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RESEARCH PAPER

Nimesulide-Modified Gum Karaya Solid Mixtures: Preparation, Characterization, and Formulation Development

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ABSTRACT

Solid mixtures of nimesulide (NS) and modified gum karaya (MGK) were prepared to improve the dissolution rate of NS. The effect of drug-carrier ratio on dissolution rate of NS was investigated by preparing the solid mixtures of different ratios by cogrinding method. Solid mixtures were also prepared by physical mixing, kneading, and solid dispersion techniques to study the influence of method of preparation. Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and equilibrium solubility studies were performed to explain the results of in vitro dissolution rate studies. It was clearly evident from the results that the NS dissolution rate was dependent on the concentration of MGK in the solid mixtures, and optimum weight ratio was found to be 1:4 (NS:MGK). Though the dissolution rate of NS from all solid mixtures prepared by different methods improved significantly, maximum improvement in dissolution rate was observed with solid dispersions. The order of methods basing on their effect on dissolution efficiency is solid dispersion > kneading > cogrinding > physical mixing > pure NS. Tablets of pure drug and solid mixtures (1:4 w/w, NS:MGK) were prepared. Though the best results from the dissolution test were obtained for the tablets containing solid dispersions, tablets containing cogrinding mixture were found to be suitable, from a practical point of view, for commercialization.

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Key Words: Nimesulide; Modified gum karaya; Dissolution enhancement; Solid mixtures.

INTRODUCTION

Nimesulide (NS) is a nonsteroidal antiinflammatory drug of the sulfanilide class that exhibits an acidic character by virtue of sulfonamide rather than a carboxylic group. It shows high antiinflammatory, antipyretic, and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects, and a high therapeutic index.[1] It is widely used in the treatment of musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis.[2] Nimesulide is poorly soluble in water,[3] and many attempts were made to improve its solubility and dissolution rate.[4,5]

It is well evident from the recent literature that the applicability of natural polymers as carriers for the improvement of dissolution rate of poorly water-soluble drugs has been increasing.[6–8] Particularly, hydrophilic polymers with high swelling capacity are found to be suitable for this application.[9] Recently, our research group reported the applicability of modified gum karaya as a carrier in the improvement of dissolution rate[10] and oral bioavailability[11] of a poorly water-soluble drug, nimodipine. The modified form of gum karaya was prepared from gum karaya by thermal method.[12,13]

In light of past work, modified gum karaya (MGK) was evaluated for its suitability as a carrier for the dissolution enhancement of NS. A cogrinding technique was used to prepare solid mixtures in different weight ratios (1:1, 1:4, and 1:9; NS:MGK) to study the effect of drug-to-carrier ratio on the dissolution rate of NS. Solid mixtures were also prepared in 1:4 w/w ratio (NS:MGK) using physical mixing, kneading, and solid dispersion methods to assess the effect of method of preparation on the dissolution characteristics of NS.

Since 1960s, there have been numerous publications investigating various aspects of solid dispersions, however, there are very few marketed products utilizing this technology. This poor success rate has often been attributed to processing difficulties or physical instability.[14] Hence, an attempt was also made to formulate the tablets using the prepared solid mixtures, in comparison with pure drug alone. The tabletting properties including in vitro dissolution rate profiles are also presented.

EXPERIMENTAL

Materials

The materials used were nimesulide (Gift sample from M/s Dr. Reddy's Laboratories Ltd., Hyderabad, India); Gum karaya, viscosity of 1% w/v aqueous solution 1800 cps (Purchased from M/s Dr. Girijan Co-operative Corporation Ltd., Visakhapatnam, India); Ethanol Excela R, Methanol Excela R, and Sodium lauryl sulphate (Qualigens Fine Chemicals, Mumbai, India), and microcrystalline cellulose (Avicel PH 102, FMC Europe, Brussels, Belgium). All other chemicals used were of analytical grade.

METHODS

The MGK used in this study was prepared by the method reported by Murali Mohan Babu et al. 2000.[12,13]

Briefly, powdered gum was placed in a porcelain bowl and subjected to heating using a sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling properties similar to GK, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GK samples were charred, when heated at 140°C. In the preparation of the modified form of GK, no further change in viscosity of GK was observed by heating it at 120°C for more than 2 h. Hence, these conditions of heating at 120°C for 2 h were selected to prepare a modified form of GK. The prepared modified form of GK was finally resieved (100 mesh) and stored in airtight container at 25°C.

Preparation of Solid Mixtures

Nimesulide was sifted through a sieve no. 100 before preparation of solid mixtures.

Physical Mixing Technique

For physical mixtures, the drug and carrier were weighed accurately and blended thoroughly with a spatula and finally sifted through a sieve no. 100.

Cogrinding Technique

Weighed quantities of carrier and drug were taken in a mortar, cogrinding the mixture for 20 min and finally sifted through a sieve no. 100.

Kneading Technique

The required quantities of drug and carrier were weighed and placed in a mortar and then the mixture was kneaded with 70% v/v ethanol (1.5 times by w/v) for 20 min. The resultant mass was dried at 40°C, pulverized, and sifted through a sieve no.100.

Solid Dispersion Technique

Nimesulide was dissolved in 70% v/v ethanol to obtain a clear solution. Modified gum karaya was added to the solution and dispersed well. The solvent was evaporated at reduced pressure at 60°C with constant mixing. The resultant residue was dried under vacuums for 3 h and stored overnight in a desiccator. Finally, the mass obtained was crushed, pulverized, and sifted through sieve no. 100.

Preparation of Treated Samples of Drug

In order to ascertain the effect of method and/or carrier on the dissolution rate of NS, ground (NS_1), kneaded (NS_2), and recrystallized NS (NS_3) were prepared using the above conditions except the addition of MGK.

To avoid frequent repetition of long phrases, we abbreviate all the prepared products as given in Table 1.

Table 1. Abbreviations used for solid mixtures of nimesulide and modified gun karaya.

Factor	Process variable	Abbreviation
Effect of carrier concentration[a]	1:1 w/w	CM_2
	1:4 w/w	CM_5
	1:9 w/w	CM_{10}
Effect of method of preparation[b]	Physical method	PM_5
	Cogrinding method	CM_5
	Kneading method	KM_5
	Solid dispersion method	SD_5

[a]Solid mixtures were prepared by cogrinding method.
[b]NS:MGK 1:4 w/w.

Characterization of Solid Mixtures

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC 220C, SEIKO, JAPAN) was used to obtain the DSC curves representing the rates of heat uptake with respect to temperature. About 10 mg of sample was weighed in a standard open aluminum pan. An empty pan of the same type was utilized as the reference. Thermograms were recorded at a heating rate of 10°C/min from 30° to 300°C in an atmosphere of nitrogen. Calibrations of temperature and heat flow were performed with indium.

X-ray Diffraction Studies (XRD)

X-ray diffraction (XRD) patterns each pure ingredient, treated samples of NS, and solid mixtures were obtained using Phillips Diffractometer (PW1140) and CU-Kα radiation. Measurements were carried out using 40 kV voltage and 20 mA current. Diffractograms were run at a scanning speed of 2°/min and a chart speed of 2°/2cm/2θ.

Solubility Studies

The apparent solubility of NS from pure drug, treated NS samples, and solid mixtures was determined in water at 37°C. A sample equivalent to 50 mg of NS was added to 50 mL of water in a conical flask with Teflon-lined screw caps. The conical flasks were kept on a shaker incubator maintained at 37° ± 0.5°C for 48 h. After shaking, the flasks were kept in an incubator at 37° ± 0.5°C for equilibration for 12 h. The samples were filtered through a 0.45 μm syringe filter, diluted, and analyzed spectrophotometrically at 230 nm. Each experiment was repeated three times, and mean of the results is given.

In Vitro Dissolution Rate Studies

In vitro dissolution rate of NS from pure drug, treated samples, and various solid mixtures was studied using the USP 21 3-station Dissolution Rate Test Apparatus (M/S Campbell Electronics, Model: DR-3) in 900 mL of borate buffer (pH 8.4) with a paddle stirrer. Samples equivalent to 50 mg of NS, a speed of 50 rpm, and a temperature of 37° ± 0.5°C were used in each test. Samples of dissolution media were withdrawn at different time intervals, filtered through a 0.45 μm syringe

filter, suitably diluted, and assayed spectrophotometrically for NS at 230 nm (Shimadzu UV-205, Japan). Each dissolution rate test was repeated three times, and the average values are reported.

The dissolution efficiency (DE) suggested by Khan[15] was employed to compare the dissolution data. Dissolution effiency is defined as the area under the dissolution curve up to the time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.

$$\text{Dissolution efficiency (DE)} = \left(\frac{\int_0^t y.dt}{y_{100}.t}\right)100$$

The dissolution efficiency can have a range of values depending on the time interval chosen. In any case, constant time intervals should be chosen for comparison. The DE_{10} and DE_{30} values were calculated from the dissolution data of each product and used for comparison.

Preparation of Tablets

Solid mixtures prepared in 1:4 w/w (NS:MGK) equivalent to 100 mg of NS were mixed well with talc (1.5% w/w) and magnesium stearate (1.5% w/w). Powder weighing the equivalent of 515 mg was compressed into tablet using a 11 mm flat-faced punch on a Cadmach single punch tablet machine (Cadmach Machinery Co. Pvt. Ltd., India). Each time, tablets of 100 were prepared for all the solid mixtures. Tablets of pure NS alone were prepared by using microcrystalline cellulose (Avicel PH-102) (400 mg/tablet) to raise the total bulk of each tablet to 500 mg. Talc (1.5% w/w) and magnesium stearate (1.5% w/w) were used as lubricants, and tablets were compressed as described above.

Characterization of Tablets

The tablets were tested for hardness, friability, disintegration time, drug content, and in vitro dissolution performance. Hardness of tablets was determined by using the Monsanto hardness tester. Friability of the tablets was measured by using the Roche friabilator. Disintegration time was determined in a Thermonic Tablet Disintegration Test Apparatus using distilled water as medium. The drug content of all the prepared tablets was estimated by the following procedure. Twenty tablets were placed in a mortar and crushed into powder. A powdered solid mixture equivalent to 50 mg of NS was placed in a 100-mL volumetric flask. Methanol (60 mL) was added, and the contents were mixed thoroughly to dissolve the drug from the solid mixtures. The solution was made up to volume with methanol. Then solution was filtered through a 0.45 μm syringe filter, diluted, and assayed for NS spectrophotometrically at 230 nm. The in vitro dissolution rate of NS from the tablets was determined by the method described previously.

The recorded values are the mean of six tablets for disintegration, ten for the friability, five for hardness, and three for in vitro dissolution study.

Statistical Analysis

The differences in solubility values as well as DE values were statistically evaluated using analysis of variance (ANOVA). In the case of normally distributed results, the equal variance test was used, while Kruskal-Wallis One Way Analysis of Variance on Ranks was used for non-normal distributed data.

RESULTS AND DISCUSSION

Solid State Characterization

DSC Studies

Figure 1 depicts the DSC curves of the pure drug in comparison with treated samples. Pure NS exhibits a sharp melting endotherm at 152°C. The thermograms of NS_1, NS_2, and NS_3 exhibited endothermic peaks at 152.2, 152.4, 152.5°C, respectively, indicating that there is no alteration in the thermal features of NS after any treatment.

The DSC curves of the pure compounds and solid mixtures are shown in Fig. 2. The DSC thermograms of MGK exhibited broad endothermic peak at 109.5°C owing to its amorphous character. The broad endothermic peak of MGK is due to the release of water molecules during heating. The DSC thermograms of CM_2, CM_5, and CM_{10} showed the endothermic peaks corresponding to pure drug at 150.2, 149.5, and 150.2°C, respectively. It was also observed that the size of the endothermic peak reduced as the concentration of MGK increased, however, the

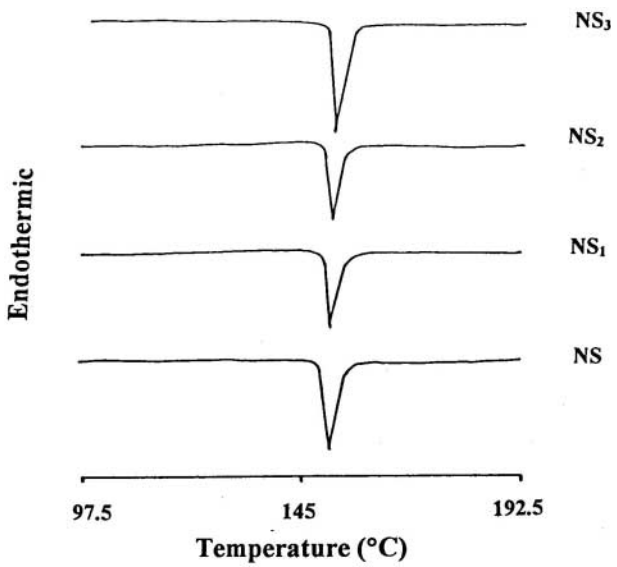

Figure 1. DSC thermograms of NS_1, NS_2, and NS_3 in comparison with pure NS.

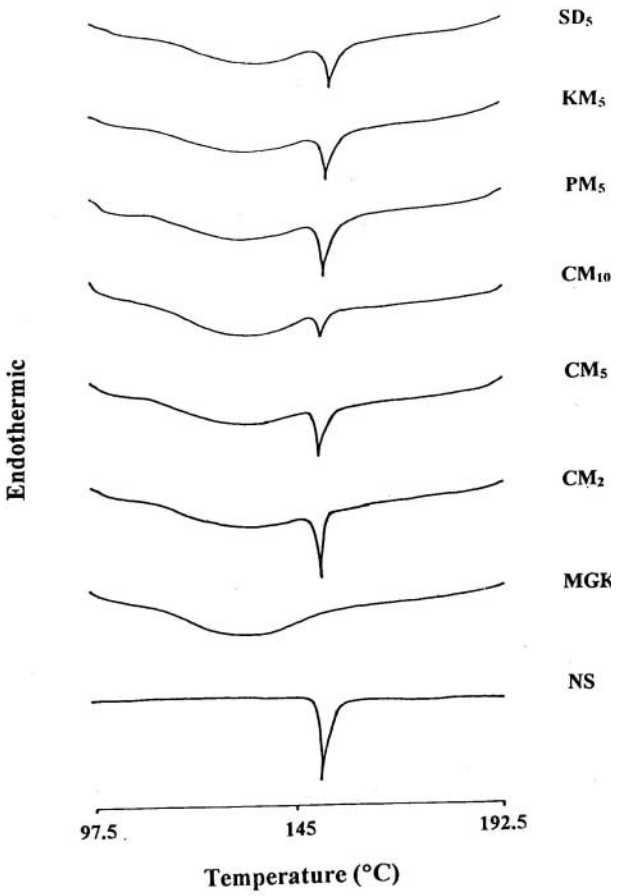

Figure 2. DSC thermograms of solid mixtures of NS and MGK in different weight ratios and prepared by different methods in comparison with pure NS and MGK.

peak did not disappear. The thermograms showed no evidence of the formation of a solid complex or any chemical interaction between drug and polymer.

The DSC thermograms of PM_5, KM_5, and SD_5 showed the peaks at 150.2, 149.6, and 150.3°C, respectively, corresponding to melting of NS. It was noticed that the intensity of endothermic peak of NS in physical mixture was slightly lower than that of pure NS. Though all the solid mixtures showed endothermic peak corresponding to the melting of NS, it was observed that the intensity of endothermic peak was reduced in cogrinding, kneading, and solid dispersions compared to that of pure drug. The reduction in the peak intensity in solid mixtures is probably due to (a) lower loading of the drug per unit weight of the solid mixtures, and (b) partial conversion of crystalline form of NS to amorphous form. The thermograms showed no evidence of the formation of solid complex or any chemical interaction between drug and carrier.

As there was no alteration of thermal features of NS in any one of the treated samples, the influence of method preparation on the thermal features of NS in the absence of carrier could be ruled out. In the physical mixture, the intensity of endothermic peak of NS was slightly reduced. Mere presence of carrier was also not affecting the thermal features of NS. However, the thermal feature of NS in the cogrinding mixture, kneading mixture, or solid dispersion markedly differed from that of the pure drug. Collectively, these results indicated that the crystallinity of NS was markedly affected by the method of treatment only in the presence of MGK.

XRD Studies

The XRD patterns of pure NS in comparison with NS_1, NS_2, and NS_3 are shown in Fig. 3. The diffractogram of pure NS exhibited a characteristic diffraction pattern with numerous distinctive peaks, showing that the drug is highly crystalline in nature. All the peaks observed in NS were also shown in the by three treated samples. However, it was observed that the intensity of peaks were slightly reduced in NS_1 and NS_2, whereas in NS_3 the intensity was slightly increased. The slight reduction in endothermic peak intensities of NS_1 and NS_2 could be attributed to partial amorphization of NS, whereas increased peak intensity of NS_3 could be due to increased crystallinity after recrystallization of NS. These results are in good agreement with our previous studies.[10] It was also noticed that there were slight differences among the

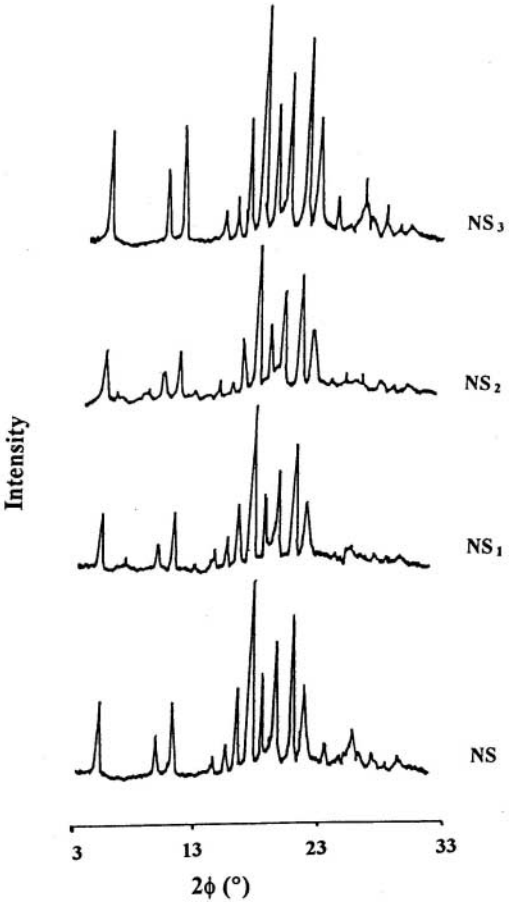

Figure 3. XRD patterns of NS_1, NS_2, and NS_3 in comparison with pure NS.

XRD patterns of treated samples and pure drug, which might be due to damage of lattice structure, causing the disordered region.[16] However, further characterization studies are required to find out the reason for the changes.

The XRD patterns of the pure compounds and solid mixtures are shown in Fig. 4. The MGK exhibited a characteristic single peak with low intensity at 19.8°, indicating its amorphous nature. The diffractograms of CM_2, CM_5, and CM_{10} indicated that the peak height intensities of NS decreased with the increased carrier concentration. These results clearly indicated that the increased polymer concentration in solid mixtures reduced the crystallinity of drug.

The physical mixture possessed the diffraction peaks of NS crystals, indicating that NS was in the crystalline state. However, the XRD patterns of KM_5 and SD_5 showed many of the sharp diffraction peaks of pure NS, but their peak heights were much

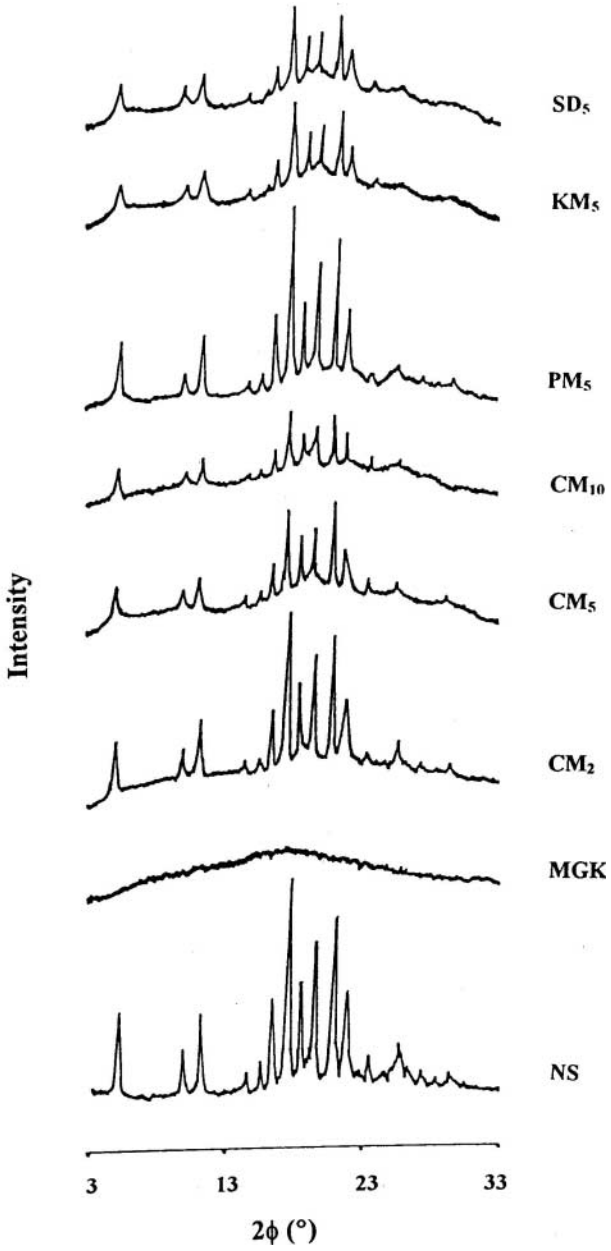

Figure 4. XRD patterns of solid mixtures of NS and MGK in different weight ratios and prepared by different methods in comparison with pure NS and MGK.

reduced. The presence of peaks with reduced peak heights indicates that part of the drug is present in the microcrystalline form.

Solubility Studies

The solubility of NS was not increased significantly after any of the treatments, as indicated by

Table 2. Solubility and dissolution efficiency (DE) values of nimesulide from treated samples and various solid mixtures in comparison with pure drug (mean ± S.D.).

Product	Solubility (μg/mL)	DE_{10}	DE_{30}
NS	14.32 ± 1.23	1.79 ± 0.32	8.44 ± 0.94
NS_1	15.19 ± 0.98	1.89 ± 0.40	8.78 ± 0.91
NS_2	14.53 ± 1.86	2.06 ± 0.33	8.96 ± 1.02
NS_3	14.29 ± 1.09	1.54 ± 0.38	7.85 ± 0.65
CM_2	29.39 ± 1.88	13.91 ± 1.46	29.98 ± 1.73
CM_5	67.59 ± 2.67	26.21 ± 1.38	55.22 ± 1.63
CM_{10}	79.23 ± 1.89	27.26 ± 1.65	55.85 ± 2.05
PM_5	15.29 ± 1.39	5.85 ± 0.66	15.06 ± 1.07
KM_5	69.29 ± 2.09	29.26 ± 0.87	59.70 ± 1.09
SD_5	73.19 ± 1.73	32.62 ± 1.31	64.91 ± 1.11

($n = 3$).

the solubility data given in Table 2. The solubility of NS from cogrinding mixtures was increased significantly ($p < 0.01$) as the MGK concentration increased. The enhancement of solubility directly related to the increase in the polymer content could be attributed to the hydrophilic nature of the carrier and the progressive amorphization of the drug. KM_5 and SD_5 also showed increase in the solubility of NS in comparison with pure NS or NS-samples treated. On the other hand, no remarkable increase in NS solubility was noticed in the physical mixture. These differences could be due to a deeper entrapment into the network of polymer, realized during the preparation of solid mixtures, while in physical mixtures a simple deposition of the polymer on the drug was obtained. In addition to improvement of the wetting of the hydrophobic NS crystals, reduction in crystallinity of NS in solid mixtures prepared by cogrinding, kneading, or the solid dispersion method as confirmed by XRD data, could also contribute to significant improvement of NS solubility. These results are in accordance with results of Egawa et al.[17] It has been reported that the solubility of cephalexin varied with the changes in the degree of crystallinity.

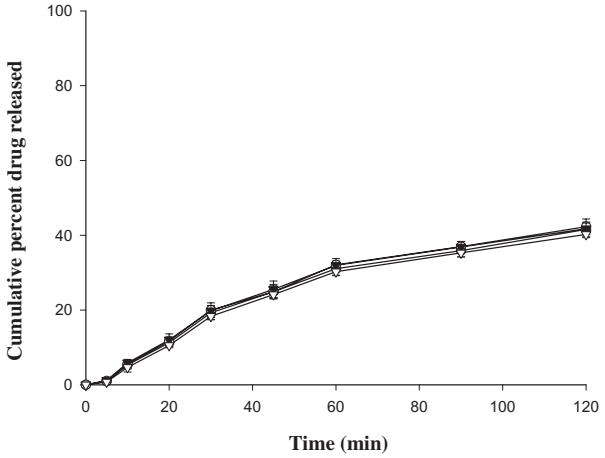

Figure 5. Comparative in vitro dissolution profiles of NS with those of treated samples of NS. ●NS ○NS_1 ▼NS_2 ▽NS_3.

In Vitro Dissolution Rate Studies

In vitro dissolution profiles of NS from treated samples in comparison with pure drug shown in Fig. 5 clearly indicate that the rate of dissolution of NS was not influenced by the method of preparation in the absence of a carrier, though the XRD data showed slight differences in their crystallinity (Fig. 3). It must be taken into account that the particle size reduction of drug alone may cause aggregation and agglomeration of drug particles to some extent.[18] The DE values calculated from the dissolution profiles (Table 2) further confirmed that there is no significant effect of method of preparation on the dissolution rate of NS in the absence of carrier.

Figure 6 compares the mean percent NS from pure drug and three solid mixtures (CM_2, CM_5, and CM_{10}) containing different proportions (50%, 80%, 90% w/w) of MGK in borate buffer (pH 8.4) vs. time. The DE_{10}, and DE_{30} values of these solid mixtures are given in Table 2. The dissolution rate of NS from cogrinding mixtures was increased by increasing the carrier concentration up to 80%, and further increase in polymer concentration had no significant effect on the dissolution rate of NS (1:9). Hence, it was concluded that the 1:4 weight ratio of NS to MGK

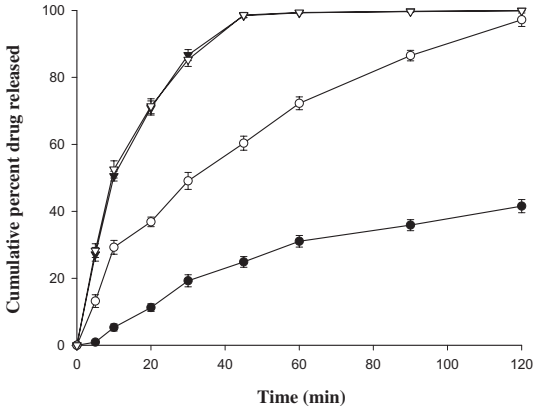

Figure 6. In vitro dissolution profiles of NS from co-grinding mixtures containing varying concentrations of carrier in comparison with pure drug. ●NS ○CM_2 ▼CM_5 ▽CM_{10}.

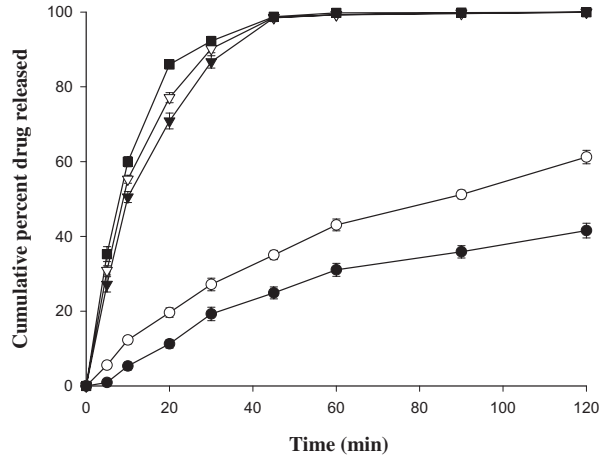

Figure 7. In vitro dissolution profiles of NS from solid mixtures (NS:MGK; 1:4 w/w) prepared by different methods in comparison with pure drug. ●NS ○PM_5 ▼CM_5 ▽KM_5 ■SD_5.

was considered to be optimum for enhancement of dissolution rate of NS.

Figure 7 shows the dissolution profiles of NS from pure NS in comparison with that of PM_5, CM_5, KM_5, and SD_5. The DE values given in Table 2 clearly indicate that solid mixture prepared by solid dispersion method was shown to produce a maximum dissolution rate. The order of products based on DE values is $SD_5 > KM_5 > CM_5 > PM_5 >$ NS.

Dissolution of NS from its physical mixtures was significantly higher than that for the pure drug. Improvement of dissolution properties of NS from solid mixtures prepared by the physical mixing method indicated the hydration of the carrier. Dry mixing brings the drug in close contact with the hydrophilic polymer, and the increased dissolution rate can thus be explained as a result of increased wettability and dispersibility of NS. Indeed, during dissolution experiments, it was noticed that physical mixtures immediately sink to the bottom of the dissolution vessel as solid mixtures do, whereas the pure drug floats for a long period on the surface of the dissolution medium. It is evident that NS dissolves faster in mixtures ground with MGK than in physical mixtures (Fig. 7). This enhancement in the dissolution rate may be attributed not only to the dispersion of NS in the MGK after cogrinding, but also to the partial amorphous state of such a system. This assumption has been confirmed by the DSC and XRD data. Intimate mixing of drug and carrier in the presence of 70% v/v ethanol (kneading agent) resulted in a uniform distribution of drug on the carrier and thus an increase in dissolution rate of NS from kneading mixtures. Ford,[19] reviewed mechanisms of increased dissolution rate from solid dispersions. Lack of crystallinity, increased wettability, and reduction of drug particle size, were considered to be predominant factors in controlling dissolution.

The swelling ability of the carrier could also contribute to the improvement of NS dissolution rate. Because micronized drug particles are fairly evenly distributed on relatively large hydrophilic carrier, particles can prevent the reagglomeration of drug particles during dissolution. Moreover, the strong and rapid swelling ability of the MGK could immediately increase the surface area available for dissolution process as the particles are exposed to dissolution medium.[10,12,13] The strong fluence of swelling ability of the carrier on dissolution rate of poorly soluble drugs has been proved. The improvement of the dissolution rate was found to be better in systems with strongly swelling super disintegrants than from systems with a hydrophilic soluble carrier such as lactose or with a carrier with limited swelling properties such as potato starch.[20,21]

In order to evaluate the feasibility of formulating a tablet dosage form using solid mixtures, tablets were formulated by using pure drug alone or solid mixtures of NS and MGK (1:4 w/w) prepared by physical, cogrinding, kneading, and solid dispersion techniques. The parameters of all the tablets prepared were satisfactory (Table 3). No difficulties during compression into tablets were observed. All the tablets were found to contain NS within 100% ± 3% of the labeled claim. Hardness of the tablets was found to be within the range of 4–5 kg/sq cm.

Table 3. Tableting and dissolution characteristics of prepared tablets.

Tablet	Weight[a] (mg)	Drug content[a] (%)	Hardness[b] (kg/cm^2)	Friability[c] (%)	D.T.[d] (min)	DE_{10}[e] (%)	DE_{30}[e] (%)
NS	514.23 ± 1.69	100.03 ± 2.16	4.36 ± 0.45	0.59	11	2.37 ± 0.36	11.27 ± 0.87
PM_5	515.41 ± 2.61	100.26 ± 2.69	4.26 ± 0.39	0.76	3.5	5.14 ± 1.07	14.20 ± 1.28
CM_5	516.32 ± 2.09	99.49 ± 2.89	4.59 ± 0.75	0.51	3.8	24.07 ± 0.71	53.86 ± 1.12
KM_5	514.29 ± 3.07	99.89 ± 2.78	4.67 ± 0.29	0.49	3.5	26.27 ± 0.65	58.31 ± 0.80
SD_5	515.19 ± 1.69	99.79 ± 2.51	4.79 ± 0.67	0.45	3.6	28.36 ± 0.80	63.05 ± 1.12

D.T. represents disintegration time.
[a]Mean ± S.D., $n = 20$ tablets.
[b]Mean ± S.D. $n = 5$ tablets.
[c]Mean of three determinations, $n = 10$ tablets.
[d]Mean, $n = 3$ tablets.
[e]Mean ± S.D., $n = 3$ tablets.

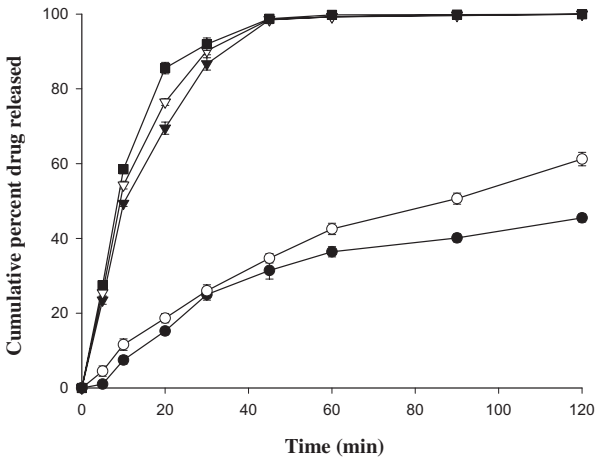

Figure 8. In vitro dissolution profiles of NS from tablets of solid mixtures (NS:MGK; 1:4 w/w) prepared by different methods in comparison with that of tablets containing pure drug. ●NS ○PM_5 ▼CM_5 ▽KM_5 ■SD_5.

Friability of tablets was less than 1% w/w. Disintegration time of the tablets was found to be less than 4 min except for the tablets prepared with pure drug alone. The disintegrating properties of MGK were well documented.[12,13] Due to its rapid and strong swelling nature, tablets containing solid mixtures disintegrated rapidly.

The release studies of NS from tablets confirmed the results obtained for the powder samples as shown in Fig. 8. It was found that there was a significant difference between the DE_{10} values of tablet formulations (Table 3) and those of powder samples (Table 2). These differences could be due to of compression of solid mixtures into tablet form. However, no significant difference is observed among the DE_{30} values (Table 3) as these tablets disintegrated rapidly. As shown in Table 3, the DE values of NS from tablets containing solid mixtures are much greater than those from tablets of pure drug. After 30 min of dissolution, 83.31, 85.52, and 89.37% of NS was dissolved from tablets containing the cogrinding mixture, kneading mixture, or solid dispersion, respectively. These values are approximately 4–5 times greater than those from tablets formulated with the pure drug.

Based on the above results, the solid mixtures with MGK significantly improved the dissolution rate of NS, when compared to pure drug. It is important to note the utility of the process of combining the carrier with drug to produce systems giving a rapid dissolution rate. The improvement of dissolution rate of NS was highest at NS:MGK weight ratio 1:4. Though all the methods used for the preparation of solid mixtures significantly improved the dissolution rate of NS, maximum dissolution was produced by solid dispersions. The proposed tablet formulations with solid mixtures ensure good pharmaceutical availability of NS. As the tablets of cogrinding mixtures also showed comparable pharmaceutical properties with that of tablets of solid dispersions, it is advised that the cogrinding method would be useful for the preparation of solid mixtures with enhanced dissolution rate for poorly water-soluble drugs.

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