Drug Development and Industrial Pharmacy, 25(8), 967–972 (1999)

COMMUNICATION

The Dissolution and Complexing Properties of Ibuprofen and Ketoprofen when Mixed with *N*-Methylglucamine

Melgardt M. de Villiers, Wilna Liebenberg, Sarel F. Malan,[1] and Jan J. Gerber[2]

Research Institute for Industrial Pharmacy and Departments of Pharmaceutical [1]Chemistry and [2]Practice, School of Pharmacy, Potchefstroom University for CHE, Potchefstroom 2520, South Africa

ABSTRACT

The objectives of this study were to improve the aqueous dissolution properties of the poorly soluble nonsteroidal anti-inflammatory drugs ibuprofen and ketoprofen and to explore the use of N*-methylglucamine (meglumine) to enhance the dissolution properties of poorly water-soluble drug powders. Changes in both differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) results indicate that possibly complexes were produced between ibuprofen and* N*-methylglucamine. Similar changes were not observed for equivalent ketoprofen and* N*-methylglucamine mixtures. The results of solubility and dissolution studies in water at 25°C and 37°C showed that* N*-methylglucamine, in mixtures and coprecipitates, increased the solubility, intrinsic dissolution, and powder dissolution of ketoprofen and ibuprofen.* N*-Methylglucamine significantly improved the solubility and dissolution properties of both ibuprofen and ketoprofen even when DSC and XRD behavior did not indicate the formation of complexes.*

INTRODUCTION

The formation of solid dispersions is an effective method of increasing the dissolution rate of poorly soluble drugs, and hence of improving their bioavailability (1). For instance, several workers have reported the preparation of sugar glass dispersions and how it increased the dissolution rates of poorly soluble drugs such as corticoid steroids (2) and sulfamethoxazole (3). This study reports the preparation of solid dispersions, by mechanical mixing or coprecipitation, of ibuprofen and ketoprofen, both poorly soluble, with *N*-methyl glucamine (meglumine). *N*-Methylglucamine is an organic base prepared from D-glucose and methylamine and is used for the preparation

of salts of organic acids, including contrast media (4). Veronesi (5) prepared the water-soluble acid addition salts of the nonsteroidal drugs aspirin, fenbufen, piroxicam, and naproxen with glucamine or *N*-methylglucamine, while Motola et al. (6) prepared a water-soluble salt of ibuprofen and *N*-methylglucamine. The objective was to improve the aqueous dissolution properties of the poorly water-soluble propionic acid derivatives ibuprofen and ketoprofen by the addition of *N*-methylglucamine.

MATERIALS AND METHODS

Materials

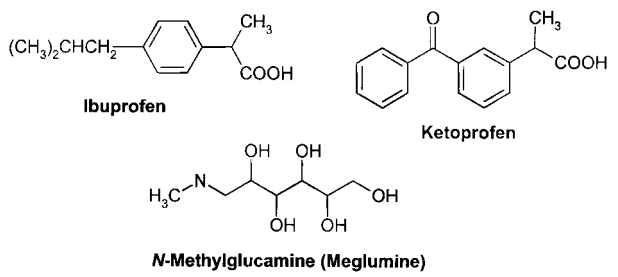
N-Methylglucamine, ibuprofen, and ketoprofen (Scheme 1) were obtained from Sigma Chemical Company (St. Louis, MO). Absolute ethanol (Saarchem, Krugerdorp, South Africa) and water fit for chromatography were used as solvents.

Preparation of Mixtures

Mixtures of *N*-methylglucamine and ibuprofen or ketoprofen were prepared by one of three methods:

1. Mixing of the two powders in a V-blender for 15 min at 60 rpm.
2. Mixing in a planetary ball mill (Pulverisette 7, Fritzch, Germany) for 15 min.
3. Precipitation of a solution of the two powders in a mixture of ethanol and water (90:10 v/v) by evaporation in a rotating evaporator (Buchi, Rotavapor R110, Switzerland).

Mixtures containing the drugs in concentrations ranging from 10% to 90% w/w were prepared.



Scheme 1. Structure of the propionic acid derivatives and *N*-methylglucamine.

Differential Scanning Calorimetry

A Shimadzu DSC-50 or Perkin Elmer DSC-7 were used to obtained differential scanning calorimetry (DSC traces at a heating rate of 10°C min^{-1} under a nitrogen purge of 20 ml · min^{-1}. A mass not exceeding 5 mg was tested in sealed aluminum sample pans.

X-ray Powder Diffractometry

X-ray powder diffractometry (XRD) profiles were obtained at room temperature with a Philips PM9901/00 diffractometer. The measurement conditions were CuK_{α}; nickel filter; 40 kV voltage; 20 mA current; 0.1-mm slit; 2° min^{-1} scanning speed. Approximately 200-mg samples were loaded into the aluminum sample holder, taking care not to introduce a preferential orientation of the crystals.

Solubility Measurements

An amount of powder or mixtures sufficient to ensure supersaturation were measured in 10-ml test tubes. To each tube, 10 ml water was added, and the tubes were sealed. The tubes were rotated at 70 rpm for 24 hr in a water bath controlled at 25°C, then the tubes were filtered. The concentrations of drug in the filtered samples were determined spectrophotometrically at 261 nm for ketoprofen and 265 nm for ibuprofen.

Dissolution Rate Measurements

The intrinsic dissolution rates (IDRs) were determined as described by Singh et al. (7). Samples were slowly compressed into 13-mm diameter tablets with a Beckman IR press at 3.8×10^5 kg · cm^{-2} with a dwell time of 1 min. The dissolution medium was 400 ml water at 25°C, and the stirrer was rotated at 150 rpm. Powder dissolution rates were measured according to a method described by Lötter et al. (8) using apparatus II of the USP. The dissolution medium was 900 ml water at 37°C, and the stirrer was rotated at 100 rpm. The amount dissolved per time was determined by following the ultraviolet absorbance of suitably diluted solutions.

RESULTS AND DISCUSSION

Thermal Behavior of Mixtures

The melting point of undiluted ibuprofen was 79°C, and for ketoprofen it was 98°C. Mixing ketoprofen with

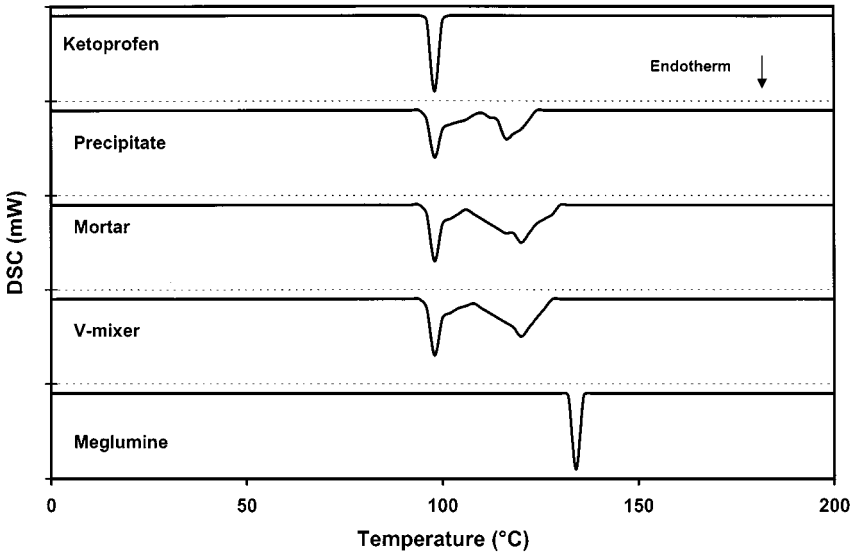


Figure 1. DSC thermograms of 1:1 *N*-methylglucamine:ketoprofen mixtures.

N-methylglucamine (Fig. 1) did not change the melting point of ketoprofen. However, the melting point of ibuprofen increased slightly in physical mixtures and eventually disappeared when coprecipitated with *N*-methylglucamine. A new melting endotherm appeared at 100°C–107°C (Fig. 2). DSC results indicated the formation of a complex between ibuprofen and *N*-methylglucamine.

X-ray Diffraction Properties of Mixtures

The XRD analysis of 1:1 mixtures of the drugs and *N*-methylglucamine (Table 1) showed that essentially the XRD patterns of mixtures between ketoprofen and *N*-methylglucamine were the same, and it was possible to detect ketoprofen in mixtures. It was not possible to detect ibuprofen in the XRD pattern of the coprecipitated

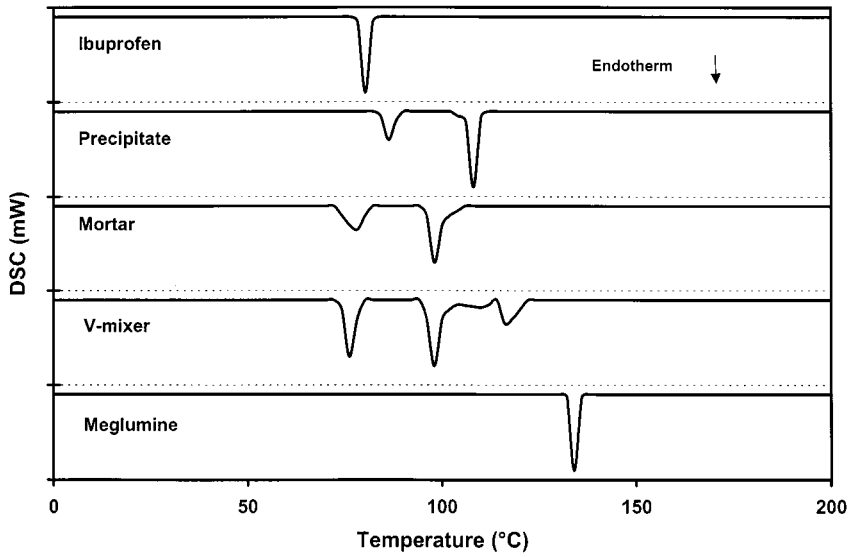


Figure 2. DSC thermograms of 1:1 *N*-methylglucamine:ibuprofen mixtures.

Table 1

Main X-ray Diffraction Relative Intensities (% I/I_0) for the Single Components and 1:1 Mixtures

N-Methylglucamine		Ketoprofen		Ibuprofen	
Angle (°2θ)	I/I_0 (%)	Angle (°2θ)	I/I_0 (%)	Angle (°2θ)	I/I_0 (%)
9.0	100	23.0	100	6.0	100
22.0	36.1	18.5	79.3	22.3	81.4
28.0	23.5	22.0	69.4	16.0	65.4
17.3	22.0	6.5	46.2	20.4	52.7
18.1	21.9	19.5	51.3	12.3	30.7
Ketoprofen *N*-Methylglucamine Mixtures					
V-mixer		Ball Mill		Precipitate	
22.1	100	22.0	100	9.0	100
23.0	99.5	9.1	93.6	22.1	99.0
9.2	98.0	23.0	93.2	23.1	82.4
18.5	79.2	18.5	74.1	18.5	67.3
19.5	51.4	19.5	48.1	19.5	43.7
Ibuprofen *N*-Methylglucamine Mixtures					
V-mixer		Ball Mill		Precipitate	
9.0	100	9.0	100	9.0	100
6.1	99.7	22.5	53.7	18.5	67.3
22.5	81.3	20.2	32.7	19.5	43.7
16.3	68.8	16.5	29.9	24.2	35.9
20.5	52.8	18.3	22.1	14.5	31.2

sample (Table 1), but ibuprofen was present in the physical mixtures. As did DSC results, the XRD pattern of the coprecipitated sample suggested the formation of a complex between ibuprofen and *N*-methylglucamine.

Solubility of Mixtures

The solubility of pure ibuprofen in water at 25°C was 0.068 ± 0.021 mg · ml^{-1}, and for ketoprofen it was 0.101 ± 0.045 mg · ml^{-1}. Overall, *N*-methylglucamine (Table 2) increased the solubility of both ibuprofen and ketoprofen. The pH measurements shown in Fig. 3 indicated that *N*-methylglucamine significantly increased the pH of the water. The increase in solubility was therefore the result of an increase in pH since both drugs are acidic, being more soluble at a higher pH. However, even at low *N*-methylglucamine concentrations (Table 2), for which the increase in pH is not yet significant (Fig. 3), the solubilities of both drugs were significantly increased.

Powder Dissolution of Mixtures

The powder dissolution profiles of ibuprofen or ketoprofen and *N*-methylglucamine coprecipitates are shown in Figs. 4 and 5. *N*-Methylglucamine increased the dissolution rate of both ibuprofen and ketoprofen. An increase in *N*-methylglucamine concentration led to an increase in dissolution rate. In Table 3, the $t_{80\%}$ values for dissolution of the mixtures are listed. The $t_{80\%}$ of dissolution of pure ketoprofen at 37°C decreased from 92 min to 8, 14, and 29 min, respectively, for coprecipitates containing 25%, 50%, and 75% drug. The $t_{80\%}$ dissolution of the equivalent ibuprofen mixtures decreased from 116 min to 10, 19, and 36 min.

Intrinsic Dissolution Rate of Mixtures

The IDR dissolution profiles of 1:1 ibuprofen or ketoprofen and *N*-methylglucamine mixtures were linear because the regression coefficients ranged from 0.957 to

Table 2

Aqueous Solubility at 25°C of Drug: N-*Methylglucamine Mixtures and Coprecipitates*

	Ibuprofen			Ketoprofen		
Ratio[a]	V-M (mg ml^{-1})	B-M (mg ml^{-1})	C-P (mg ml^{-1})	V-M (mg ml^{-1})	B-M (mg ml^{-1})	C-P (mg ml^{-1})
1:9	>10	>10	>10	>10	>10	>10
1:3	7.7 ± 0.45	8.1 ± 0.38	7.9 ± 0.44	>10	>10	>10
1:1	4.2 ± 0.58	4.3 ± 0.32	4.5 ± 0.42	6.8 ± 0.55	8.0 ± 0.48	6.9 ± 0.61
3:1	2.1 ± 0.68	1.9 ± 0.29	2.3 ± 0.22	3.6 ± 0.82	3.6 ± 0.12	3.7 ± 0.21
9:1	0.9 ± 0.32	0.9 ± 0.26	1.0 ± 0.12	1.3 ± 0.22	1.4 ± 0.51	1.4 ± 0.19

V-M = V-mixer; B-M = ball mill; C-P = coprecipitate.
[a] Ratio of drug of *N*-methylglucamine.

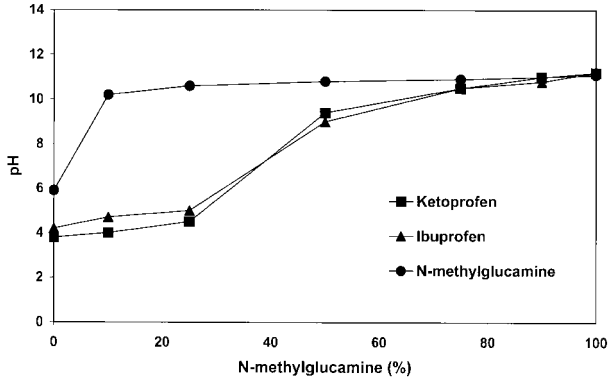


Figure 3. Change in dissolution medium pH with increasing amounts of *N*-methylglucamine and *N*-methylglucamine mixed with either ibuprofen or ketoprofen.

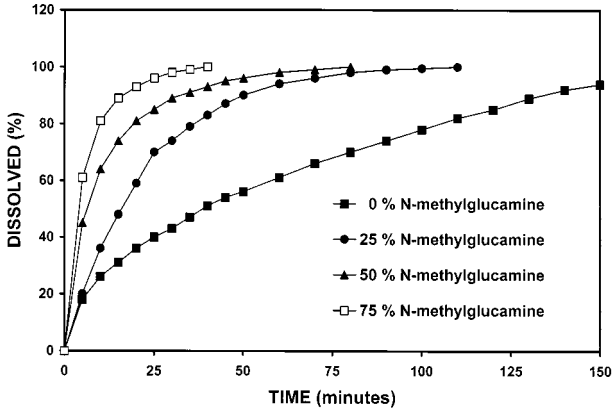


Figure 4. Dissolution kinetics of ibuprofen coprecipitated with 75%, 50%, 25%, or 0% *N*-methylglucamine.

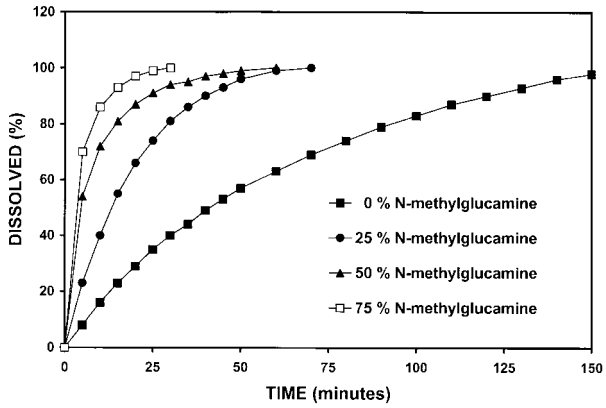


Figure 5. Dissolution kinetics of ketoprofen coprecipitated with 75%, 50%, 25%, or 0% *N*-methylglucamine.

0.998. *N*-Methylglucamine increased the IDR of both ibuprofen and ketoprofen. In Table 4, the IDR values for dissolution of 1:1 mixtures are listed. The IDR for undiluted ketoprofen was 0.536 ± 0.045 μg · cm^{-2} · min^{-1} and for ibuprofen was 0.361 ± 0.033 μg · cm^{-2} · min^{-1}. *N*-Methylglucamine increased the IDR for ketoprofen almost 25 times and for ibuprofen almost 58 times.

CONCLUSIONS

Although changes in the DSC behavior was observed, XRD did not indicate the formation of complexes between ketoprofen and *N*-methylglucamine. Changes in both DSC and XRD results indicate that possibly complexes were produced between ibuprofen and *N*-methylglucamine. The results of solubility and dissolution studies in water at 25°C and 37°C showed that *N*-methylglucamine, in mixtures and coprecipitates con-

Table 3

The $t_{80\%}$ Dissolution Times for Mixtures Between the Drugs and N*-Methylglucamine*

	Ibuprofen			Ketoprofen		
Ratio	V-M (min)	B-M (min)	C-P (min)	V-M (min)	B-M (min)	C-P (min)
1:9	18 ± 1.6	15 ± 2.6	9 ± 1.1	13 ± 2.3	10 ± 1.9	9 ± 0.5
1:3	26 ± 3.3	27 ± 2.8	18 ± 3.6	10 ± 2.8	12 ± 2.6	8 ± 0.4
1:1	43 ± 4.4	38 ± 2.9	29 ± 1.6	16 ± 3.4	15 ± 2.2	14 ± 1.2
3:1	52 ± 2.6	48 ± 3.3	36 ± 2.8	35 ± 5.2	34 ± 3.8	30 ± 4.2
9:1	85 ± 6.2	86 ± 6.2	78 ± 5.1	60 ± 4.3	56 ± 4.7	52 ± 3.6

V-M = V-mixer; B-M = ball mill; C-P = coprecipitate.

Table 4

Intrinsic Dissolution Rates in $\mu g \cdot cm^{-2}min^{-1}$ *for 1:1 Mixtures Between the Drugs and* N*-Methylglucamine*

	Ketoprofen			Ibuprofen		
Ratio	V-M	B-M	C-P	V-M	B-M	C-P
1:1	12.3 ± 0.4	13.8 ± 0.5	15.6 ± 0.5	18.4 ± 0.7	21.8 ± 2.0	22.6 ± 1.8

V-M = V-mixer; B-M = ball mill: C-P = coprecipitate.

taining from 10% to 90% of the drugs, increased the solubility, intrinsic dissolution, and powder dissolution of ketoprofen and ibuprofen. Furthermore, *N*-methylglucamine significantly improved the solubility and dissolution properties of both ibuprofen and ketoprofen even when melting and XRD behavior did not indicate the formation of complexes. The increase in drug solubility and dissolution in the absence of complexation could be the result of water-soluble salts formed between the acidic drugs and meglumine. These salts might also act as surfactants (4).

ACKNOWLEDGMENT

This work was supported by the Foundation for Research and Development of South Africa.

REFERENCES

1. J. L. Ford, Drug Dev. Ind. Pharm., 13(9–11), 1741–1777 (1987).
2. L. V. Allen, V. A. Yanchilk, and D. D. Maness, J. Pharm. Sci., 66(4), 494–497 (1977).
3. A. Ghamen, M. Meshau, and Y. Ibraheem, J. Pharm. Pharmacol., 32, 675–677 (1980).
4. Merck and Company, *Merck Index*, 12th ed., Author, Whitehouse Station, NJ, 1996.
5. P. A. Veronesi, U.S. Patent Number 474 8174, 1988.
6. S. Motola, A. R. Branfman, G. R. Agisim, and D. J. Quirk, U.S. Patent Number 5028625, 1991.
7. P. Singh, S. J. Desai, D. R. Flanagan, A. P. Simonelli, and W. I. Higuchi, J. Pharm. Sci., 57, 959–965 (1968).
8. A. P. Lötter, D. R. Flanagan, N. R. Palepu, and J. K. Guillory, Pharm. Technol., 7(4), 56–66 (1983).