Effect of Polysulfonate Resins and Direct Compression Fillers on Multiple-Unit Sustained-Release Dextromethorphan Resinate Tablets

Submitted: February 11, 2005; Accepted: March 7, 2005; Published: September 30, 2005

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ABSTRACT

The purpose of this work was to investigate the effect of different polysulfonate resins and direct compression fillers on physical properties of multiple-unit sustained-release dextromethorphan (DMP) tablets. DMP resinates were formed by a complexation of DMP and strong cation exchange resins, Dowex 50 W and Amberlite IRP69. The tablets consisted of the DMP resinates and direct compression fillers, such as microcrystalline cellulose (MCC), dicalcium phosphate dihydrate (DCP), and spray-dried rice starch (SDRS). Physical properties of tablets, such as hardness, disintegration time, and in vitro release, were investigated. A good performance of the tablets was obtained when MCC or SDRS was used. The use of rod-like and plate-like particles of Amberlite IRP69 caused a statistical decrease in tablet hardness, whereas good tablet hardness was obtained when spherical particle of Dowex 50 W was used. The plastic deformation of the fillers, such as MCC and SDRS, caused a little change in the release of DMP. A higher release rate constant was found in the tablets containing DCP and Dowex 50 W, indicating the fracture of the resinates under compression, which was attributable to the fragmentation of DCP. However, the release of DMP from the tablets using Amberlite IRP69 was not significantly changed because of the higher degree of cross-linking of the resinates, which exhibited more resistance to deformation under compression. In conclusion, the properties of polysulfonate resin, such as particle shape and degree of cross-linking, and the deformation under compaction of fillers affect the physical properties and the drug release of the resinate tablets.

KEYWORDS: polysulfonate resins, dextromethorphan resinate tablets, direct compression filler, sustained-release

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INTRODUCTION

Oral sustained-release dosage forms have been used for improving therapeutic efficacy and patient compliance. These dosage forms can be classified into 2 types: single unit and multiple unit. Multiple-unit dosage forms have been accepted to provide advantages over single unit dosage forms.[1] The multiple-unit dosage forms consist of many small particles, which are contained in a capsule or a tablet. The small particles are mixed with the contents in gastrointestinal tract and are distributed over a large area. Thus, high-local concentration of the drug is avoided, and the risk of local irritations is reduced. Moreover, multiple units are also less variable and less dependent on gastric transit time, resulting in a reproducible bioavailability of the drug.

A polymer incorporating with drugs to form small particles, such as microparticles,[2-4] pellets,[5] and beads,[6] has been used as a drug reservoir in the multiple-unit tablets. Compaction of small particles into tablets could result either in disintegrating tablets to provide individual particles or in intact tablets because of the fusion of particles into a larger compact. Moreover, polymers used to form the small particles and excipients used as filler in the tablets affected on fracture of the small drug reservoirs after compression.[4] These led to a change of drug-release pattern from the drug reservoirs.

Ion exchange resins have been used as drug carriers in pharmaceutical dosage forms for taste masking[7] and controlling release.[8-10] These resins are cross-linked, water-insoluble, polymer-carrying, ionizable functional groups. Drugs can be loaded onto the resins by an exchanging reaction, and, hence, a drug-resin complex (drug resinate) is formed.[11] The drug is released from the resinates by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion.[12] The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resinates[13,14] and by selecting a degree of cross-linking and particle size of the resins without a coating process.[15,16] Moreover, the drug resinate can also be used as a drug reservoir, which caused a change of the drug release in hydrophilic polymer tablets.[17]

Dextromethorphan (DMP) hydrobromide (HBr), an amine compound, had a bitter taste and a short half-life. The complexation of DMP HBr with cation exchange resins

to form DMP resinates can reduce a bitter taste in liquid dosage form, and prolonged release of DMP was also obtained. DMP resinates prepared using polysulfonate resins Dowex 50 W and Amberlite IRP69 had a difference in particle shape and degree of cross-linking, but they provided a similar sustained-release pattern of DMP compared with a previous study.[18] This leads us to apply these resinates as drug reservoirs in the tablets, which rapidly disintegrated to provide individual multiple units of the resinates, and the release of DMP was controlled by the resinates. Therefore, the aim of this study was to investigate the effect of polysulfonate resins, namely, Dowex 50 W and Amberlite IRP69, and some direct compression fillers on physical properties of the resinate tablets. Additionally, the change of in vitro DMP release from the resinates after compression was also investigated.

MATERIALS AND METHODS

Materials

DMP HBr was a gift from F. Hoffmann-La Roche (Basel, Switzerland). Polysulfonate resins Dowex 50 W (100 to 200 dry mesh; 4% degree of cross-linking) and Amberlite IRP69 (100 to 500 wet mesh; 8% degree of cross-linking) were purchased from Aldrich Chemical Co, Milwaukee, WI. Amberlite IRP69 was used after sieving with 100 and 140 mesh screen, whereas Dowex 50 W was used as received. Microcrystalline cellulose ([MCC] Avicel PH102, Asahi Chemical Industry Co, Tokyo, Japan), dicalcium phosphate dihydrate ([DCP] Emcompress, Edward Mendell Co, Patterson, NY), spray-dried rice starch ([SDRS] Era-tab, Erawan Pharmaceutical Research and Laboratory Co, Bangkok, Thailand), sodium starch glycolate (Explotab, Rama Production Co, Thailand), and magnesium stearate (Mallinckrodt Inc, St Louis, MO) were used as tablet excipients. Methanol, benzene, and 37% HCl were analytical grade and used as received.

Purification of Ion Exchange Resins

Dowex 50 W was purified using the method reported by Irwin et al.[16] Resin (30 g) was washed successively with distilled water, methanol (300 mL), benzene (300 mL), methanol (300 mL), and several times with distilled water to eliminate organic and color impurities. Amberlite IRP69 was washed several times with distilled water.[19] Then, the wet resins were activated by 0.1 mol/L of HCl 300 mL and washed several times with distilled water. The wet resins were dried overnight in hot air oven at 50°C and kept in an amber glass vial.

Preparation of DMP Resinates

DMP resinates were prepared using a batch process. Resin (10 g) was placed in an Erlenmeyer flask, and then 500 mL of 2% w/v DMP HBr solution was added. The mixture was shaken in the water bath at 37°C for 2 hours. Then, the DMP resinates were separated from filtrate by filtration and washed several times with distilled water to remove any unreacted drug and other ions. The DMP resinates were dried overnight at 50°C and kept in a desiccator. The amount of free drug in the filtrate, as well as in the washing water, was determined spectrophotometrically at a wavelength of 278 nm (Model UV-1201, Shimadzu, Kyoto, Japan). Determinations were conducted in duplicate for each preparation. The difference in weights between the initial amount of drug added and the remaining amount of drug in the solution was the amount of drug loaded onto the resins.[20,21] The percentage of drug in the resinates was calculated in the form of DMP-free base and related to the dry weight of the resinates. The DMP loading of the resinates using Dowex 50 W was 43.3 ± 0.3% w/w, whereas that using Amberlite IRP69 was 32.9 ± 0.3% w/w.

Particle Size Determination

Particle size of the DMP resinates was determined using LS Particle Size Analyzer (Beckman Coulter Inc, Fullerton, CA). The dry resinates were resuspended in 0.1% w/v polysorbate 80 and then immediately counted. $D_{10\%}$, $D_{50\%}$, and $D_{90\%}$, which are the volume-number diameters where the given percentage of the particles is smaller than that size, were determined. In addition, the size distribution was computed in terms of a polydispersity index (PI) expressed as:

$$PI = \frac{D_{90\%} - D_{10\%}}{D_{50\%}} \quad (1)$$

Table 1. Particle-Size Analysis of DMP Resinates*

Resin	Volume-Number Diameter			PI
	$D_{10\%}$ (μm)	$D_{50\%}$ (μm)	$D_{90\%}$ (μm)	
Dowex 50 W	108.1 ± 0.8	170.9 ± 0.6	229.2 ± 0.3	0.71 ± 0.01
Amberlite IRP69	118.9 ± 1.9	165.5 ± 0.6	222.4 ± 0.7	0.62 ± 0.01

*Data are the mean ± SD from 3 determinations.

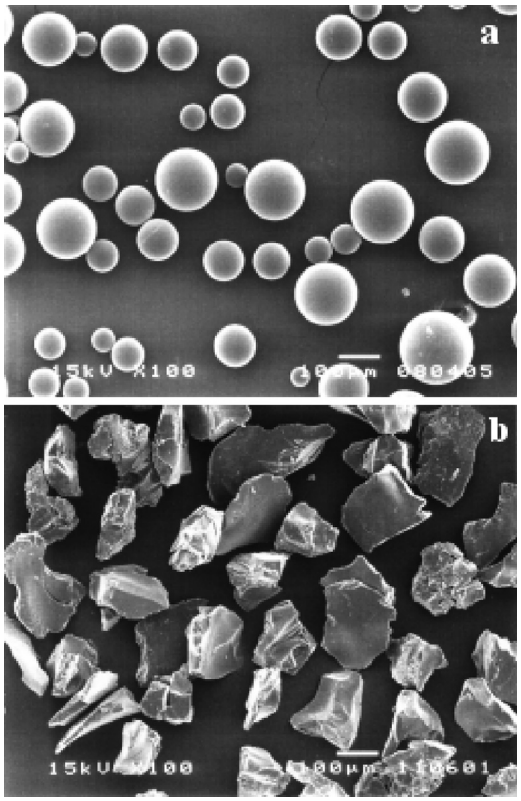

Figure 1. SEM photographs of DMP resinates using Dowex 50 W (a) and Amberlite IRP69 (b).

Preparation of Tablets

The tablets consisted of DMP resinates equivalent to DMP HBr 30 mg, sodium starch glycolate (10% w/w), magnesium stearate (1% w/w), and direct compression filler. The total weight of tablets using MCC and SDRS was 300 mg, whereas that using DCP was 400 mg. The DMP resinates, filler, and sodium starch glycolate were mixed in a roto-mixer for 20 minutes. Magnesium stearate sieved through a 180-μm sieve was mixed with the mixture for 5 minutes before tableting. Tablets were prepared by placing each mix into 10-mm diameter flat-faced punches and die and pressing at different compression pressures (1, 2, and 4 MPa) with a hydrostatic press (Model 3126, Shimadzu, Kyoto, Japan) with no holding time.

Evaluation of DMP Resinate Tablets

Thickness and Hardness

The thickness of the tablets was determined using a digital caliper (Model 500-136, Mitutoyo, Japan). The hardness of tablets prepared was determined using a tablet hardness tester (Model 40-2100, Vankel, Cary, NC).

Disintegration Time

The disintegration time of the DMP resinate tablets was determined using a basket-rack assembly disintegration test apparatus (Model QC-21, Hansan Research, Northridge, CA). The disintegration medium was distilled water maintained at 37.0 ± 0.5°C. Each tablet was placed into the basket, and the disintegration time was recorded at the point at which the tablet disintegrated and passed through the screen of the basket.

Microscopic Morphology

Surface morphology and internal structure of the DMP resinate tablets were studied using scanning electron

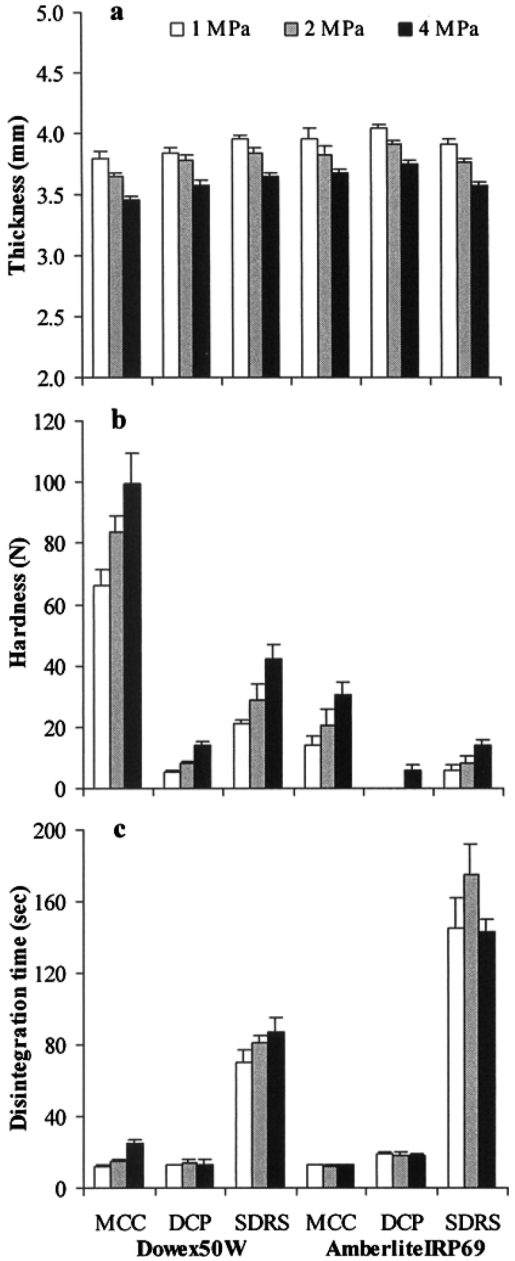

Figure 2. Thickness (a), hardness (b), and disintegration time (c) of DMP tablets prepared using various fillers at different compression pressures. Each point is the mean ± SD (n = 5).

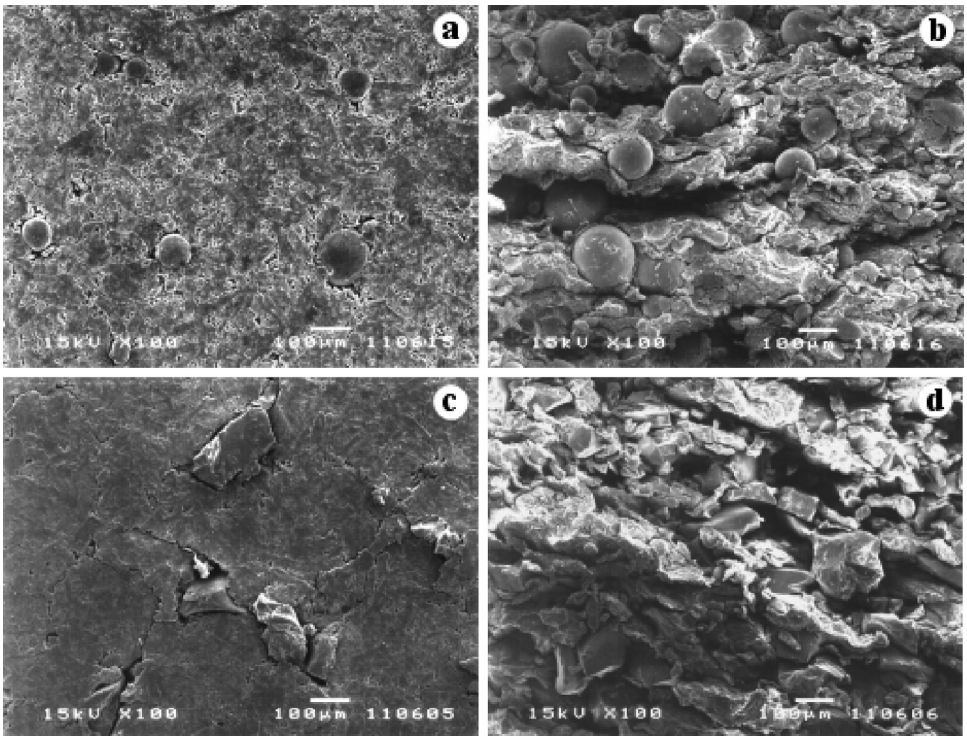

Figure 3. Surface morphology and internal structure of DMP-resinate tablets prepared using MCC at 4 MPa compression pressure: Dowex 50 W (a and b) and Amberlite IRP69 (c and d).

microscopy (SEM). Samples were mounted onto stubs, sputter coated with gold in a vacuum evaporator, and viewed using a scanning electron microscope (Model JSM-5800LV, Jeol, Tokyo, Japan).

In Vitro Release Studies

A US Pharmacopeia dissolution apparatus 2 (paddle method, Hanson Research, Northridge, CA) was used to characterize the release of DMP from the tablets. The release studies were performed in 0.1 mol/L HCl (500 mL) at 37.0 ± 0.5°C, and the rotation speed of paddle was 50 rev/min. Samples (20 mL) were collected and replaced with a fresh medium at various interval times. The amount of DMP released was analyzed spectrophotometrically at a wavelength of 278 nm.

The release kinetic of DMP from the resinates can be described using a particle diffusion-controlled model.[22] The release of drug from the resinates could be expressed by the following equation:

$$-\ln(1-F) = 1.59\left(\frac{6}{d_p}\right)^{1.3} D^{0.65}t^{0.65} \qquad (2)$$

where F is fractional release of drug from drug resinate, d_p is mean particle size of resin, D is apparent diffusion coefficient or diffusivity, and t is time. An approximation of the equation could be shown by plotting $-\ln(1-F)$ and $t^{0.65}$ as presented by equation 3, and the slope of this relationship could be calculated using linear regression analysis.

$$-\ln(1-F) = kt^{0.65} \qquad (3)$$

where k is the release rate constant.

Statistical Analysis

One-way analysis of variance with the least significant difference test for multiple comparisons was performed to determine the significant effect of physical properties and release data of the DMP resinate tablets. Differences were considered to be significant at a level of $P < .05$. All of the statistical tests were run on SPSS program for MS Windows, release 10.0 (SPSS Inc, Chicago, IL).

RESULTS AND DISCUSSION

Particle Size of DMP Resinates

The particle size of the DMP resinates using Dowex 50 W and Amberlite IRP69 is shown in Table 1. Both DMP resinates had a comparable volume-number diameter. PI was found to be 0.71 ± 0.01 for Dowex 50 W and 0.62 ± 0.01 for Amberlite IRP69, indicating a wider size distribution of the DMP resinates prepared using Dowex 50 W. Moreover, both resinates showed the difference in particle

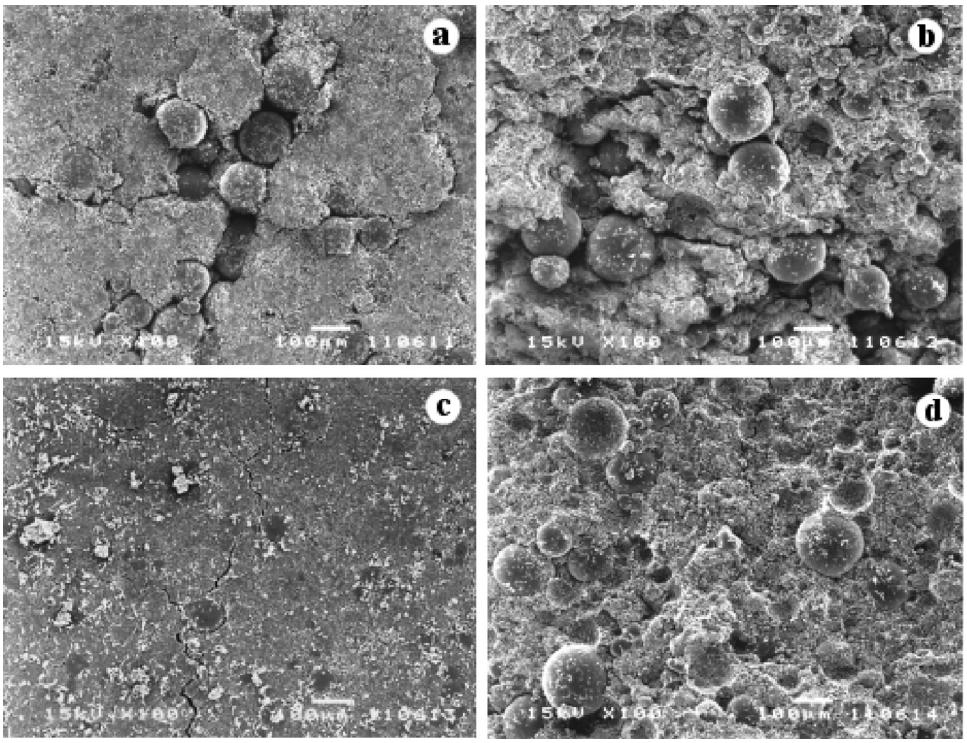

Figure 4. Surface morphology and internal structure of DMP-resinate tablets prepared using Dowex 50 W at 4 MPa compression pressure: DCP (a and b) and SDRS (c and d).

shape, which was observed using SEM (Figure 1). The resinates prepared using Dowex 50 W had a spherical shape, whereas those using Amberlite IRP69 showed rod-like and plate-like particles.

Physical Properties of DMP Resinate Tablets

As expected, the thickness of the DMP resinate tablets using both resinates and various fillers decreased significantly ($P < .05$) with increasing compression pressure (Figure 2A), and a statistically greater hardness of the tablets was found ($P < .05$). The hardness of the tablets using MCC was significantly higher ($P < .05$) than that using SDRS and DCP (Figure 2B). A statistically lower hardness of the tablets using Amberlite IRP69 was observed compared with the tablets using Dowex 50 W ($P < .05$). In addition, the hardness of the tablets using DCP 1 and 2 MPa compression pressures was not measurable because of very low hardness. The disintegration time of the tablets using MCC and DCP was less than 30 seconds, whereas the tablets using SDRS gave a higher disintegration time (Figure 2C). Using SEM, the DMP resinates were distributed and embedded into the MCC matrix, which provided a dense structure of the tablets (Figure 3). On the other hand, the resinates were embedded inside the deaggregation particles of DCP and SDRS (Figure 4). A loose structure was observed from the tablets using DCP. From this examination, some resinates had a matrix deformation under compaction.

MCC, DCP, and SDRS are the most common tablet fillers for the direct compression method. MCC was a partially depolymerized cellulose and its powder composed of porous particles, which had a concave-convex shape.[23] SDRS was spherical and made up almost entirely of agglomerated rice starch grains,[24] whereas DCP was made up of irregular-shaped agglomerates and large-plate crystal.[25] In this study, the tablets using MCC gave an acceptable performance when compared with those using SDRS and DCP, especially regarding the hardness of the tablets. This was attributable to good compactibility of MCC, where it has been reported that the order of decreasing compactibility was MCC > SDRS > DCP.[26] However, a decrease of tablet hardness in all of the fillers was found when Amberlite IPR69 was used. The DMP resinates using Amberlite IRP69 had about 10% lower DMP loading than that using Dowex 50 W, so a higher amount of this resinate in the tablets was used. As an explanation for this, using the dilution potential of the filler, the compactibility decreased as the amount of noncompressible component was increased. The tablets using MCC had a good hardness, indicating that it was superior to another filler in terms of dilution potential.[26] However, the use of different particle shapes of the resinates caused a decrease in tablet hardness. The rod-like and plate-like particle of Amberlite IRP69 might reduce the contact surface of the fillers. Furthermore, Amberlite IRP69 provided a stronger polymer matrix and a slower progressive deformation with time under constant stress compared with Dowex 50 W. This was attributable

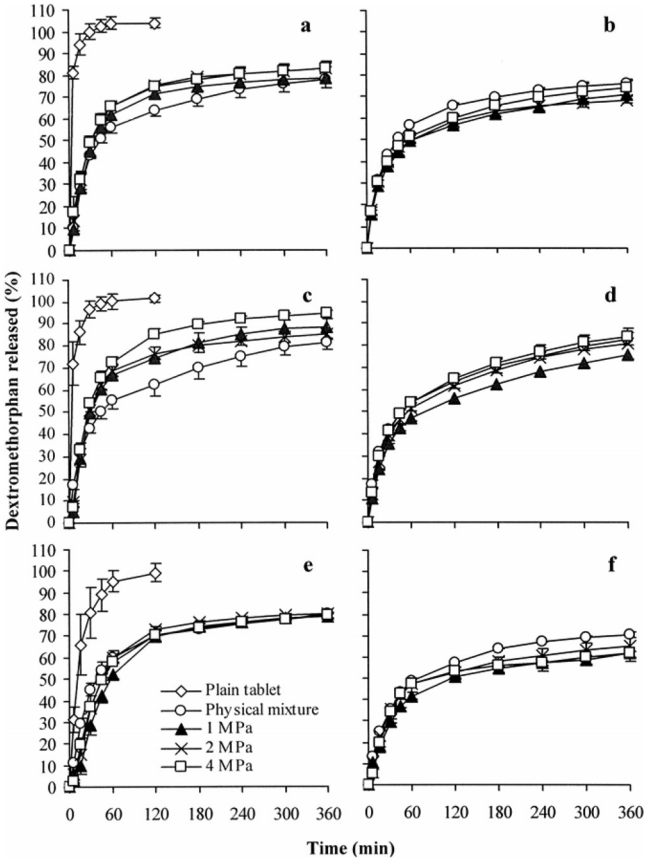

Figure 5. Release profiles of DMP-resinate tablets prepared using Dowex 50 W (a, c, and e) and Amberlite IRP69 (b, d, and f) in 0.1 mol/L HCl: MCC (a and b), DCP (c and d), and SDRS (e and f). Each point is the mean ± SD (n = 3).

to a higher degree of cross-linking of Amberlite IRP69,[27] which led to a lower deformation of this resinate under compression pressure, resulting in a decrease in contact area of the fillers as well.

The fillers in the tablets affected the disintegration time, although the tablets contained a superdisintegrant, sodium starch glycolate. The disintegration time of the tablets using MCC and DCP was shorter than that using SDRS. A higher disintegration time of the tablets using SDRS could result from a gel-forming matrix when exposed to distilled water. Although the tablets using MCC gave a higher hardness, a fast disintegration was obtained, because MCC exhibited disintegration property.[23,28] On the other hand, the tablets using DCP possessed a fast disintegration. This was because of the low hardness of the tablets.

In Vitro Release of DMP Resinate Tablets

The release profiles in 0.1 mol/L HCl of the DMP tablets with various fillers, prepared at different compression forces, are shown in Figure 5. An incomplete release of DMP was obtained, because the drug release was driven by the ion exchange toward an equilibrium.[11,18] The release of DMP resinate tablets was determined in comparison with a plain tablet, which had 30 mg of DMP HBr and were prepared using a single compression pressure (4 MPa). It can be seen that the release of all of the DMP resinate tablets provided a sustained-release behavior of DMP when compared with the plain tablets. The $-\ln(1 - F)$ value showed a good correlation with $t^{0.65}$ ($R^2 > 0.98$), indicating that the release of DMP can be described using a particle diffusion-controlled model (equation 2). Using Dowex 50 W, the release rate constant of the tablets using MCC and DCP was significantly increased ($P < .05$) when compared with the physical mixture (Table 2). The use of SDRS gave an insignificant difference ($P > .05$) for the release rate constant with the physical mixture. The different results were obtained from the tablets using Amberlite IRP69.

Table 2. Release Parameters of DMP-Resinate Tablets Using Different Polysulfonate Resins*

		Dowex 50 W		Amberlite IRP69	
Filler	**Compression Pressure (MPa)**	**$k \times 10^2$ ($min^{-00.65}$)**	**DMP Released at 5 Min (%)**	**$k \times 10^2$ ($min^{-00.65}$)**	**DMP Released at 5 Min (%)**
MCC	PM	6.2 ± 0.5	10.2 ± 1.2	5.7 ± 0.3	16.4 ± 1.5
	1	7.7 ± 0.6	9.9 ± 2.0	4.4 ± 0.1	15.4 ± 1.4
	2	8.3 ± 0.2	13.2 ± 2.7	4.3 ± 0.1	17.3 ± 2.0
	4	7.7 ± 0.3	17.7 ± 6.6	4.6 ± 0.2	16.8 ± 1.9
DCP	PM	5.4 ± 0.9	17.1 ± 1.5	5.0 ± 0.6	17.4 ± 2.3
	1	9.3 ± 1.2	5.2 ± 3.8	4.6 ± 0.2	10.6 ± 1.5
	2	9.5 ± 1.0	9.6 ± 1.8	5.2 ± 0.2	13.0 ± 0.2
	4	10.7 ± 0.8	7.2 ± 2.9	5.5 ± 0.1	13.4 ± 2.9
SDRS	PM	6.7 ± 0.7	10.7 ± 2.5	4.6 ± 0.2	13.0 ± 0.9
	1	6.4 ± 0.3	3.1 ± 1.1	3.9 ± 0.2	10.4 ± 3.1
	2	7.7 ± 0.4	5.8 ± 4.1	4.6 ± 0.4	10.7 ± 4.7
	4	7.4 ± 0.1	2.5 ± 1.1	5.2 ± 0.4	5.3 ± 1.9

*Data are the mean ± SD, n=3. PM indicates physical mixture.

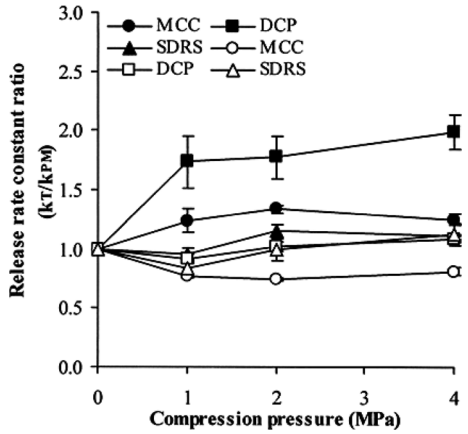

Figure 6. Release-rate constant ratio of DMP-resinate tablets using Dowex 50 W (closed symbols) and Amberlite IRP69 (open symbols). Each point is the mean ± SD (n = 3).

The release rate constant of the tablets using MCC tended to decrease with increasing compression pressure, whereas those using DCP and SDRS were slightly increased.

The degree of coated membrane damage under compression pressure has been evaluated previously by comparing the initial drug release rate of the coated particles and the tablet.[3] This method was used for evaluating the fracture of DMP resinates under compaction. Defining the release rate constant of tablets at different compression forces and physical mixtures of resinates as k_T and k_{PM}, respectively, the release-rate constant ratio (k_T/k_{PM}) was the degree of fracture of DMP resinates caused by tableting, which is shown in Figure 6. Using Dowex 50 W, the tablets using DCP gave a significantly higher release-rate constant ratio than those using MCC and SDRS, indicating a higher fracture of DMP resinates. In contrast to Amberlite IRP69, the release-rate constant ratio had little change and tended to decrease, especially the tablets using MCC.

From these results, the deformation of the filler under pressure and the properties of the resin were important to the fracture of the resinates. In the case of Dowex 50 W, DCP had the less protective effect, because the main deformation was the fragmentation of DCP particles.[29] This finding agreed with the previous study,[4] in which microcapsules were used as drug carriers in the tablets. On the other hand, MCC was more porous and underwent the plastic deformation,[24,29] so it could absorb higher compression forces. However, the fracture of the resinates was found but did not correlate with increasing compression pressure. This finding was similar to a previous report.[2] SDRS had a good protective effect on the resinates under compression pressure in this study. The deformation of this filler underwent deaggregation as small particles and showed plastic deformation with increasing compression pressure.[24] Small particles of this filler, which had plastic deformation, could cover the surface and prevent the fracture of the microparticles in the tablets.[2,3]

Amberlite IRP69 had a higher degree of cross-linking (8%) than Dowex 50 W (4%). The high degree of cross-linking of polystyrene was more resistant to deformation, which was described in a previous section. This led to a lower fracture of this resinate under compression pressure. However, the lowest release-rate constant ratio was observed when MCC was used. This may be because of the fusion of MCC and Amberlite IRP69, which caused a decrease of surface area for release.

The percentage of DMP released at 5 minutes with the tablets using MCC was not statistically difference, whereas those using DCP and SDRD were decreased significantly ($P < .05$) when the compression pressures were applied (Table 1). The release of DMP at 5 minutes indicated the disintegration of the tablets in 0.1 mol/L HCl under the condition of a dissolution test, which can be visually observed. The slow disintegration of the tablets using DCP and SDRS was observed, because DCP was slowly dissolved in the acid medium, whereas SDRS formed a gel matrix. The fast disintegration of the tablets was obtained when MCC was used, suggesting that this tablet rapidly provided multiple-unit DMP resinates, and the release of DMP could be controlled by the resinates.

CONCLUSION

Physical properties of DMP resinate tablets depended on the properties of polysulfonate resin and direct compression fillers. A particle shape and degree of cross-linking of the resinates affected the tablet hardness and the DMP release from the tablets. Moreover, the use of direct compression fillers, which gave plastic deformation, could prevent the fracture of the resinates under compression pressure.

ACKNOWLEDGMENTS

We thank the National Science and Technology Development Agency (Pathumthani, Thailand) for research funding (Grant No. CO-B-06-2E-12-401), and Faculty of Pharmaceutical Sciences, Khon Kaen University (Khon Kaen, Thailand) for instrument supports. We also thank Faculty of Pharmacy and Health Sciences, Mahasarakham University (Mahasarakham, Thailand) for the supported equipment of LS Particle Size Analyzer.

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