Drug Development and Industrial Pharmacy, 26(8), 891–894 (2000)

COMMUNICATION

Improved Dissolution Rate of Poorly Soluble Drug by Incorporation of Buffers

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ABSTRACT

This study focused on comparing dissolution rates of indomethacin after cocompressing with three different buffers (calcium carbonate, sodium carbonate, and sodium citrate) at pH 2 and 7. Factors affecting the dissolution rate were also examined, such as type and particle size of buffer and weight-to-weight ratio of drug to buffer. It was found that, at pH 7, the release rates of indomethacin with sodium carbonate (<74 μm, all proportions) and sodium citrate (<74 μm, 75% loading) at a 20-min test time were about 10-fold and 6-fold greater, respectively, than that of indomethacin alone. When the drug and buffer were compressed into tablets using a tableting machine, the release rates of indomethacin for the control, sodium carbonate incorporated (25% and 75% buffer loading), and sodium citrate incorporated (75% buffer loading) at a 15-min test time were 50%, 90%, 66%, and 67%, respectively.

Key Words: *Buffers; Dissolution rate; Poorly soluble drug.*

INTRODUCTION

Many methods have been attempted to improve the dissolution of poorly soluble drugs in solid dosage forms (1–4). Since most drugs are weak acids or bases, their dissolution rates from a dosage form are dependent on pH according to the Henderson-Hasselbalch equation (5). The dissolution of ionizable drugs may be increased by incorporation of buffers. An explanation for this behavior is that the dissolving buffer alters the microenvironmental pH around the drug particles, increasing the ionization of the drug and thus its dissolution rate (6,7). Inclusion

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of buffer has been shown to improve dissolution rate of poorly water soluble drug (naproxen) (7). However, few attempts have been made to demonstrate this strategy to improve the drug dissolution rate (6,7). The objective of this evaluation, therefore, was to illustrate the effects of using basic buffers to increase the dissolution rate of the poorly water soluble acidic drug. Indomethacin was used as a model drug.

EXPERIMENTAL

Materials

Indomethacin used in this study was purchased from T. O. Chemical, Limited, Bangkok, Thailand. Calcium carbonate (light) and sodium carbonate were obtained from Vidhyasom Company, Limited, Bangkok, Thailand. Sodium citrate dihydrate was bought from Carlo Erba, Bangkok, Thailand. Disodium hydrogen phosphate and hydrochloric acid were obtained from Carlo Erba and J. T. Baker, Incorporated, Thailand, respectively.

Methods

Preparation of Drug-Buffer Cocompression (Using Hydraulic Press)

Buffer sizes used were in the range 125–149, 105–125, and less than 74 μm (Table 1), whereas indomethacin was used only in the size range 105–125 μm. Indomethacin and buffer at three ratios were blended in various weight proportions (50:16.6, 50:50, and 50:150, respectively). Each cocompressed tablet contained 50 mg of indomethacin. The powders of indomethacin and buffer were mixed, then compressed into a tablet using a punch and die in a hydraulic press (Shimadzu P/N 202-32010) at 2 kgf/cm^2 for 1 min. The diameter of the tablet was maintained at 1/4 inch.

In Vitro Release Studies

The dissolution rate measurements were performed using USP dissolution apparatus 2 (paddle; Pharma Test, Hamburg, Germany). The dissolution was evaluated in 0.02 M KCl-HCl solution (pH 2.0) and 0.02 M phosphate solution (pH 7.0). The dissolution medium (750 ml) was constantly stirred at 100 rpm. The dissolution flasks were immersed in a water bath maintained at 37°C ± 0.5°C. Tablets containing only indomethacin were used as a control study. Samples (5 ml) of the dissolution medium were taken at appropriate intervals and replaced by an equal amount of fresh medium. These samples were filtered and diluted to obtain ultraviolet (UV) absorbance (Cecil UV/Visible spectrophotometer) at a wavelength of 318 nm. Experiments were run in triplicate, and the results were averaged.

Preparation of Indomethacin Tablets (Using Single Punch Tableting Machine)

Three promising formulations were prepared in tablet form using a single-punch tableting machine (Yeo Heng

Table 1

Comparison of Percentage Indomethacin Dissolved from Indomethacin-Buffer Tablets in Phosphate Buffer Dissolution Medium pH7 (Mean ± SD)

Composition (Indomethacin:Buffer)	% Indomethacin Dissolved (min)		
	5	10	20
Plain IND	0.57 ± 0.07	0.89 ± 0.24	1.58± 0.28
IND-CCarb 50:16.6	0.10 ± 0.07	0.44 ± 0.04	1.05 ± 0.15
IND-CCarb 50:50	0.24 ± 0.01	0.40 ± 0.05	0.93 ± 0.01
IND-CCarb 50:150	0.82 ± 0.08	1.18 ± 0.18	1.70 ± 0.21
IND-SCarb 50:16.6	49.56 ± 5.74	78.45 ± 1.65	84.60 ± 0.92
IND-SCarb 50:50	36.16 ± 0.78	59.78 ± 0.71	84.07 ± 1.49
IND-SCarb 50:150	21.77 ± 1.84	41.53 ± 4.04	70.75 ± 4.08
IND-SCitr 50:16.6	0.33 ± 0.13	0.65 ± 0.11	1.14 ± 0.11
IND-SCitr 50:50	0.45 ± 0.07	0.87 ± 0.09	1.32 ± 0.23
IND-SCitr 50:150	0.17 ± 0.00	2.75 ± 1.22	22.33 ± 2.13

Indomethacin and buffer sizes were 105–125 and <74 μm, respectively.
IND = indomethacin; CCarb = calcium carbonate; SCarb = sodium carbonate; SCirt = sodium citrate.

Table 2

Formulation of Indomethacin-Buffer Tablets

Components	Formulation (mg)			
	A[a]	B	C	D
Indomethacin	50	50	50	50
Lactose	168	151.3	18	18
Sodium carbonate	—	16.7	150	—
Sodium citrate	—	—	—	150
PVP K30	8.37	8.37	8.37	8.37
Magnesium stearate	1% of dry granules			
Aerosil	0.25% of dry granules			

Size of indomethacin used was 105–125 μm.
Size of sodium carbonate used was <74 μm.
Size of sodium citrate used was <74μm.
PVP K30 (15% W/V) was dissolved in water for preparing binder solution.
[a] Control study.

Co., Ltd., Thailand) equipped with 8-mm flat-face tooling. Tablets were prepared according to the formulas shown in Table 2 by the wet granulation method. Tablets were compressed to a target weight of 229 mg and to 5–5.5 kg hardness. The dissolution tests were performed in a manner similar to that described above at pH 7.

RESULTS AND DISCUSSION

Drug-Buffer Cocompression (Using Hydraulic Press)

In general, the increase in dissolution rate of indomethacin induced by buffers was in the order sodium carbonate > sodium citrate > calcium carbonate (Table 1). Moreover, it is also obvious that the drug dissolved better at pH 7 than at pH 2 (data not shown). At pH 7, when calcium carbonate was used as the buffering agent, it was found that not more than 6% of indomethacin was dissolved after variation of any parameter. Incorporation of sodium carbonate significantly improved the dissolution rate of indomethacin, as indicated by the observation that more than 70% of drug was dissolved within 20 min in all sizes and proportions of sodium carbonate used (Fig. 1, for example). When sodium carbonate less than 74 μm was used, at the first 5 min, the 25% buffer proportion enhanced the dissolution rate better than the 50% and 75% proportions, with 49%, 34%, and 21% drug dissolved, respectively. Increasing the sodium citrate content from 25% to 50% weight ratio resulted in only a small increase in dissolution rate. Very interestingly, at 75% buffer loading, sodium citrate improved the dissolution rate of indomethacin, especially when the size less than 74 μm was used, as more than 75% drug was dissolved within 45 min and more than 90% was dissolved in 100 min. There was a clear trend that the dissolution-enhancing ability of sodium citrate buffer decreased as a function of particle sizes in the order less than 74 > 105–125 > 125–149 μm.

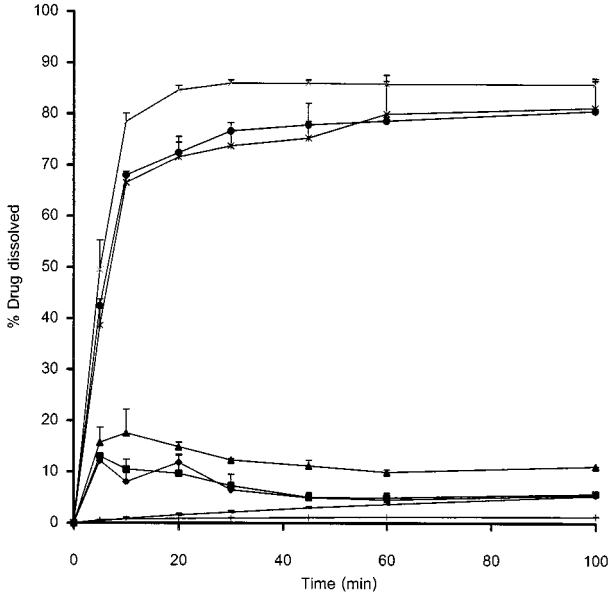

Figure 1. Dissolution profiles of indomethacin from indomethacin–sodium carbonate cocompressed tablets with a 25% buffer weight ratio ($n = 3$): ◆, buffer size <74 μ at pH 2.0; ■, buffer size 105–125μm at pH 2.0; ▲, buffer size 125–149 μm at pH 2.0; ×, buffer size <74 μm at pH 7.0; *, buffer size 105–125 μm at pH 7.0; ●, buffer size 125–149 μm at pH 7.0; |, control study at pH 2.0; –, control study at pH 7.0.

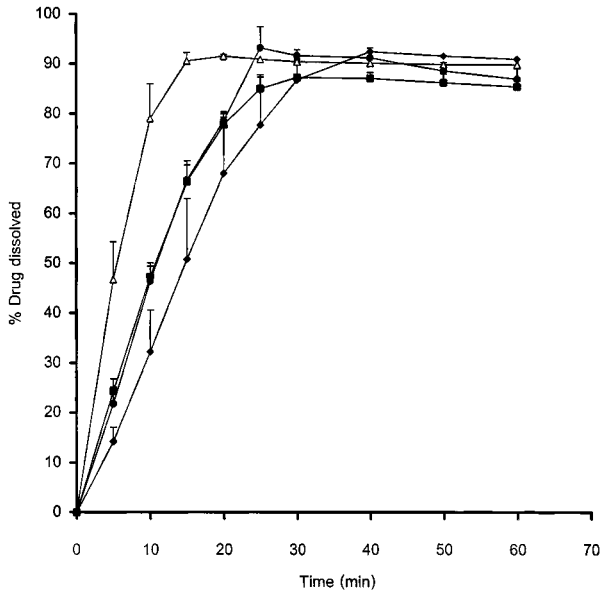

Figure 2. Dissolution profiles of indomethacin from buffered tablets and control study (n = 3): ◆, formulation A; △, formulation B; ■, formulation C; ●, formulation D.

Drug-Buffer Cocompressed Tablets (Using Single-Punch Tableting Machine)

The two promising buffers (sodium carbonate and sodium citrate) were chosen to prepare cocompressed tablets with indomethacin using a single-punch tableting machine in a manner of tablet production (Table 2). It was found that 90%, 66%, and 67% indomethacin were dissolved within 15 min when sodium carbonate (25% and 75% buffer proportion) and sodium citrate (75% buffer proportion) were used, respectively, compared to 50% of the control study (Fig. 2). These results show that freely soluble buffer improves the dissolution rate of the poorly soluble drug better than a buffer of low solubility. This finding is in contrast to the results previously reported, which recommended the use of a less soluble buffer than drug (naproxen) to improve the dissolution (7). Therefore, further studies are required to investigate the influence of buffer properties in enhancing the drug dissolution rate, including aging effects and compression force on tableting.

CONCLUSION

This investigation demonstrated that basic buffers can improve the dissolution rates of a weakly acidic drug. Indomethacin exhibited significantly improved dissolution rates when sodium carbonate and sodium citrate buffers were employed compared to the rates of plain indomethacin or if calcium carbonate buffer was used. This technique has the potential to produce faster release of the poorly soluble drug indomethacin and may be applicable to many other drugs that exhibit low dissolution rates.

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