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Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine

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Abstract

Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine (NM). The advantages of MGK over the parent gum karaya (GK) were illustrated by differences in the in vitro dissolution profiles of respective solid mixtures prepared by co-grinding technique. The influence of process variable, such as polysaccharide concentration and method of preparation of solid mixture on dissolution rate was studied. Solubility studies were also performed to explain the differences in dissolution rate. Solid mixtures were characterized by differential scanning calorimetry (DSC), X-ray diffraction studies (XRD) and scanning electron microscopy (SEM). The dissolution rate of NM was increased as the MGK concentration increased and optimum ratio was found to be 1:9 w/w ratio (NM:MGK). It is found that method of preparation of solid mixtures was significantly effected the dissolution rate of NM from solid mixtures. The order of method of preparation in according to their Dissolution Efficiency is physical mixture < co-grinding mixture < swollen carrier mixture < kneading mixture (water as kneading agent) < kneading mixture (70% v/v ethanol as kneading agent) < solid dispersion. Though, the solid mixtures prepared by other methods like solid dispersion, swollen carrier mixture and kneading technique gave faster release, co-grinding mixture prepared in 1:9 w/w ratio (NM:MGK) was found to exhibit a significant improvement in dissolution rate without requiring addition of organic solvents or high temperatures for its preparation and the process is less cumbersome. Hence, co-grinding technique appears to be more easier and the most convenient method from a practical point of view.

Keywords: Gum karaya; Modified gum karaya; Nimodipine; Dissolution enhancement; Solid dispersion; Kneading; Co-grinding; Swollen carrier mixture

1. Introduction

Improvement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Many approaches, such as salt formation, solubilization

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and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs (Wadke et al., 1989). However, all these techniques have potential limitations (Serajuddin, 1999; Leuner and Dressman, 2000). All poorly soluble drugs are not suitable for improving their solubility by salt formation. Use of co-solvents or surfactants to improve dissolution rate pose problems, such as patient compliance and commercialization. Even though particle size reduction increases the dissolution rate, the formed fine powders showing poor wettability and flow properties (Sjokvist et al., 1989; Temeljotov et al., 1996). Solid dispersion technique has come into existence to eliminate all these problems. This technique has been extensively used to enhance the dissolution characteristics of the sparingly soluble drugs (Iwata and Veda, 1996; Moneghini et al., 1998; Velaz et al., 1998; Chowdary and Rama Rao, 1999; Kohri et al., 1999). However, the practical applicability of these systems has remained limited mainly due to difficulties in methods of preparation (Goldberg et al., 1966; Chiou and Riegelman, 1971), poor reproducibility of physicochemical properties (Mc Gunity et al., 1984), difficulties in dosage form development (Ford and Rubinstein, 1980) and less feasibility for scale up of manufacturing processes (Yakou et al., 1984). Many carriers used in solid dispersions also cause problems due to their hygroscopic nature (Leuner and Dressman, 2000). Hence, continuous search for new carriers and new techniques is going on, which are useful for large-scale manufacturing.

In the last few years, the use of semi-synthetic hydrophilic polymers as carriers to enhance the dissolution rate and bioavallability of poorly water-soluble drugs has been demonstrated by a number of investigators (Giunchedi et al., 1990; Suzuki and Sunada, 1998; Chowdary and Rama Rao, 1999; Yamada et al., 1999). But many of these polymers also limit their application as carriers for dissolution enhancement by their high viscosity (Portero et al., 1998) and toughness (Kohri et al., 1999). Hence, development of carriers with high swelling and low viscosity may offer better alternative to overcome this problem.

The usage of natural polymers as drug carriers is on increasing side because of their low cost, biocompatibility and biodegradability (Sawayanqagi et al., 1983; Imasi et al., 1991; Acaturk et al., 1992; Portero et al., 1998). Gum karaya (GK) is a natural gum exudate of *Sterculia urens*, a tree native to India belongs to the family 'Sterculiaceae' (Gershon and Pader, 1972). It is widely used in food industry, as it is an approved food additive (Amderson, 1989). The wider applications of GK due to its unique features such as high swelling and water retention capacity, high viscosity properties, inherent nature of anti-microbial activity and abundant availability (Gauthami and Bhat, 1992). It is also evidenced from the literature that the GK was used as laxative due to its high swelling ability and formation of discontinuous mucilage (Whistler, 1973). Our research group reported the preparation of modified form of GK (MGK) that has low viscosity and comparable swelling capacity with that of the GK and its applicability as disintegrant (Murali Mohan Babu et al., 2000). As MGK has low viscosity and comparable swelling capacity with that of the GK that are beneficial properties for overcoming the processing and handling problems occurred in the preparation of solid mixtures, the present investigation aimed to study the influence of MGK on dissolution rate of poorly water soluble drug.

The drug selected for the evaluation of MGK as carrier for dissolution enhancement is nimodipine. Nimodipine (NM) is a dihydropyridine calcium blocker, used in the treatment of senile dementia and in the prophylaxis of the vascular hemierania (Manhold, 1985; Freedman and Waters, 1987) The NM is practically insoluble in water (Grunenberg et al., 1995), thereby exhibits low bioavailability after oral administration. Therefore, the improvement of NM dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficiency. Various studies have been conducted in order to increase the NM dissolution rate, mainly via the use of solid dispersions with HPMC (Chowdary et al., 1995), PEG 6000 (Lu et al., 1995) and cyclodextrins (Kopecky et al., 1998).

The effect of various formulation and process variables including type of GK, MGK to NM

ratio and method of preparation of solid mixtures on the dissolution rate was investigated. Apparent solubility studies, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), and X-ray diffraction technique (XRD) were used to explain the results.

2. Materials and methods

2.1. Materials

Nimodipine was a gift sample from Dr Reddy Laboratories Ltd (Hyderabad, India). Girijan Co-operative Corporation Ltd (Visakhapatnam, India) supplied gum karaya (Grade 1). All other materials were of analytical reagent grade.

2.2. Methods

2.2.1. Preparation of modified gum karaya

The crude tears of gum were pulverized, sieved through mesh no. 100 and for further studies. Preparation of MGK was done by the method reported by Murali Mohan Babu et al. (2000).

Briefly, powdered gum was taken in a porcelain bowl and subjected to heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling property 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 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 modified form of GK (Murali Mohan Babu et al., 2000). The prepared modified form of GK was finally re-sieved (100 mesh) and stored in airtight container at 25 °C.

2.2.1.1. Characterization of GK/MGK

Swelling and water retention capacity. The swelling and water retention capacity of the GK and MGK were estimated by a slightly modified method described by Gauthami and Bhat (1992). About 1.0 g of GK powder was accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100-ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h. Swelling capacity of GK/MGK was expressed in terms of swelling index as follows.

Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$\mathrm{SI} = \left(\frac{X_t - X_0}{X_0}\right) \times 100$$

where, X_0 is the initial height of the powder in graduated cylinder and X_t denotes the height occupied by swollen gum after 24 h.

The contents from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of water collected was noted and the difference between the origina1 volume of the mucilage and the volume drained was taken as water retained by the sample referred as water retention capacity or water absorption capacity of the polysaccharide.

Determination of volatile acid content. About 1 g of gum was accurately weighed, transferred to a 700 ml long necked flask. 100 ml of water and 5 ml of orthophosphoric acid were added and allowed to 'stand for 6 h until the gum was completely swollen. Then it was boiled for 2 h under a reflux condenser, and then steam distilled until 800 ml of the distillate was obtained. The distillate was titrated with N/10 sodium hydroxide using phenolphthalein as indicator. The procedure was repeated omitting the sample. The difference between the two titrations represented the amount of alkali required to neutralize the volatile acid.

Each ml of 0.1 N NaOH $\equiv$ 0.006005 g of $C_2H_4O_2$.

Viscosity measurement. The viscosity of 1% (w/v) GK/MGK solution was measured according to

the USP XXII at 37 °C using a Rheomat 115, MS-DIN 145, and module 4/3.

2.2.2. Preparation of samples

NM is light sensitive but to a lesser degree than nifedipine. The degradation half-lives of nimodipine are 16 and 56 h following exposure of aqueous solutions of the drug to UV light (360 nm wavelength, 300 lux) and daylight, respectively (Jackobsen and Mikkelsen, 1980). Hence, all experiments were carried out under light protected conditions to prevent the photodecomposition of NM.

2.2.2.1. Physical mixture. The physical mixture (PM_{10}) of drug and MGK was obtained by simple blending the NM and MGK in 1:9 w/w ratio (drug:polymer) with a spatula.

2.2.2.2. Co-grinding mixture. Co-grinding mixture (CM_{10}) of MGK and NM was obtained by co-grinding the mixture of NM and MGK in 1:9 w/w ratio for 20 mm in a ceramic mortar and sieved through 100 mesh. For comparing the effect of carrier on dissolution rate, NM and GK co-grinding mixture in 1:9 w/w ratio was also prepared and denoted as CM-GK_{10}.

2.2.2.3. Kneading mixture. Kneading mixtures were prepared by weighed quantities of drug and polymer (1:9) placed in a mortar and then the mixtures were kneaded with 1.5 times their amount of either ethanol 70% v/v or water for 20 min. The kneading mixtures were dried in oven at 40 °C until it reached uniform weight and then pulverized and screened through 100 mesh. Kneading mixture prepared with ethanol (70% v/v) is named as KM_{10}, whereas kneading mixture with water as WM_{10} in the further studies.

2.2.2.4. Solid mixture prepared by solid dispersion technique. Solid dispersions of NM in MGK were prepared by the solvent method as follows. To a solution of NM (300 mg) in 70% v/v ethanol (25 ml) and the appropriate amount of MGK was added. Next, the solvent was evaporated under reduced pressure at 60 °C with constant mixing. Then the resulting residue dried under vacuum for 3 h and was stored overnight in a desiccator. The mass obtained then crushed, pulverized and sieved through a mesh no. 100. Solid dispersions prepared with MGK in 1:1, 1:4, 1:9 and 1:14 w/w (NM:MGK) are represented as SD_2, SD_5, SD_{10} and SD_{15}, respectively.

2.2.2.5. Swollen carrier mixture. In this method 5% w/v aqueous MGK dispersion was used as carrier. Required quantity of MGK (nine parts) was added to measured quantity of water and mixture to complete swelling for 24 h. Then weighed quantity of drug (one part) was added, and mixed thoroughly. The drug containing polymer solution was cast on glass petridish and the solvent dried at 40 °C until uniform weight was obtained. The film obtained was then crushed, pulverized and sieved through 100 mesh and denoted as SW_{10}.

In order to ascertain the effect of method and/or carrier on dissolution rate of NM, NM alone was grounded for 20 min or kneaded with ethanol (70% v/v) for 20 min or recrystallized and the resultant products are represented as NM_1, NM_2 and NM_3, respectively. All the samples were stored in a desiccator (containing calcium chloride) at room temperature.

2.2.3. Characterization of the solid mixtures

2.2.3.1. Scanning electron microscopy. The SEM photographs of samples were obtained by Scanning Electron Microscope (Jeol, JSM-840 A, Japan) with 20 kV accelerating voltage.

2.2.3.2. Differential scanning calorimetry. DSC curves were obtained by a Differential Scanning Calorimeter (DSC 220C, SEIKO, JAPAN) at a heating rate of 10 °C/min from 30 to 300 °C in nitrogen atmosphere.

2.2.3.3. X-ray diffraction studies. Powder XRD patterns were recorded using Philips diffrac-

tometer (PW 1140) and Cu-kα radiation, Diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2ϕ.

2.2.4. Solubililty studies

The apparent solubility of NM, NM_1, NM_2, NM_3 and solid mixtures was determined in water at 37 °C. Each preparation equivalent to 50 mg of drug was added to 50 ml of water in a conical flask with Teflon-lined screw caps. Then the conical flasks were kept on a shaker incubator maintained at 37 ± 0.5 °C for 24 h. After shaking, the flasks were kept in an incubator at 37 ± 0.5 °C for equilibrium for 12 h. The solution was then filtered through 0.45 μm millipore filter and the filtrate was assayed spectrophotometrically at 240 nm.

2.2.5. Dissolution rate studies

Dissolution rates from different mixtures were determined in 900 ml of distilled water (pH 5.5–6) containing 0.2% SLS w/v at 37 °C with a stirrer rotation speed of 50 rpm using the USP XXI dissolution rate test apparatus employing paddle stirrer (Method II). A 5 ml aliquot of dissolution medium was withdrawn at different time intervals with pipette containing prefilter. Then samples were filtered through 0.5 μm millipore filter and the filtrate was assayed spectrometrically at 240 nm (Chowdary et al., 1995). Each dissolution rate test is repeated for three times.

Khan (1975) suggested Dissolution Efficiency (DE) as a suitable parameter for evaluation of in vitro dissolution data. DE_{10}, DE_{30} values are calculated from dissolution data and were used to evaluate the dissolution rate. The difference between DE values were statistically evaluated by calculating analysis of variance (ANOVA) based on model independent method.

3. Results and discussion

Research for alternative carriers has been increasing to suit for the industrial applications and to reduce the production cost and toxic effects. Recently, many conventional carriers have been evaluated for their use in new applications. Chitosan (Portero et al., 1998), pregelitinized starch (Chowdary and Rama Rao, 1999), superdisintegrants (Bolhuis et al., 1997) are such carriers which are reported to increase the dissolution rate and efficiency of poorly water-soluble drugs.

GK has some distinguishing features over the other gums. GK has high viscosity and swelling capacity (Gauthami and Bhat, 1992). The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, which prevents the drug release during dissolution (Te wierik et al., 1992). Pulverization of the product is also another important draw back with the high viscosity carriers (Kohri et al., 1999) Many researchers used the polymer:drug ratio in decreasing order to prevent the processing problems, such as pulverization and drug release (Chowdary et al. 1995). However, it is reported that the swelling ability of the carrier profound influence on the improvement of dissolution rate of poorly water-soluble drugs (Bolhuis et al., 1997). As the viscosity of the used carrier imparts negative effect on the preparation of solid mixtures and rate of dissolution, it is useful to modify the gum in such a way that its swelling ability is remained same and viscosity is reduced.

The viscosity of GK is directly proportional to its volatile acetyl content (Goldstein and Alter, 1973). Hence, it is assumed that the removal of volatile acetyl content in the gum will reduce the viscosity of the gum. Removal of volatile acetyl

Table 1
Characterization of gum karaya and modified gum karaya (mean ± S.D.)

Products	Viscosity (cps)	Volatile acid number	Swelling index (%)	Water retention capacity (ml)
GK	1800 ± 56	18.23 ± 1.87	3510 ± 32.26	36.66 ± 2.67
MGK	550 ± 35	8.13 ± 2.49	3495 ± 25.05	34.60 ± 2.98

$n = 3$.

content from the GK was done by heating (Murali Mohan Babu et al., 2000).

The results of the characterization of the GK and MGK are given in Table 1. The results indicated that the viscosity of MGK was markedly lower when compared to GK. It is also found that volatile acetyl content of MGK significantly less than that of GK ($P < 0.00l$). These findings further confirmed the results of Goldstein and Alter (1973). The swelling and water retention capacity of MGK was not reduced significantly rather than that of the GK ($P < 0.00l$). Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug is markedly enhanced (Westerberg et al., 1986). Water retention capacity of carrier is the amount of water retained in it that indicates ability of carrier towards hydrophilic nature.

The effect of type of polymer with varying viscosity was studied by preparing the solid mixtures in 1:9 w/w ratio (drug:carrier) using co-grinding technique. The SEM photographs of NM, NM_1, GK, MGK and co-grinding mixtures are shown in Fig. 1. Analysis of SEM revealed that the relatively longer and elongated crystals of NM, and multifaceted, slippery surfaced granules of GK and MGK. In the case of NM_1, reduction in particle size of NM was observed. It was clearly visible that larger crystalline forms of NM particles were transformed to smaller crystalline structures and finely dispersed on the surfaces of gum particles in both of the co-grinding mixtures. These observations provided further confirmed by the results of DSC and XRD studies.

The DSC thermograms of NM, NM_1, GK, MGK and co-grinding mixtures are depicted in Fig. 2. The thermograms of the pure NM and NM_1 exhibited two endothermic peaks at 115, 125.9, and 114, 125.5 °C respectively, corresponding to the melting of its two polymorphs (Grunenberg et al., 1995), while GK and MGK exhibited a broad endothermic peak owing to its amorphous nature. The DSC thermograms of CM-GK_{10} and CM_{10} solid mixtures showed identical peaks corresponding to pure drug indicated the absence of a well-defined chemical interaction between NM and GK/MGK. Further, the decrease in sharpness of NM endothermic peak in both the solid mixtures may be due to the low amount of the drug in the dispersions and the conversion of crystalline form of NM to amorphous form.

Fig. 3 shows the XRD patterns recorded for pure NM, NM_1, GK, MGK, CM-GK_{10} and CM_{10}. Characteristic peaks appeared in the XRD pattern of NM at a diffraction angle of 6.42, 12.16, 12.72, 17.1, 20.00, 20.48 and 24.62° suggesting that the drug is present as a crystalline material. NM_1 showed all the peaks showed by pure NM, however, the intensity of found peaks was slightly reduced when compared with that of NM. GK and MGK produced almost identical X-ray diffractograms, exhibited characteristic single peak at 19.8° with low intensity indicating their amorphous nature. The X-ray diffractograms of both the co-grinding mixtures showed almost identical peaks. It was also observed that some peaks showed by pure NM are absent and the intensity of found peaks was markedly reduced in the XRD patterns of both the co-grinding mixtures.

Solubility data for NM, NM_1, CM-GK_{10} and CM_{10} are given in Table 2. The solubility of NM_1 not differed significantly with that of pure NM, indicated the grinding of the pure NM not changed the solubility characteristics of NM. ANOVA ($P < 0.00l$) performed on the solubility parameter demonstrated that there was statistically significant difference between the solubility of NM from co-grinding mixtures with that of NM_1. It was also found that there was no statistically significant difference between the solubility of CM_{10} from that of CM-GK_{10} indicated that GK and MGK have similar effect on improving the solubility of NM.

Fig. 4 shows in vitro dissolution profiles of CM-GK_{10}, CM_{10} and NM_1 in comparison with pure drug. The values of DE_{10} and DE_{30} are given in Table 3. It is evident that the dissolution rate of pure NM or NM_1 is very low compared with those of both the co-grinding mixtures. ANOVA ($P < 0.001$) performed on the DE_{10} and DE_{30} parameters of NM and NM_1 demonstrated that the difference between the dissolution rate of NM and NM_1 was statistically insignificant. The DE values of NM/NM_1, CM_{10} and CM-GK_{10} were

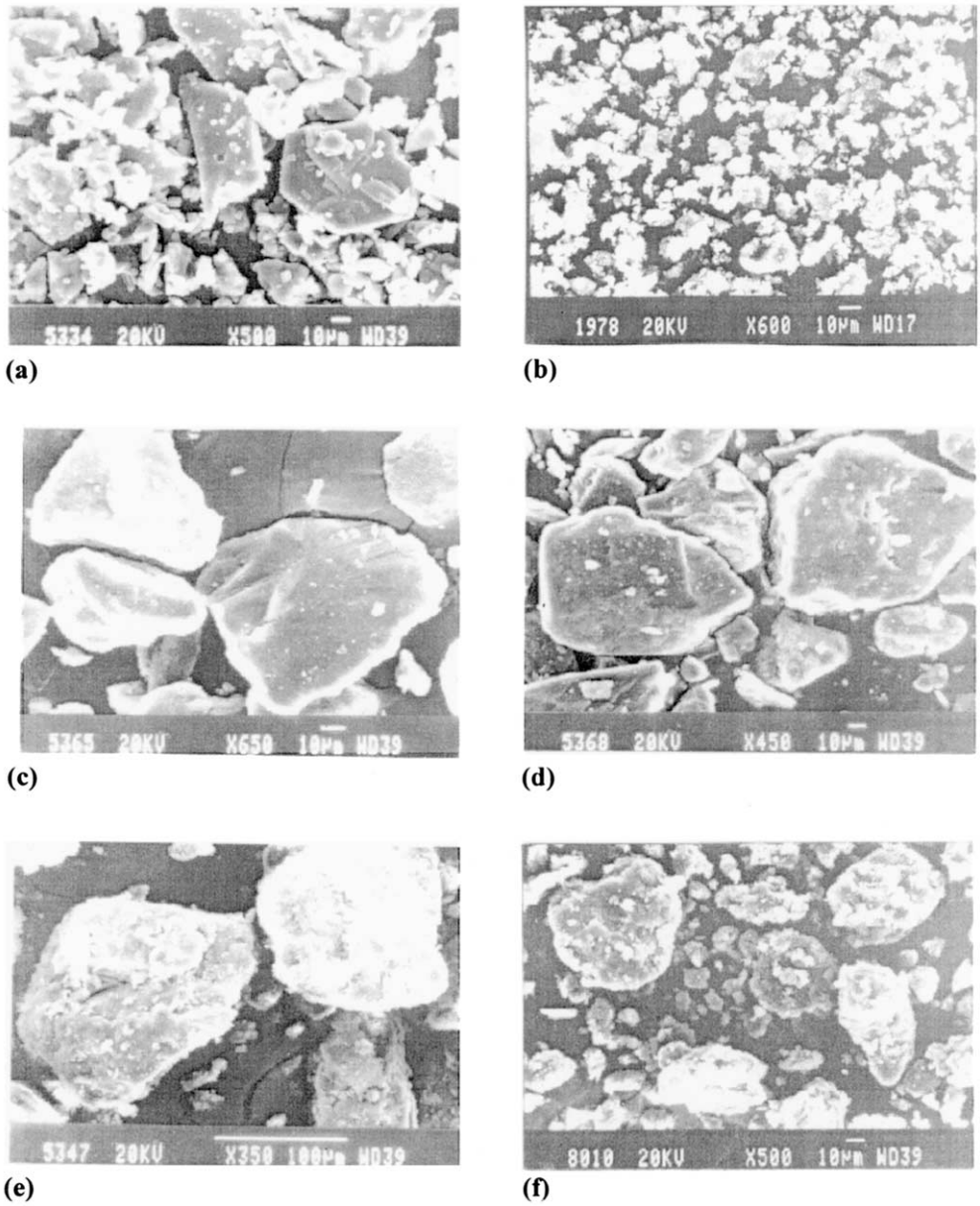

Fig. 1. SEM photographs of pure NM, NM_1 GK, MGK and co-grinding mixtures of NM and GK/MGK (1:9). (a) Pure NM; (b) NM_1; (c) GK; (d) MGK; (e) CM_{10}; (f) CM-GK_{10}.

found to be significantly different indicated the dissolution rate of NM improved in the presence of GK/MGK. These results confirmed that the improvement in dissolution rate of NM was due to the presence of GK/MGK, but not due to the decrease in particle size of NM during grinding. CM_{10} showed faster dissolution rate than that of the CM-GK_{10} as shown in Fig. 4. However, the DE values of CM-GK_{10} are significantly higher than that of pure NM/NM_1. Finally, the order of dissolution rate is pure NM/NM_1 < CM-GK_{10} < CM_{10}. From the results obtained, the factors con-

tributing to improvement rate of NM from the co-grinding mixtures are decreased crystallinity increased solubility of drug particles. The increased solubility of co-grinding mixtures may be due to increased dispersibility and improved wettability of NM.

It was proved that, as the viscosity of the carrier increased the dissolution rate was decreased (Portero et al., 1998; Tantishaiyakul et al., 1999). During the process of dissolution, as soon as the drug-carrier particles come in contact with dissolution fluid, seeping in of dissolution medium in to the drug–carrier particle is taking place, which initiated the formation of gel layer of carrier around the particle. The diffusion of dissolved drug through the gelatinous layer is determining factor in the enhancement of dissolution rate (Tantishaiyakul et al., 1999). From the Stokes–Einstein equation, the diffusion coefficient is inversely proportional to viscosity. The viscosity of 1% w/v solution of MGK at 28 °C is 550 cps, which is about three times lower than that of GK. Though NM solubility improved significantly from CM-GK_{10} and the drug is in the amorphous form as indicated by XRD studies, the dissolution rate of NM is low from co-grinding mixture containing high viscous GK. During dissolution process, the drug-carrier particles are to be dispersed

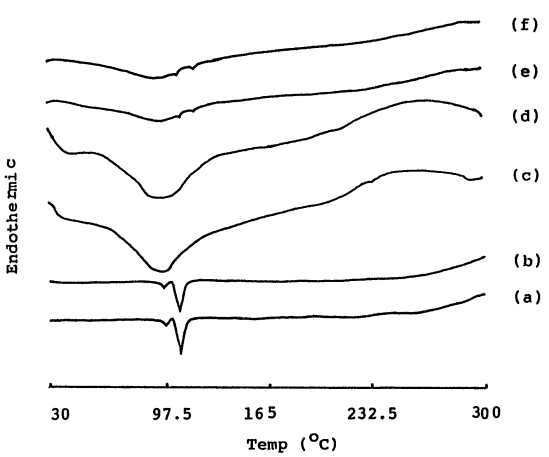

Fig. 2. DSC thermograms of co-grinding mixtures of NM and GK/MGK (1:9) in comparison with pure NM, NM_1, GK and MGK. (a)Pure NM; (b) NM_1; (c) GK; (d) MGK; (e) CM_{10}; (f) CM-GK_{10}.

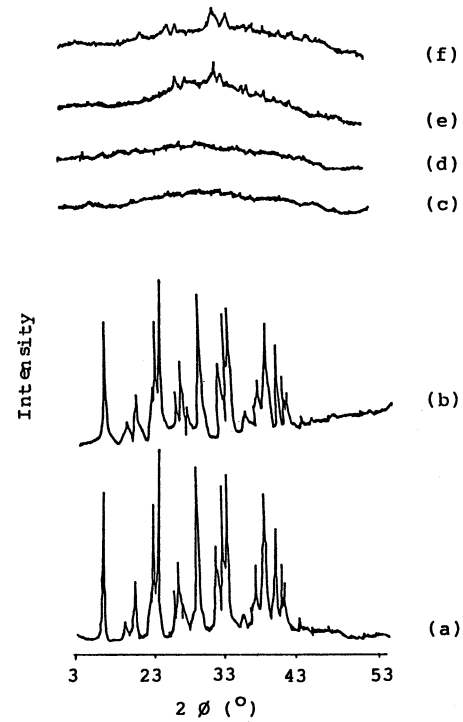

Fig. 3. Powder XRD patterns of co-grinding mixtures of NM and GK/MGK (1:9) in comparison with pure NM, NM_1, GK and MGK. (a)Pure NM; (b) NM_1; (c) GK; (d) MGK; (e) CM_{10}; (f) CM-GK_{10}.

rapidly throughout the dissolution medium to promote the drug release. It was observed that the GK, which is more viscous than MGK resulted in formation of lumps of drug-carrier particles during dissolution, where as NM-MGK particles, dispersed rapidly. This factor also contributed significant difference between dissolution rate of CM_{10} and CM-GK_{10}.

The effect of polymer concentration on the dissolution rate was estimated using the solid mixture prepared by solid dispersion technique with NM and MGK in weight ratio varying from 1:1, 1:4, 1:9 and 1:14. SEM photographs of NM_3, SD_2, SD_5, SD_{10} and SD_{14} are shown in Fig. 5. It was observed that the crystallinity of NM_3 (recrystallized NM) increased compared with that of pure NM. All the solid dispersions showed that NM was finely dispersed in the gum. It was also observed that the crystallinity of the NM was decreased as the polymer concentration increased.

Table 2
Solubility studies of nimodipine (mean ± S.D.) from treated samples and solid mixtures in comparison with pure drug

Product	Solubility (μg/ml)
NM	2.78 ± 0.4
NM_1	2.79 ± 0.6
NM_2	3.02 ± 0.8
NM_3	3.01 ± 0.5
CM_{10}	12.23 ± 1.2
CM-GK_{10}	11.91 ± 1.7
SD_2	5.15 ± 0.4
SD_5	7.96 ± 0.8
SD_{10}	13.00 ± 2.1
SD_{15}	16.98 ± 1.3
PM_{10}	3.51 ± 0.6
KM_{10}	12.59 ± 0.9
WM_{10}	11.59 ± 1.5
SW_{10}	12.19 ± 1.2

$n = 3$.

Table 3
Dissolution efficiency (DE) values (mean ± S.D.) of nimodipine and various solid mixtures

Product	DE_{10}	DE_{30}
NM	4.95 ± 0.390	9.03 ± 0.926
NM_1	5.01 ± 0.430	9.36 ± 0.990
NM_2	5.14 ± 0.420	935 ± 1.110
NM_3	4.85 ± 0.310	8.64 ± 0.620
SD_2	20.98 ± 1.239	37.72 ± 1.776
SD_5	38.38 ± 1.085	57.96 ± 2.066
SD_{10}	60.11 ± 1.142	82.64 ± 1.420
SD_{15}	57.59 ± 1.060	79.18 ± 1.202
CM_{10}	49.37 ± 2.118	74.75 ± 1.871
CM-GK_{10}	22.52 ± 0.776	38.84 ± 1.580
KM_{10}	50.91 ± 1.060	75.27 ± 1.484
WM_{10}	51.39 ± 1.306	70.44 ± 2.213
SW_{10}	53.61 ± 1.998	75.90 ± 2.250
PM_{10}	10.82 ± 1.196	16.17 ± 1.417

$n = 3$.

The DSC thermograms of NM, NM_3 and dispersions are shown in Fig. 6 and observed that NM and NM_3 produced almost similar melting endotherm. As the concentration of MGK increased, broadening in endotherms of solid dispersions was also observed. However, the drug peak did not disappear. The thermograms showed no evidence of the formation of a solid complex or any chemical interaction between drug and polymer. Fig. 7 illustrates the powder XRD pattern of NM, NM_3, MGK and NM-MGK dispersions. Though, NM_3 showed all the peaks shown by pure NM, the intensity of found peaks slightly increased. The number of peaks and peak height was reduced in NM-MGK dispersions as the polymer concentration increased. These results suggested that the NM crystals were well dispersed into the MGK matrix in dispersions with higher weight ratios. This finding is compatible with the enhanced dissolution of dispersions as the polymer concentration increased.

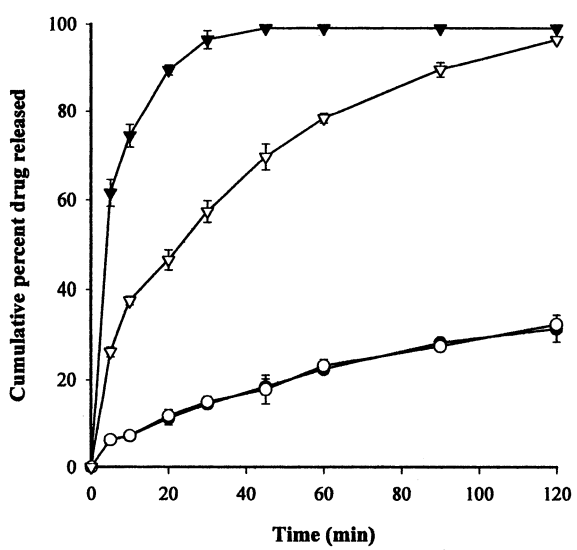

Fig. 4. Dissolution profiles co-grinding mixtures of NM and GK/MGK (1:9) in comparison with pure NM and NM_1. (●) Pure NM; (○) NM_1; (▼) CM_{10}; (▽) CM-GK_{10}.

Though there was no significant difference between the solubility of NM and NM_3, solid mixtures exhibited significant improvement in solubility as the concentration of polymer increased as given in Table 2 ($P < 0.001$). It can be inferred that there could be marked influence of carrier on the improvement in solubility of NM rather than method of preparation.

The in vitro dissolution profiles of NM from the pure drug, recrystallized drug and solid dispersions as shown in Fig. 8 indicated that the dissolution profile of NM_3 was almost similar with that of NM. It was also clearly indicated that the solid dispersions of NM with MGK markedly

enhanced the dissolution rate of NM compared with that of the pure drug for all polymer- drug ratios. The results of DE_{10}, and DE_{30} are given in Table 3. The insignificant difference between DE values of NM and NM_3 indicated that the method of preparation of solid mixtures has no effect on dissolution rate of NM. The results of DE values also indicated that there is significant difference between the DE values of NM or NM_3 and all the prepared solid dispersions ($P < 0.001$). It was observed that the DE values of solid dispersions increased up to 1:9 w/w ratio (SD_{10}). However,

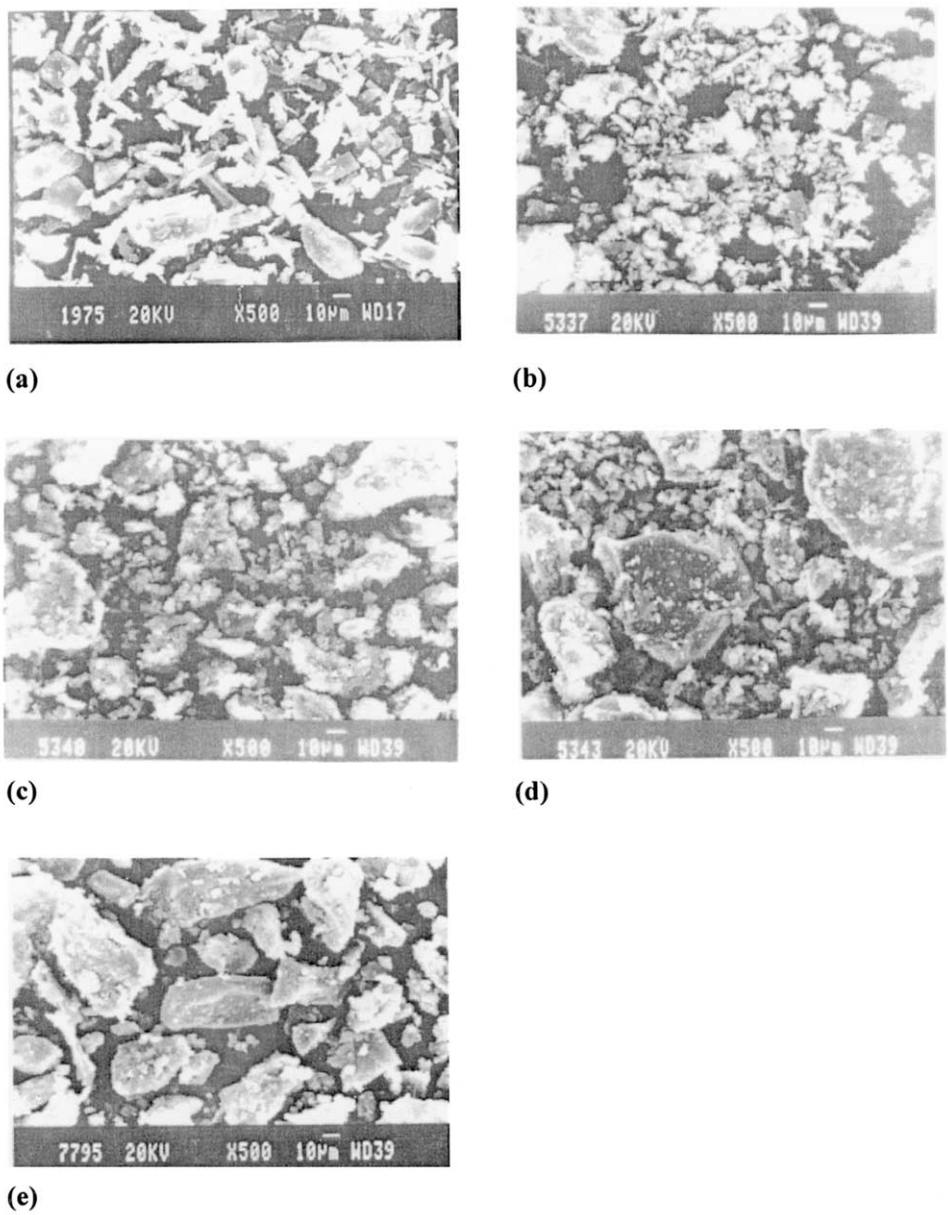

Fig. 5. SEM photographs of recrystallized NM (NM_3) and solid dispersions of NM and MGK of different ratios. (a) NM_3; (b) SD_2; (c) SD_5; (d) SD_{10}; (e) SD_{15}.

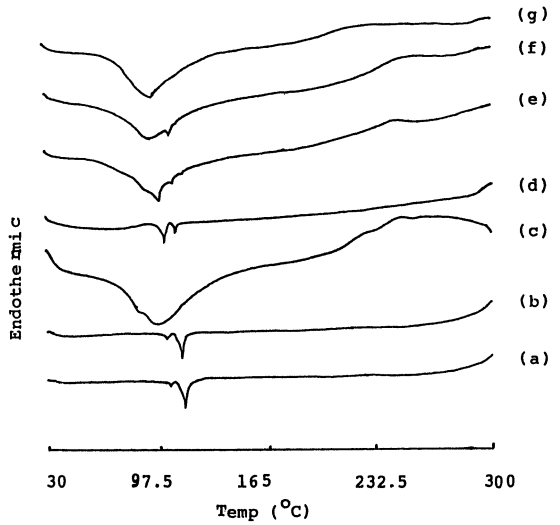

Fig. 6. DSC thermograms of solid dispersions of NM and MGK of different ratios in comparison with pure NM, NM_3 and MGK. (a)Pure NM; (b) NM_3; (c) MGK; (d) SD_2; (e) SD_5; (f) SD_{10}; (g) SD_{15}.

there is no significant difference between the DE values of SD_{10} and SD_{15} ($P < 0.001$), though there was a significant difference in solubility of SD_{10} and SD_{15} (Table 2). Goodlinear relationship was observed between MGK concentration and DE_{30} up to 90% w/w concentration of MGK. When the MGK concentration was 93.3% w/w, there was no significant difference between the DE_{30} of SD_{10} and SD_{15}. Hence, it was concluded that the 1:9 w/w drug to polymer ratio was considered to be optimum for enhancement of dissolution rate of NM.

From the results of the above study, it was concluded that the solid dispersions of NM with MGK markedly enhanced drug dissolution and the enhancement of dissolution rate influenced by the polymer drug ratio. The improvement in NM dissolution rate was optimum at a ratio of 1:9 w/w (NM:MGK). The enhancement of the NM dissolution rate by solid dispersion technique compared with that of the pure drug, could presumably be explained by the following factors: (i) swelling ability of the carrier, (ii) low viscosity of the carrier (iii) a decrease in crystallinity and size of the drug crystals in the solid dispersion (iv) increased solubility and (v) an improved drug wettability.

Even though solid dispersion technique is widely used to improve dissolution rate of poorly soluble drugs in laboratory scale, its application in industries is very limited (Serajuddin, 1999). Hence, it was focused on the selection of the most suitable procedure that is feasible in the large scale manufacturing of solid mixtures, which are showing higher DE. The investigated methods were physical mixtures, co-grinding, kneading with 70% v/v ethanol, kneading with water; swollen carrier mixing and solid dispersion. The chosen polymer was MGK, which had showed the marked effect on drug dissolution. The selected NM:MGK weight ratio was 1:9.

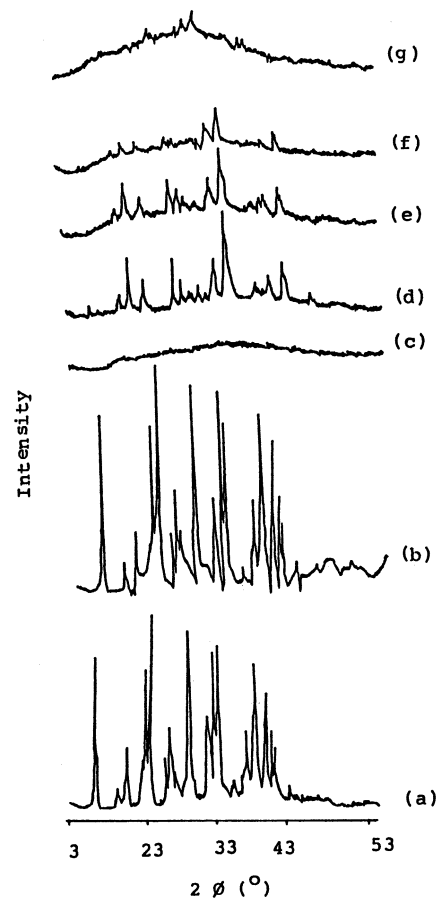

Fig. 7. Powder XRD patterns of solid dispersions of NM and MGK of different ratios in comparison with pure NM, NM_3 and MGK. (a)Pure NM; (b) NM_3; (c) MGK; (d) SD_2; (e) SD_5; (f) SD_{10}; (g) SD_{15}.

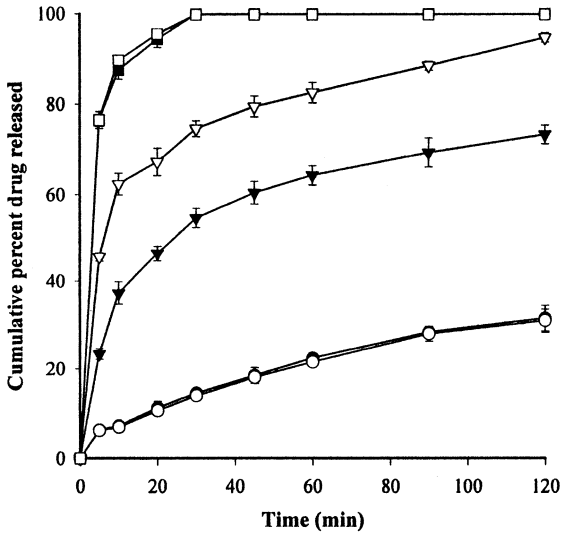

Fig. 8. Dissolution profiles of solid dispersions of NM and MGK of different ratios in with pure NM and NM_3. (●) Pure NM; (○), NM_3; (▼) SD_2; (▽) SD_5; (■) SD_{10}; (□) SD_{15}.

The SEM photographs of solid mixtures showed that in all the solid mixtures, there is reduction in the crystallinity of NM than that of pure NM as shown in Fig. 9. The SEM photographs of NM_1, NM_2 revealed that the crystallinity was reduced, where as NM_3 showed increase in crystallinity. The order of crystal size of NM in solid mixtures is NM, PM_{10}, SW_{10}, CM_{10}, KM_{10}, WM_{10} and SD_{10}. The reduced crystallinity of NM in different solid mixtures is further confirmed from the results of XRD patterns and dissolution profiles. The thermal behavior of NM-MGK solid mixtures was studied using DSC in order to study the occurrence of any chemical interaction between the drug and carrier in all selected methods. Thermograms shown in Fig. 10 indicated that the NM_1, NM_2 and NM_3 showed almost similar thermal behavior. The DSC thermograms of all solid mixtures showed identical peaks corresponding to pure drug indicated that no evidence of any chemical interaction between drug and polysaccharide for all systems.

The powder XRD patterns of pure drug (NM), NM_1, NM_2, NM_3, MGK and solid mixtures prepared by different methods are illustrated in Fig. 11. NM_1, NM_2, showed slight decrease in peak intensity, where as NM_3 showed slight increase in peak intensity when compared with that of pure NM. All the diffraction patterns of solid mixtures showed fewer and less intense peaks than that of pure drug. The diffraction patterns of CM_{10}, KM_{10} and SD_{10} showed fewer and less intense peaks than that of NM_1, NM_2 and NM_3, respectively, indicating that the profound influence of MGK on crystallinity of NM. The order of reduction in peak intensity is $PM_{10} < CM_{10} < KM_{10} < WM_{10} < SW_{10} < SD_{10}$, which would explain their increased dissolution rate. It is found that the intensity of diffraction patterns of NM in KM_{10} and WM_{10} are identical, indicating that the state of NM is identical in both of the mixtures. The swollen carrier mixture (SW_{10}) produced less and fewer intense peaks comparable with that of the other solid mixtures except SD_{10}, indicating that by using this method, solid mixtures can be produced in which drug is available in less crystalline form compared with that of other solid mixtures except SD_{10}.

The solubility data of pure drug, treated drug samples (NM_1, NM_2 and NM_3) and solid mixtures prepared by different methods given in Table 2, indicated that there was no significant difference between the solubility of pure drug and treated drug samples. All solid mixtures showed a significant improvement in solubility of NM except physical mixture ($P < 0.001$). However, it was found that there was no significant difference between the solubility of NM from $WM_{10,}$ CM_{10}, KM_{10}, SD_{10} and SW_{10}.

The dissolution characteristics of NM, treated drug samples and different solid mixtures are shown in Fig. 12 and the corresponding values of DE_{10}, DE_{30} are given in Table 3. NM_1, NM_2 and NM_3 exhibited similar dissolution profile with that of pure NM as confirmed by DE values (Table 2). In all cases, solid mixtures exhibited faster dissolution rates than that of pure drug. Existence of significant differences between the calculated parameters DE_{10} and DE_{30} was confirmed by ANOVA ($P < 0.001$) and the order of solid mixtures basing on their DE values is as follows: $PM_{10} < CM_{10} < KM_{10} < WM_{10} < SW_{10} < SD_{10}$ (for DE_{10}) and $PM_{10} < WM_{10} < KM_{10} < SW_{10} < CM_{10} < SD_{10}$ (for DE_{30}).

From the above results, it can be concluded that there is no influence of the method of preparation on the dissolution profile of NM from different treated samples, however, the use of MGK as carrier has improved the dissolution rate of NM from all the solid mixtures. The improvement of dissolution rate of NM by PM_{10} compared with pure drug might be the solubilization effect and wetting ability of the MGK on NM. The further improvement in the dissolution rate of NM from CM_{10} compared with that of PM_{10} could be explained on the basis of transformation

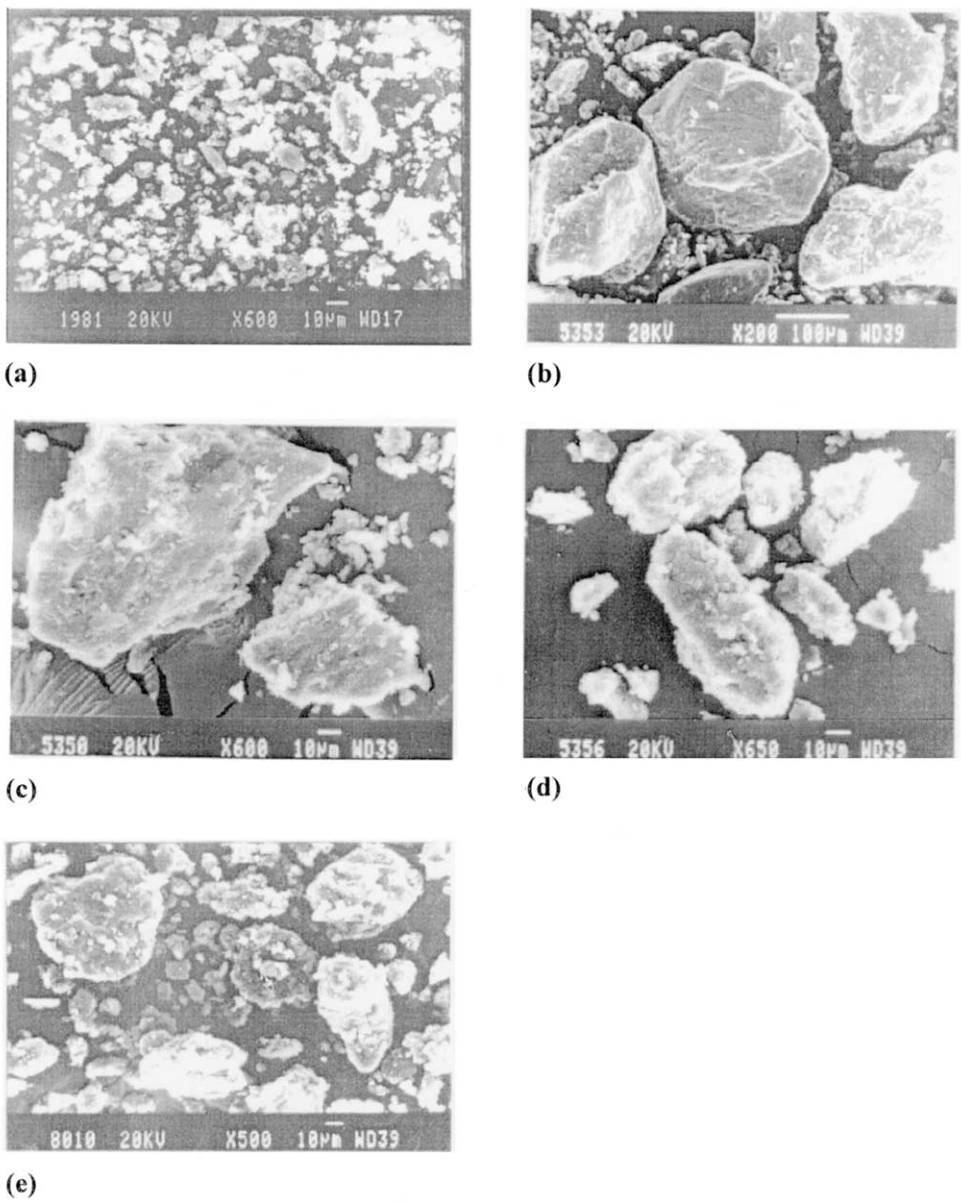

Fig. 9. SEM photographs of kneaded NM (NM_2) and solid mixtures of NM and MGK in 1:9 w/w ratio prepared by different methods. (a)NM_2; (b) PM_{10}; (c) KM_{10}; (d) WM_{10}; (e)SW_{10}.

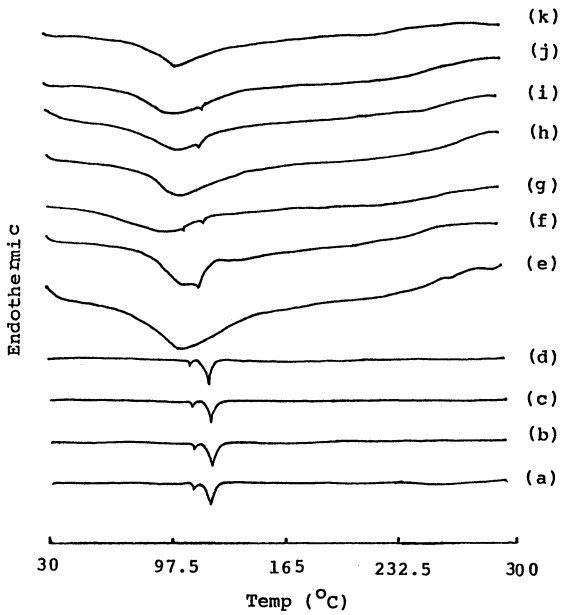

Fig. 10. DSC thermograms of solid mixtures of NM and MGK in 1:9 w/w ratio prepared by different methods in comparison with pure NM, treated NM samples and MGK. (a)Pure NM; (b) NM_1; (c) NM_2; (d) NM_3; (e) MGK; (f) PM_{10}; (g) CM_{10}; (h) KM_{10}; (i)WM_{10}; (j) SW_{10}; (k) SD_{10}.

of large crystals of NM to smaller crystals or amorphous state in CM_{10} along with the solubilization effect and wettability of MGK on NM.

In the kneading method, synergistic effect of trituration and solubilization effect of used solvent further reduced the crystallinity leading to improvement in dissolution rate. As the solvent used influences the dissolution characteristics (Mc Ginity and Harris, 1980), the influence of solvent used in kneading method was also studied. The results indicated that the dissolution rate of NM from WM_{10} is less than that of KM_{10}. This may be due to co-solvent effect of 70% v/v ethanol on NM. Interestingly, it is found that WM_{10} showed higher dissolution efficiency than that of CM_{10}. This may be due to formation of efficient dispersed mixture of polymer and drug resulting in increased contact between drug and polymer leading to more wettability.

The reason for higher dissolution rate of SW_{10} when compared with PM_{10}, CM_{10}, KM_{10} or WM_{10}, may be due to availability of more surface area for the deposition of NM resulting in improved solubility, higher dispersibility and increased wettability.

In solid dispersion, fine suspension of drug and carrier particles will be formed. With the smaller particle size and better wettability of the drug

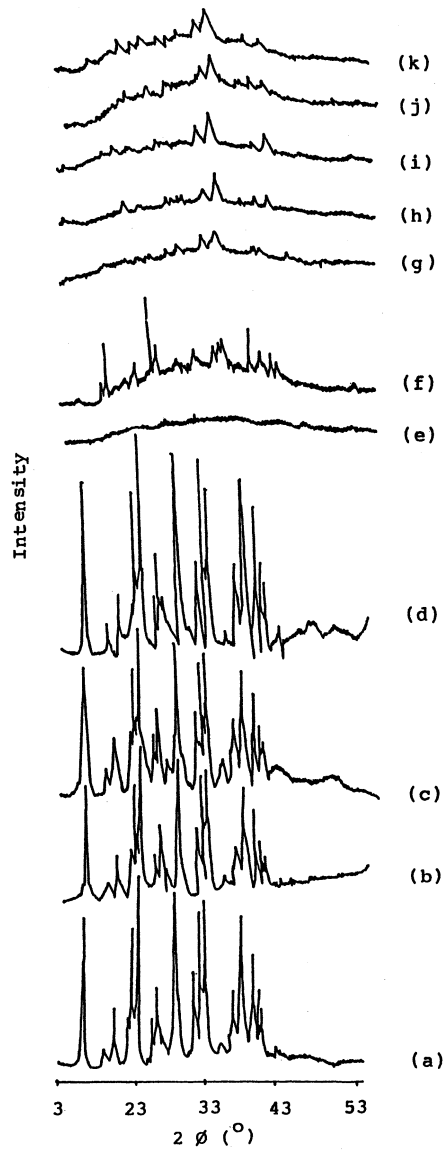

Fig. 11. Powder XRD patterns of solid mixtures of NM and MGK in 1:9 ratio prepared by different methods in comparison with pure NM, treated NM samples and MGK. (a) Pure NM; (b) NM_1; (c) NM_2; (d) NM_3; (e) MGK; (f) PM_{10}; (g) CM_{10}; (h) KM_{10}; (i) WM_{10}; (j) SW_{10}; (k) SD_{10}.

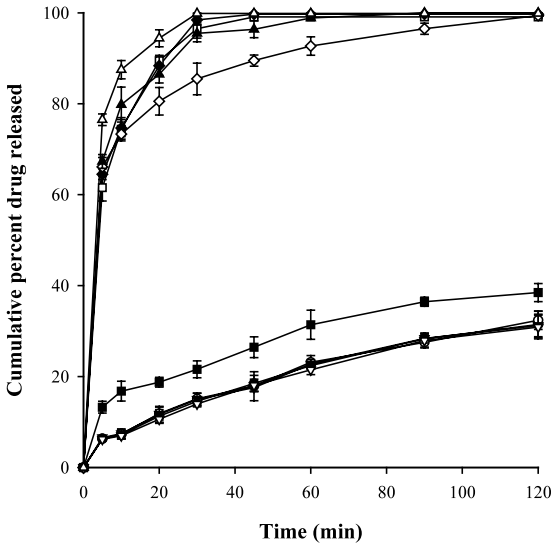

Fig. 12. Dissolution profiles of solid mixtures of NM and MGK in 1:9 ratio prepared by different methods in comparison with pure NM and treated NM samples. (●) Pure NM; (○) NM_1; (▼) NM_2; (▽) NM_3; (■) PM_{10}; (□) CM_{10}; (◆) KM_{10}; (◇) WM_{10}; (▼) SW_{10}; (△) SD_{10}.

particle in the suspension contributes to a faster dissolution rate (Sekiguchi et al., 1969) compared with all the other methods studied.

4. Conclusion

In conclusion, our studies showed that, MGK could be used as a potential carrier in the dissolution rate enhancement of NM. Though there is no much difference in the crystallinity of NM in GK and MGK solid mixtures (as evident by DSC and XRD patterns), the dissolution rate of NM from solid mixture of GK, was low when compared with solid mixture of MGK. This may be due to the high viscosity generated by GK in the microenvironment of drug–carrier particle during dissolution reducing the diffusion rate of NM, there by decreasing the dissolution efficiency. Due to high viscosity and toughness of GK, it also posed processing problems during trituration. The increase in apparent solubility of NM from solid mixtures also contributed to improvement of dissolution rate of NM. Since, no drug carrier interaction in the solid mixtures has been evidenced, increased wettability, dispersibility and reduced crystallinity of NM can account for the increased dissolution rate in systems containing GK or MGK. The results demonstrated that optimum NM:MGK ratio is 1:9.

Among the various methods used in the preparation of solid mixtures, though solid dispersions gave higher dissolution rates of all the methods, the characteristics like simplicity in preparing, reliability in the method, avoidance of the use of organic solvents or high temperatures and less cumbersome technique like co-grinding technique appears to be more the easier and the most convenient method from a practical point of view.

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