCC was far superior to every filler in terms of dilution potential or carrying capacity, and PS was probably the worst since the hardness of the tablets containing 20% or more of ascorbic acid was less than 10 N. SDRS, L, and DCP showed comparable dilution potential; however, at the compression force of 125 MPa, SDRS seemed to be slightly better than the other two fillers.

Dissolution Study

Two active drugs representing water-soluble and poorly water-soluble properties were studied. To elucidate the effect of filler on the dissolution of the drug, each drug was formulated with various direct compression fillers.

Dissolution characteristics of the HCTZ tablets are shown in Fig. 5. Since the formulation did not contain any additional disintegrating agent, the filler possessing disintegrating activity would be preferable in order to break the tablets apart and release the drug into the dissolution medium. It can be seen that both SDRS- and MCC-based tablets gave faster initial dissolution than did the others. SDRS is the agglomerated form of rice starch; the tablets produced from SDRS are expected to disintegrate into starch grains in the aqueous medium. Therefore, drug particles are released into the dissolution medium, resulting in fast and complete dissolution. The incomplete dissolution of HCTZ was observed with MCC-based tablets; this finding could be due to the entrapment of the active drug within the MCC network. Shangraw (7) suggested that MCC underwent plastic deformation upon compression and the formulations containing more than 80% MCC could slow the dissolution rates of low-water-soluble drugs. He explained that drug particles could get trapped between the de-

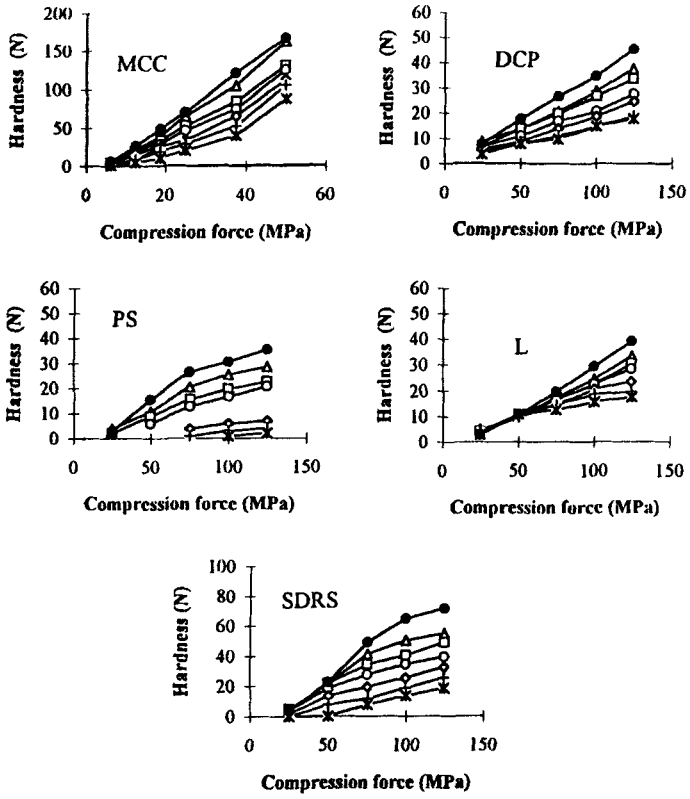

Figure 4. Effect of ascorbic acid concentration on the compressibility of various fillers. (●) 0%, (Δ) 5%, (□) 10%, (○) 15%, (◇) 20%, (+) 25%, (*) 30%.

formed MCC particles. It might be difficult for some drug particles to be released into the dissolution medium. As a consequence, the incomplete dissolution was obtained.

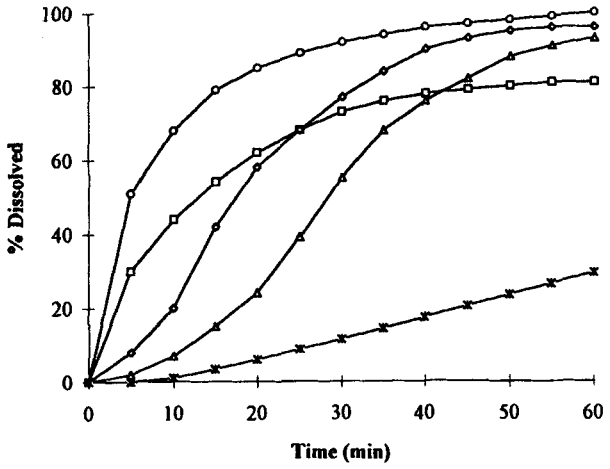

Figure 5. Effect of filler on dissolution of hydrochlorothiazide tablets. (□) MCC, (Δ) PS, (◇) L, (○) SDRS, (*) DCP.

L-based tablets normally shows erosion of the matrix rather than disintegration. The dissolution process proceeds with the wear out of the tablets. Therefore, slow but complete dissolution could be anticipated. The gelation at the surface of PS-based tablets caused the viscous layer and delayed the penetration of the water into the tablets, and thus prolonged the dissolution of the poorly water-soluble drug. Since DCP-based tablets did not disintegrate and DCP itself was a water-insoluble filler, the dissolution of HCTZ was undoubtedly slow and incomplete within the time specified.

Dissolution profiles of PPNL tablets obtained from each filler, except DCP, were comparable, as shown in Fig. 6. PPNL itself is water soluble and able to dissolve easily as water penetrates into the tablets. Visavarungroj et al. (21) also observed that pregelatinized starch granules swelled and formed a viscous gel barrier in contact with water. They found that the viscous gel blocked the tablet pores and hindered further water uptake. Since PPNL tablets were prepared at the strength of 40 mg, it was conceived that there were drug particles distributing on the surface of the tablets as well as in the tablets. These drug particles would interrupt the gel formation caused by PS at the tablet surface. Therefore, the penetration of water would be enhanced. The release of PPNL from DCP-based tablet was better than that of HCTZ from DCP-based tablets. However, the results were still far from satisfactory.

It could be clearly seen that the physical properties of filler play a significant role in dissolution characteristic of tablets, especially with the poorly water-soluble drug. It is not advisable to incorporate a water-insoluble

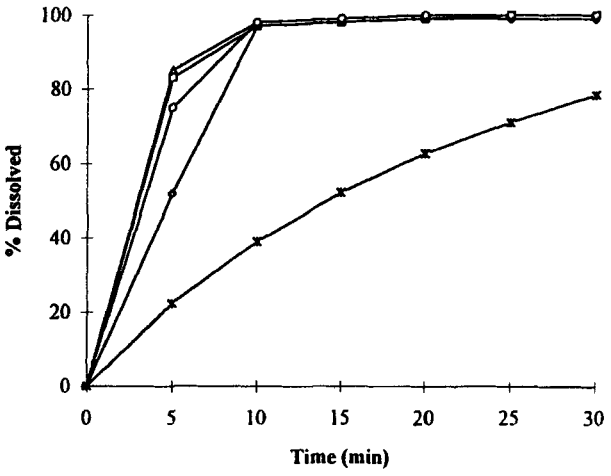

Figure 6. Effect of filler on dissolution of propanolol hydrochloride tablets. (□) MCC, (Δ) PS, (◇) L, (○) SDRS, (*) DCP.

filler with a water-insoluble drug. The dissolution of a water-soluble drug is less affected by the nature of the filler. Effects of fillers on disintegration and dissolution of soluble and insoluble drugs were studied elsewhere (22,23) and the results reported agreed with the findings in this study.

CONCLUSIONS

SDRS is a spray-dried form of rice starch. Since it is free-flowing and compressible, its main application is as direct compression filler. Flow properties of the fillers were evaluated using Carr's compressibility indices and flow rates through a given orifice. The results revealed that SDRS and DCP possessed excellent flow properties. PS could flow moderately. L and MCC exhibited flow problems. The increase in alkali stearate lubricant markedly reduced the hardness of plastic and elastic materials, especially starch-based fillers. Disintegration of SDRS was found to be independent of the compression force and lubricant level employed in the study. Dilution potential was determined by using ascorbic acid. MCC had the highest carrying capacity while PS had the lowest. SDRS, L, and DCP possessed comparable carrying capacities for ascorbic acid. The study suggested that SDRS possessed desirable properties for direct compression filler. It offered excellent flowability, compactibility, and disintegration property as well as acceptable carrying capacity. Regardless of the solubility of active drug, dissolution of the drug from SDRS-based tablets was both fast and complete.

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