AAPS PharmSciTech 2007; 8 (2) Article 36 (http://www.aapspharmscitech.org).

Tablet Formulation Studies on Nimesulide and Meloxicam-Cyclodextrin Binary Systems

Submitted: September 20, 2006; Accepted: December 14, 2006; Published: May 11, 2007

Buchi N. Nalluri,[1,3] K.P.R. Chowdary,[1] K.V.R. Murthy,[1] G. Becket,[2] and Peter A. Crooks[3]

[1]Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam, India
[2]School of Pharmacy, University of Otago, Dunedin, New Zealand
[3]College of Pharmacy, University of Kentucky, Lexington, KY

ABSTRACT

The objective of this work was to develop tablet formulations of nimesulide-β-cyclodextrin (NI-β-CD) and meloxicam-γ-cyclodextrin (ME-γ-CD) binary systems. In the case of nimesulide, 3 types of binary systems—physical mixtures, kneaded systems, and coevaporated systems—were studied. In the case of meloxicam, 2 types of binary systems—physical mixtures and kneaded systems—were investigated. Both drug-CD binary systems were prepared at 1:1 and 1:2 molar ratio (1:1M and 1:2M) and used in formulation studies. The tablet formulations containing drug-CD binary systems prepared by the wet granulation and direct compression methods showed superior dissolution properties when compared with the formulations of the corresponding pure drug formulations. Overall, the dissolution properties of tablet formulations prepared by the direct compression method were superior to those of tablets prepared by the wet granulation method. Selected tablet formulations showed good stability with regard to drug content, disintegration time, hardness, and in vitro dissolution properties over 6 months at 40°C ± 2°C and 75% relative humidity.

KEYWORDS: Nimesulide, meloxicam, cyclodextrins, tablet formulations, dissolution properties, stability studies.

INTRODUCTION

Cyclodextrins (CDs) are cyclic (α-1,4)-linked oligosaccharides of D-glucopyranose containing a relatively hydrophobic central cavity and a hydrophilic outer surface. CDs are able to form inclusion complexes with poorly water-soluble drugs. These inclusion complexes have been shown to improve stability, solubility, dissolution rate, and bioavailability.[1,2] This improvement in hydrophilicity may be attributed either to the formation of inclusion complexes or to the highly homogeneous assembly between CDs and drugs in the solid state. In most cases, this association increases the solubility of poorly soluble drugs. The drug-CD binary systems are also useful in dosage form development for increasing the solubility, dissolution, and absorption rates of poorly soluble drugs in tablet or capsule form.

Nimesulide (*N*-4'-nitro-2'-phenoxyphenyl methane sulfonamide) is a weakly acidic nonsteroidal anti-inflammatory drug (NSAID). It differs from other NSAIDs in that its chemical structure contains a sulfonamide moiety as the acidic group rather than a carboxylic group. Nimesulide shows high anti-inflammatory, antipyretic, and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects, and a high therapeutic index.[3] Meloxicam (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a highly potent NSAID of the enolic acid class of oxicam derivative. It is used to treat rheumatoid arthritis, osteoarthritis, and other joint diseases.[4-9] Like many NSAIDs, nimesulide and meloxicam are also very sparingly soluble in water. The very poor aqueous solubility and wettability of these drugs gives rise to difficulties in pharmaceutical formulations for oral or parenteral delivery, which may lead to variable bioavailability.[10] To overcome these drawbacks, increasing the aqueous solubility of these drugs is an important goal. Inclusion complexation of nimesulide and meloxicam with α−, β-, and γ-CDs in solution and in the solid state has been reported in previous studies.[11,12] A true inclusion of nimesulide with β-CD at 1:2M kneaded systems (KS) and coevaporated systems (CS) in the solid state was confirmed by differential scanning calorimeter (DSC), powder x-ray diffraction (X-RD), and scanning electron microscopy (SEM) studies.[11] However, in the case of meloxicam, a true inclusion was observed with γ-CD at both 1:1M and 1:2M KS and CS.[12] Three types of drug-CD binary systems—physical mixtures (PM), KS, and CS—were prepared at 1:1M and 1:2M. The solubility and dissolution properties of nimesulide and meloxicam were improved by complexation with β- and γ-CDs. Thus, in the present investigation we have evaluated the feasibility of formulating these drug-CD binary systems into tablet dosage forms. These drug-CD binary systems were formulated into tablets by both the conventional wet granulation method and the direct compression method. The tablet formulations were evaluated for their physical and dissolution properties.

Corresponding Author: Peter A. Crooks, Faculty of Pharmaceutical Sciences, University of Kentucky, College of Pharmacy, Lexington, KY 40536. Tel: (859) 257-1718; Fax: (859) 257-7585; E-mail: pcrooks@email.uky.edu

Accelerated stability studies on some selected tablet formulations were also conducted to assess the formulation shelf life and determine any possible degradation.

Materials and Methods

Materials

The nimesulide sample was supplied by Nicholas Pirmal Ltd (Mumbai, India), and the meloxicam sample was supplied by Sun Pharma Ltd (Mumbai). β-CD and γ-CD were obtained from Wacker Biochem Corp (Müchen, Germany); all other reagents and solvents were of analytical grade.

Methods

Preparation of Solid Binary Systems

Three different drug-CD binary systems in 1:1M and 1:2M were prepared from the previously sieved (75-150 μm) individual components: (1) by mixing for 20 minutes in a mortar with a spatula (PM); (2) by triturating PM in a mortar with a small volume of water-methanol (1:1 vol/vol) solution, then kneading the thick slurry for 45 minutes and drying it at 45°C (KS); and (3) by adding the aqueous solution of CD to an alcoholic solution of nimesulide, stirring the resulting mixture for 1 hour, and evaporating at 45°C until dry (CS). Each solid product was sieved, and the 75 to 150 μm sieve fraction was collected.

Preparation of Tablets

The tablet formulations containing nimesulide and meloxicam and nimesulide-β-CD (NI-β-CD) and meloxicam-γ-CD (ME-γ-CD) binary systems (equivalent to 100 mg of nimesulide and 15 mg of meloxicam) were prepared according to the formulas given in Tables 1 and 2. In each case a batch of 500 tablets was prepared.

Preparation of Tablets by Wet Granulation Method

Required quantities of pure drugs and drug-CD binary systems, and half the quantities of disintegrant, croscarmellose sodium, and diluent (lactose monohydrate), were mixed thoroughly in a mortar to obtain a uniform blend. Sufficient binding agent, that is, 2% polyvinylpyrrolidone (PVP) solution in methanol, was added and mixed to obtain a dough mass. The resulting wet mass was passed through a No 10 sieve American Society of Testing and Materials (ASTM) and dried at 50°C in a hot-air oven until dry. The dried granules were resieved through a No 20 sieve ASTM. The granules were then mixed with the remaining half of the disintegrant, talc, and magnesium stearate. The tablets (950 mg each in the case of nimesulide and 200 mg each in the case of meloxicam) were compressed on a single-punch tablet press (Cadmach, Ahmadabad, India).

Preparation of Tablets by Direct Compression Method

In the direct compression method, the appropriate pure drugs and drug-CD binary systems were mixed with filler—spray-dried lactose—in a mortar for 10 minutes. Croscarmellose sodium (4%), talc (2%), and magnesium stearate (2%) were then added in the same respective order and thoroughly mixed for 3 minutes. The resulting blend was then compressed into tablets, as described above.

Tablet Properties

The following tablet properties were measured: uniformity of weight, hardness, friability, and disintegration time. Sample sizes of 20 and 6 tablets were used for determination of weight and hardness, respectively. Friability was determined by using a Roche friabilator using 20 tablets for 4 minutes (100 revolutions). The disintegration time was determined using 6 tablets

Table 1. Formulas of the Tablets of NI and NI-β-CD Binary Systems*

	Wet Granulation				Direct Compression			
Ingredients (mg/tablet)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
NI	100	—	—	—	100	—	—	—
NI-β-CD PM 1:2M	—	837	—	—	—	837	—	—
NI-β-CD KS 1:2M	—	—	837	—	—	—	837	—
NI-β-CD CS 1:2M	—	—	—	837	—	—	—	837
Croscarmellose sodium	38	38	38	38	38	38	38	38
PVP	19	19	19	19	—	—	—	—
Talc	19	19	19	19	19	19	19	19
Magnesium stearate	19	19	19	19	19	19	19	19
Lactose monohydrate	755	18	18	18	—	—	—	—
Spray-dried lactose	—	—	—	—	774	37	37	37
Total weight of the tablet (mg)	950	950	950	950	950	950	950	950

*NI indicates nimesulide; NI-β-CD, nimesulide-β-cyclodextrin; PM, physical mixtures; KS, kneaded systems; CS, coevaporated systems; PVP, polyvinylpyrrolidone.

Table 2. Formulas of the Tablets of ME and ME-γ-CD Binary Systems*

	Wet Granulation					Direct Compression				
Ingredients (mg/tablet)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
ME	15	—	—	—	—	15	—	—	—	—
ME-γ-CD PM 1:1M	—	70.36	—	—	—	—	70.36	—	—	—
ME-γ-CD KS 1:1M	—	—	70.36	—	—	—	—	70.36	—	—
ME-γ-CD PM 1:2M	—	—	—	125.75	—	—	—		125.75	—
ME-γ-CD KS 1:2M	—	—	—	—	125.75	—	—	—		125.75
Croscarmellose sodium	8	8	8	8	8	8	8	8	8	8
PVP	4	4	4	4	4	—	—	—	—	—
Talc	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
Lactose monohydrate	165	109.64	109.64	54.25	54.25	—	—	—	—	—
Spray-dried lactose	—	—	—	—	—	165	113.64	113.64	58.25	58.25
Total weight of the tablet (mg)	200	200	200	200	200	200	200	200	200	200

*ME indicates meloxicam; ME-γ-CD, meloxicam-γ-cyclodextrin; PM, physical mixtures; KS, kneaded systems; PVP, polyvinylpyrrolidone.

in a US Pharmacopeia (USP) disintegration apparatus (Electrolab, Mumbai) without discs at 37°C, in water.

Drug Content Estimation

The powder content of 6 tablets in each case was mixed well, and a powder sample equivalent to 10 mg of nimesulide or meloxicam was placed in individual 100-mL volumetric flasks. Each drug was dissolved in 25 mL of methanol. The resulting mixture was vortexed for 5 minutes, and the volume was raised to 100 mL with methanol. The solution was filtered through a 0.45-μ nylon disc filter and was analyzed for drug content by measuring UV absorbance at 397 nm for nimesulide, and 365 nm for meloxicam.[11,12]

Dissolution Studies

In vitro dissolution studies of tablet formulations were performed in 900 mL of dissolution medium: pH 8.4 alkaline borate buffer Indian Pharmacopeia (IP) for nimesulide formulations and pH 7.4 phosphate buffer IP for meloxicam using a USP XXI type 2 dissolution rate test apparatus (Model DR-3, Campbell Electronics, Mumbai). Tablets contained 100 mg of nimesulide and 15 mg of meloxicam, and a speed of 50 rpm and a temperature of 37 ± 1°C were used in each test. A 5-mL aliquot was withdrawn at different time intervals and filtered using a 0.45-μm nylon disc filter; each sample was replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted, if necessary, and assayed by measuring the absorbance at 397 nm for nimesulide and 365 nm for meloxicam.[11,12] The dissolution experiments were conducted in triplicate.

Stability Studies

To determine whether there occurs during storage any change in the hardness, friability, or disintegration time that might affect the in vitro release profile of the drugs, stability studies were performed on formulations F7 and F8, in the case of nimesulide, and formulations F5 and F10, in the case of meloxicam. These formulations met the acceptable specifications with regard to drug release properties, that is, 80 percent of the drug was released within 45 minutes. The tablets were stored at 40°C ± 2°C and 75% relative humidity (maintained using a saturated solution of NaCl) in a desiccator.[13] Samples were withdrawn at 0-, 1-, 2-, 3-, and 6-month time

Table 3. Tablet Properties of NI and NI-β-CD Formulations*

Formulation	Drug Content (mg/tab)	Mean Weight (% deviation)	Hardness (kg/cm^2)	Friability (% wt loss)	Disintegration Time (min)
F_1	99.20	950.90 (–0.01 to 0.41)	5	0.53	6.10
F_2	100.12	951.85 (–0.01 to 0.43)	5	0.51	10.20
F_3	100.07	952.70 (–0.07 to 0.55)	4.5	0.32	9.50
F_4	99.82	951.35 (–0.06 to 0.59)	4.5	0.58	10.15
F_5	100.11	951.85 (–0.01 to 0.64)	5	0.63	4.15
F_6	99.92	952.15 (–0.01 to 0.54)	5	0.67	4.05
F_7	99.15	952 (–0.04 to 0.63)	4.5	0.71	4.20
F_8	100.17	950.20 (–0.02 to 0.82)	5	0.68	4.10

*NI indicates nimesulide; NI-β-CD, nimesulide-β-cyclodextrin. F_1 to F_4, tablet formulations prepared by the wet granulation method; F_5 to F_8, tablet formulations prepared by the direct compression method.

Table 4. Dissolution Parameters of NI and NI-β-CD Tablet Formulations (n = 3)*

Formulation	$t_{50\%}$(min) (mean ± SD)	DP_{30} (mean ± SD)	DE_{30} (%) (mean ± SD)	k(min^{-1}) (mean ± SD)
F_1	49.38 ± 2.37	32.74 ± 0.66	19.57 ± 0.46	0.013 ± 0.002
F_2	26.45 ± 0.21	55.24 ± 1.08	30.93 ± 0.30	0.026 ± 0.003
F_3	19.99 ± 0.52	64.98 ± 0.80	40.09 ± 0.67	0.034 ± 0.002
F_4	23.21 ± 0.62	60.49 ± 1.50	35.70 ± 0.58	0.030 ± 0.002
F_5	46.06 ± 2.06	34.31 ± 0.88	21.93 ± 0.22	0.013 ± 0.002
F_6	31.21 ± 1.55	48.50 ± 1.50	28.20 ± 0.60	0.021 ± 0.001
F_7	4.26 ± 0.03	96.63 ± 0.39	75.34 ± 0.23	0.110 ± 0.010
F_8	5.28 ± 0.43	89.96 ± 0.33	68.75 ± 0.49	0.074 ± 0.010

*NI indicates nimesulide; NI-β-CD, nimesulide-β-cyclodextrin. F_1 to F_4, tablet formulations prepared by the wet granulation method; F_5 to F_8, tablet formulations prepared by the direct compression method.

points and evaluated for drug content, change in in vitro drug release pattern, hardness, friability, and disintegration time.

Statistical Analysis

The statistical analysis of the data was computed using a 1-way analysis of variance using SigmaStat software (SPSS, Inc, Chicago, IL) at a significance level of $P < .05$.

Results and Discussion

Nimesulide-CD and meloxicam-CD binary systems have been successfully prepared and evaluated, as reported in previous studies.[11,12] Formation of a true inclusion complex of nimesulide with β-CD in a 1:2M ratio in KS and CS was observed. However, in the case of meloxicam a true inclusion complex was observed with 1:1M and 1:2M ratio ME-γ-CD KS. Both drug-CD binary systems showed superior dissolution properties when compared with pure drugs alone.[11,12]

The above drug-CD binary systems are useful in dosage form development for increasing solubility, dissolution, and absorption rates of poorly soluble drugs. Thus, in the present investigation, tablets containing pure nimesulide and NI-β-CD 1:2M PM, KS, and CS (equivalent to a dose of 100 mg of nimesulide); and tablet formulations containing pure meloxicam and ME-γ-CD 1:1M and 1:2M PM and KS (equivalent to a dose of 15 mg of meloxicam) were prepared by both wet granulation and direct compression methods, as per the formulas given in Tables 1 and 2. The tablets were evaluated for drug content, uniformity of weight, hardness, friability, disintegration time, and dissolution properties.

The drug content of tablets was within the 100 ± 5% of label claim, and the results were satisfactory (Tables 3 and 4). A good degree of uniformity of weight was achieved for all the batches of tablet formulations prepared. The percent deviation did not exceed 5%, indicating excellent uniformity of weight in all the batches of tablet formulations prepared. All the tablet batches exhibited good mechanical properties with regard to both hardness and friability (Tables 3 and 5). No significant difference in hardness values within the batches of tablet formulations was observed. In the friability studies, weight loss values of all the tablet batches was less than 1%. All the tablet formulations prepared by wet granulation and direct compression methods, respectively, fulfilled the compendial requirement for disintegration time for compressed tablets: less than 15 minutes (Tables 3 and 5). Tablet formulations containing drug-CD binary systems prepared by the direct compression method showed significantly lower

Table 5. Tablet Properties of ME and ME-γ-CD Formulations*

Formulation	Drug Content (mg/tab)	Mean Weight (% deviation)	Hardness (kg/cm^2)	Friability (% wt loss)	Disintegration Time (min)
F_1	15.02	200.85 (–0.07 to 1.41)	5	0.32	5
F_2	14.98	201.45 (–0.22 to 2.25)	4.5	0.43	6.55
F_3	14.82	201.85 (–0.07 to 3.39)	5	0.52	6.35
F_4	15.51	200.65 (–0.17 to 3.31)	4.5	0.35	7.20
F_5	15.09	202.20 (–0.39 to 3.56)	4.5	0.58	7.25
F_6	14.95	202 (–0.17 to 3.46)	4.5	0.61	4
F_7	15.28	203.70 (–0.14 to 3.09)	4.5	0.59	4.10
F_8	15.13	202.35 (–0.81 to 3.63)	5	0.63	4.52
F_9	14.89	203.90 (–0.04 to 4.36)	5	0.72	4.20
F_{10}	14.78	203.35 (–0.17 to 3.27)	4.5	0.65	4

*ME indicates meloxicam; ME-γ-CD, meloxicam-γ-cyclodextrin. F_1 to F_5, tablet formulations prepared by the wet granulation method; F_6 to F_{10}, tablet formulations prepared by the direct compression method.

Table 6. Dissolution Parameters of ME and ME-γ-CD Tablet Formulations (n = 3)*

Formulation	$t_{50\%}$(min) (mean ± SD)	DP_{30} (mean ± SD)	DE_{30} (%) (mean ± SD)	k(min^{-1}) (mean ± SD)
F_1	>120	15.78 ± 0.30	8.15 ± 0.22	0.006 ± 0.001
F_2	28.03 ± 0.56	53.28 ± 0.77	28.50 ± 0.45	0.026 ± 0.002
F_3	22.52 ± 0.19	62.95 ± 0.55	35.09 ± 0.38	0.033 ± 0.004
F_4	13.95 ± 0.37	62.48 ± 0.61	42.94 ± 0.47	0.032 ± 0.002
F_5	4.20 ± 0.19	94.10 ± 1.06	73.48 ± 0.80	0.090 ± 0.010
F_6	114.55 ± 0.95	30.00 ± 0.48	15.43 ± 0.30	0.012 ± 0.003
F_7	43.29 ± 0.73	37.52 ± 0.56	25.31 ± 0.30	0.015 ± 0.005
F_8	4.95 ± 0.10	95.02 ± 0.35	71.65 ± 0.44	0.098 ± 0.015
F_9	19.91 ± 0.38	59.24 ± 0.94	40.02 ± 0.30	0.029 ± 0.005
F_{10}	3.52 ± 0.02	95.26 ± 0.93	82.29 ± 0.72	0.308 ± 0.010

*ME indicates meloxicam; ME-γ-CD, meloxicam-γ-cyclodextrin. F_1 to F_5, tablet formulations prepared by the wet granulation method; F_6 to F_{10}, tablet formulations prepared by the direct compression method.

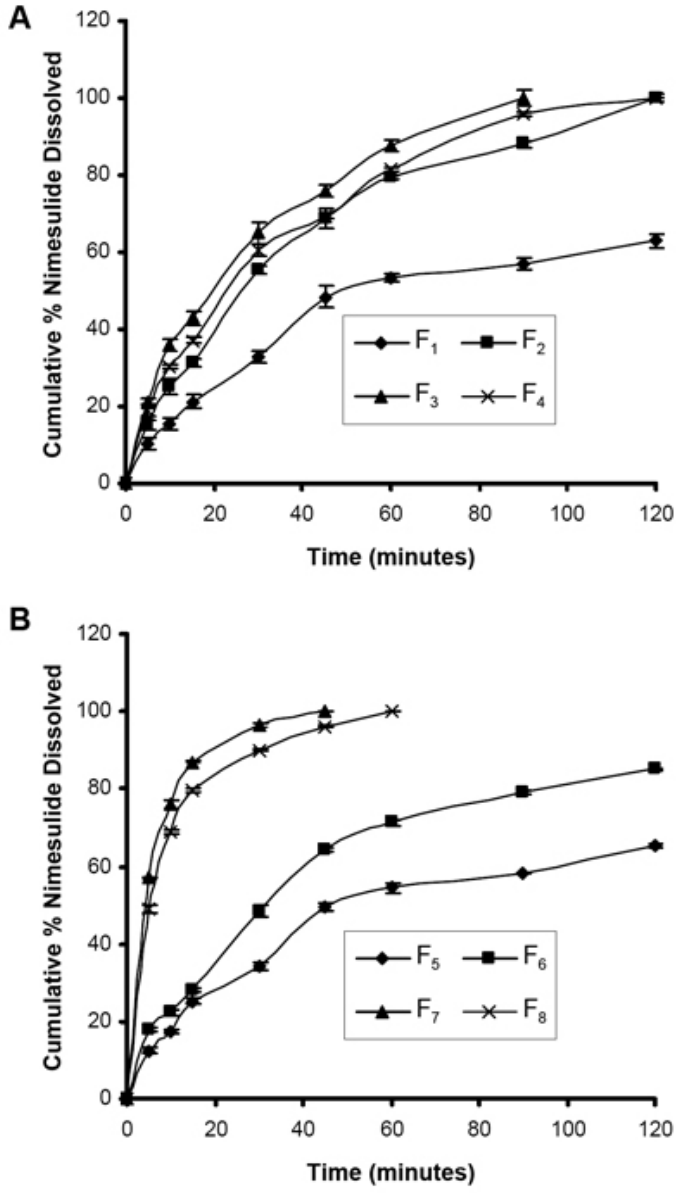

Figure 1. Dissolution profiles of nimesulide and nimesulide-β-cyclodextrin tablet formulations prepared by the wet granulation method (A) and the direct compression method (B).

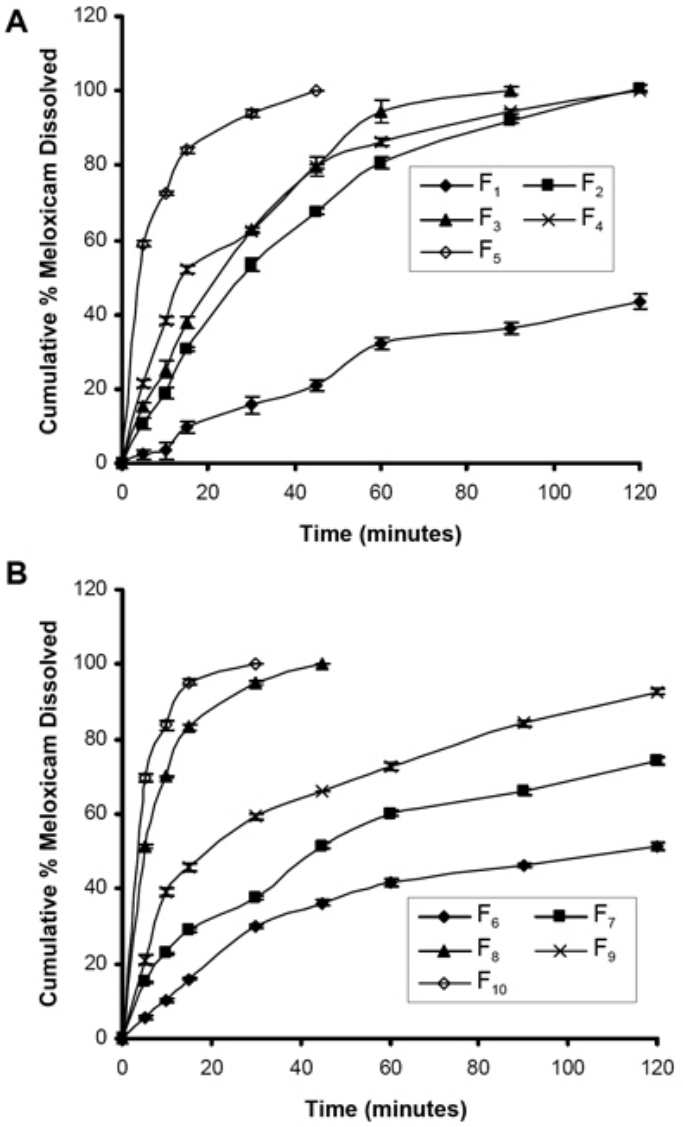

Figure 2. Dissolution profiles of meloxicam and meloxicam-γ-cyclodextrin tablet formulations prepared by the wet granulation method (A) and the direct compression method (B).

Table 7. In Vitro Drug Release Data (Mean ± SD) on NI-CD and ME-CD Tablet Formulations Obtained From Stability Studies (n = 3)*

		DP With NI Formulations		DP With ME Formulations	
Sample	Time (min)	F_7	F_8	F_5	F_{10}
Fresh	15	86.99 ± 2.23	79.86 ± 2.54	84.19 ± 1.82	95.26 ± 0.93
	30	96.63 ± 1.39	89.96 ± 1.32	94.10 ± 1.06	100.01 ± 0.07
	45	100.04 ± 2.09	96.22 ± 2.30	100.04 ± 2.07	—
6 months	15	84.25 ± 2.52	80.25 ± 2.15	85.47 ± 2.10	94.65 ± 2.63
	30	94.28 ± 2.15	90.54 ± 2.32	96.15 ± 3.25	98.69 ± 2.81
	45	98.28 ± 3.15	95.28 ± 2.52	98.56 ± 3.02	—

*NI indicates nimesulide; ME, meloxicam; CD, cyclodextrin; DP, drug percent dissolved.

disintegration time values than did the formulations prepared by the wet granulation method (Tables 3 and 5).

All tablet formulations were subjected to in vitro dissolution rate studies using alkaline borate buffer at pH 8.4 IP as the dissolution medium in the case of nimesulide tablet formulations, and phosphate buffer at pH 7.4 IP as dissolution medium in the case of meloxicam tablet formulations, to assess various dissolution properties such as $t_{50\%}$ (time to release 50% of drug), DP_{30} (percent of drug dissolved at 30 minutes), DE_{30} (dissolution efficiency at 30 minutes as a percentage),[14] and dissolution rate constant value (k). The corresponding values for nimesulide and meloxicam tablet formulations are given in Tables 4 and 6, and the dissolution profiles are shown in Figures 1 and 2. The dissolution properties of tablets prepared by direct compression were superior when compared with those of tablets prepared by wet granulation. However, tablet formulations containing PM prepared by the wet granulation method (F2 for nimesulide, and F2 and F4 for meloxicam) showed superior dissolution properties when compared with the tablets prepared by the direct compression method (F6 for nimesulide, and F7 and F9 for meloxicam). This may be attributed to the greater interparticle interaction of nimesulide with β-CD and meloxicam with γ-CD that may occur during the granulation process, where a doughlike mass is used for the preparation of granules.

The dissolution of nimesulide and meloxicam from all the tablet formulations examined followed first-order kinetics (0-30 minutes) with correlation coefficient (r) values ranging from 0.955 to 0.999. The first-order dissolution rate constant values, k(min^{-1}), are given in Tables 4 and 6. The tablet formulations containing NI-β-CD KS showed superior dissolution properties compared with formulations containing CS, irrespective of the method of tablet preparation. These results indicate that the fast releasing characteristics of these binary systems were not changed, even though they were formulated into tablets. Thus, NI-β-CD and ME-γ-CD binary systems can be used in developing tablet formulations of nimesulide and meloxicam with good tabletting and dissolution properties. Overall, tablet formulations prepared by the direct compression method showed dissolution properties superior to those of the formulations prepared by the wet granulation method. This can be better explained by the fact that for tablets prepared by direct compression, the drug is readily available to the dissolution medium and thus does not require a granule "splitting time," as is the case for tablets prepared by wet granulation.

A drug product may undergo changes in physicochemical characteristics during its storage, and these changes can affect the bioavailability of the dosage form. A unit of solid oral dosage form such as a tablet has to meet pharmacopeial specifications, such as specifications about drug content, hardness, disintegration time, and dissolution rate, during its shelf life. Hence, in the present investigation, selected nimesulide and meloxicam tablet formulations were subjected to accelerated stability studies by keeping the samples at 40°C ± 2°C and 75% relative humidity (maintained using a saturated solution of NaCl) in an oven.[13] The in vitro drug release results of stability studies on both drug formulations are given in Table 7. None of the tablet formulations showed any discoloration during storage. There were no statistical differences in the percentage of drug dissolved at 15, 30, and 45 minutes between fresh and stored samples at the different time points ($P < .05$). Also, no changes in hardness and disintegration times of the tested formulations were observed. Drug content also remained within acceptable limits. Assuming that a shelf life of 6 months at 40°C corresponds to a shelf life of 3 years at 25°C, based on the present results it can be predicted that the tablet formulations examined in Table 7 should have a shelf life of ~3 years.[15]

CONCLUSIONS

Drug-CD binary systems are useful in developing tablet formulations of nimesulide and meloxicam with improved dissolution properties. These tablets are stable, with a shelf life of up to 3 years, and meet all the pharmacopeial requirements for tablets.

REFERENCES

1. Duchene D, Wouessidjewe D. Pharmaceutical uses of cyclodextrins and derivatives. *Drug Dev Ind Pharm.* 1990;16:2487–2499.

2. Bekers O, Uijtendal EV, Beijnen JH, Bult A, Underberg WJ. Cyclodextrins in pharmaceutical field. *Drug Dev Ind Pharm.* 1991;17:1503–1549.

3. Davis R, Brogden RN. Nimesulide: an update of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy. *Drugs.* 1994;48:431–454.

4. Engelhardt G, Homma D, Schlegel K, Schnitzeler C, Utzmann R. Anti inflammatory, analgesic, antipyretic and related properties of meloxicam, a new nonsteroidal anti inflammatory agent with favourable gastrointestinal tolerance. *Inflamm Res.* 1995;44:423–433.

5. Engelhardt G, Bogel R, Schnitzeler C, Utzmann R. Meloxicam: influence on arachidonic acid metabolism. Part 1: in vitro findings. *Biochem Pharmacol.* 1996;51:21–28.

6. Churchill L, Graham AG, Shih CK, Pauletti D, Farina PR, Grob PM. Selective inhibition of human cyclooxygenase-2 by meloxicam. *Inflammopharmacology.* 1996;4:125–135.

7. Pairet M, Engelhardt G. Differential inhibition of COX-1 and COX-2 in vitro and pharmacological profile in vivo of NSAIDs. In: Vane J, Botting J, Botting R, eds. *Improved Nonsteroidal Anti-inflammatory Drugs- COX-2 Enzyme Inhibitors.* Dordrecht, The Netherlands: Kluwer Academic Publishers; 1996:103–119.

8. Distel M, Mueller C, Bluhmki E. Global analysis of gastrointestinal safety of a new NSAID, meloxicam. *Inflammopharmacology.* 1996;4: 71–81.

9. Turck D, Busch U, Heinzel G, Narjes H. Clinical pharmacokinetics of meloxicam. *Arzneimittelforschung.* 1997;47:253–258.

10. Piel G, Pirotte B, Delneuveille I, et al. Study of the influence of both cyclodextrins and L-lysine on the aqueous solubility of nimesulide; isolation and characterization of nimesulide-L-lysine-cyclodextrin complexes. *J Pharm Sci.* 1997;86: 475–480.

11. Nalluri BN, Chowdary KPR, Murthy KV, Hayman AR, Becket G. Physicochemical characterization and dissolution properties of nimesulide-cyclodextrin binary systems. *AAPS PharmSciTech.* 2003;4: E2. serial online.

12. Naidu NB, Chowdary KP, Murthy KV, Satyanarayana V, Hayman AR, Becket G. Physicochemical characterization and dissolution properties of meloxicam-cyclodextrin binary systems. *J Pharm Biomed Anal.* 2004;35:75–86.

13. Bodmeier R, Paerataku O. Constant potassium chloride release from microporous membrane-coated tablets prepared with aqueous colloidal polymer dispersions. *Pharm Res.* 1991;8: 355–359.

14. Khan KA. The concept of dissolution efficiency. *J Pharm Pharmacol.* 1975;27:48–49.

15. Carstensen JT. Stability and dating of solid dosage forms. In: Carstensen JT, ed. *Pharmaceutics of Solids and Solid Dosage Forms.* New York, NY: Wiley-Interscience; 1997:182–185.