RESEARCH PAPER

Formulation and Evaluation of Tablet Dosage Forms of Nimodipine-Modified Gum Karaya Co-grinding Mixtures

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The aim of the present study was to design nimodipine tablets with fast *in vitro* release rates using nimodipine-modified gum karaya co-grinding mixtures. Co-grinding mixtures of nimodipine and gum karaya were also prepared to highlight the efficiency of modified gum karaya. Physical mixtures of nimodipine with both the carriers were prepared for comparison. All the solid mixtures were characterized by differential scanning calorimetry and X-ray diffraction studies. Solubility studies and *in vitro* release rate studies were performed for all the solid mixtures to explain the results. Nimodipine tablets were formulated employing nimodipine-gum karaya/modified gum karaya co-grinding mixtures and their corresponding physical mixtures. The compressed tablets were evaluated for various tablet characteristics including *in vitro* dissolution rate studies. The best results from the dissolution test were obtained for tablets containing nimodipine-modified gum karaya co-grinding mixtures.

Drugs can not be administered in their pure form. They must be developed into convenient dosage forms for their clinical use and successful commercialization. Though the solid dispersion technique is an attractive alternative method, which has been widely used in the dissolution enhancement of poorly water soluble drugs, many challenges are limited its application in the design of dosage form[1]. Some of the limitations are difficulty in pulverization[2] and sifting of the dispersions, which are usually soft and tacky[3], poor flow and mixing properties resulted in poor compressibility[3], drug-carrier incompatibility and poor stability[4] of the dosage forms. Many alternative methods were attempted to enhance the dissolution rate of poorly water soluble drugs with an aim to development of suitable formulation for oral use. Ordered mixtures[5], roll mixing[6], complexation[7], co-grinding[8] and co-grinding in the presence of small amount of water[9] are some of the reported methods.

Gum karaya (GK) is a natural gum exudate, obtained from the trees *Sterculia urens* belonging to the family Sterculiaceae[10]. Chemically the gum is an anionic polysaccharide, contains 43% D-galacturonic acid, 13% D-galactose and 15% L-rhamnose[11]. GK has high acetyl value ranging from 13.4 to 22.7 and has greater solvation due to acid groups, which attracts and immobilizes large amount of water[10]. Recently our research group reported the preparation and applicability of modified form of gum karaya as disintegrant[12]. Modified gum karaya (MGK) was prepared from gum karaya by physical method.

MGK, a low viscosity form of GK was successfully evaluated as a carrier in the dissolution enhancement of poorly water soluble drug, nimodipine (NM)[13]. It was found that dissolution rate of NM significantly improved from the co-grinding mixtures of NM and MGK in 1:9 w/w ratio (NM:MGK). Though the viscosity of GK was significantly lowered on heating, the swelling and water retention capacity of MGK were not altered significantly[12,13]. These properties might be the principle reasons for improving dissolution rate and effi-

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ciency of NM from NM-MGK solid mixtures, when compared to NM-GK solid mixtures.

In the present study, formulation of tablets using NM-MGK and NM-GK co-grinding mixtures with fast dissolution characteristics was investigated. Characterization of solid mixtures was done by differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. Tablets were also prepared using physical mixtures of NM and GK/MGK. Tabletting characteristics and dissolution rate studies were performed to explain the results.

MATERIALS AND METHODS

Gum karaya (Viscosity of 1% w/v solution is 1800 cps.) was bought from M/s. Girijan Co-operative Corporation Ltd., Visakhapatnam. Nimodipine was gift sample from M/s. USV Ltd., Bangalore. Magnesium stearate used was of USP grade. All other chemicals used were of Analytical Reagent Grade.

Preparation of modified GK:

Preparation of modified form of GK was done by the method reported by Murali Mohan Babu, et al[2]. Briefly, the tears of gum were pulverized, sieved through mesh no. 100. Powdered gum was taken in a porcelain bowl and subjected to heating using sand bath at 120° for 2 h. The product was finally re-sieved (# 100 mesh) and stored in airtight container at 25°.

Preparation and characterization of solid mixtures of NM and GK/MGK:

All experiments were carried out under light protected conditions to prevent the photodecomposition of nimodipine. Co-ground mixtures of GK/MGK and NM were obtained by co-grinding the mixtures of NM and GK/MGK in 1:9 w/w ratio for 20 min in a ceramic mortar and sieved through 100 sieve. The physical mixtures of drug and GK/MGK were obtained by simple blending the NM and GK/MGK in 1:9 w/w ratio (drug:polymer) with a spatula. Co-grinding mixture prepared with GK and MGK are represented as CM-GK and CM-MGK respectively, where as physical mixtures of GK and MGK as PM-GK and PM-MGK respectively in the further studies. In order to ascertain the effect of method and/or carrier on dissolution rate of NM, NM was grounded using above conditions except the addition of GK/MGK and product is denoted as NM_1.

DSC thermograms of NM, ground NM and solid mixtures were obtained by a differential scanning calorimeter (DSC 220C, SEIKO, JAPAN) at a heating rate of 10°/min from 30 to 300° in nitrogen atmosphere. XRD patterns were recorded on a Philips PW 1140 powder X-ray diffractometer using Ni-filtered, CuKα radiation, a voltage of 45 kV and a current of 25 mA. The instrument was operated in the continuous scan mode over a 2θ range of 5 to 60° with a chart speed of 2°/2 cm/2θ. The apparent solubility of NM, NM_1 and solid mixtures was determined in water at 37°. 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° for 24 h. After shaking, the flasks were kept in an incubator at 37±0.5° for equilibration for 12 h. Then solution was filtered through 0.45 μm millipore filter and the filtrate was assayed spectrophotometrically at 240 nm.

Preparation of tablets:

Tablets of each batch of 50 were prepared for CM-GK, CM-MGK, PM-GK and PM-MGK. 70% v/v ethanol was used as solvent to prepare granules of blend. After preparing the solid mixture as per the method described above, it was taken in a mortar and mixed with 70% v/v ethanol slowly to ensure complete distribution. When enough cohesion was obtained, the wet powder mixture was granulated using a mesh no.10, and the granules obtained were dried in an oven (Tempo Instruments and Equipment Pvt. Ltd., Mumbai, India) at 60° for 2 h. After the granules were dried, they were again sieved using a mesh no. 14, lubricated with magnesium stearate (1% w/w) and compressed into tablets. Granules weighing equivalent to 30 mg of NM (303 mg) were compressed into tablets using 11 mm flat faced punch on a Cadmach single punch tablet machine (Cadmach Machinery Co. Pvt. Ltd., India).

Characterization of tablets:

The tablets were tested for hardness, friability, disintegration time and drug content. Hardness of tablets was determined by using a Monsanto hardness tester. Friability of the tablets was measured by using a Roche friabilator. Disintegration times were determined in a Thermonic Tablet Disintegration Test Apparatus using distilled water as medium. The drug content of all the prepared solid mixtures was estimated by the following procedure. Fifty milligrams of solid mixture was weighed into a 100 ml volumetric flask. Methanol (60 ml) was added and mixed the contents thoroughly to dissolve the drug from the solid mixtures. The solution was made up to volume with methanol. This solution was filtered through 0.45 μm millipore filter. Then the solution was suitably diluted and assayed for NM spectrophotometrically at 240 nm.

Dissolution rate studies:

Dissolution rates of NM (drug equivalent to 30 mg) from NM, NM_1 and solid mixtures as well as from prepared tablets were determined in 900 ml of distilled water containing 0.2% w/v sodium lauryl sulphate (SLS) at 37° with a stirrer rotation speed of 50 rpm using the USP XXI dissolution rate test apparatus employing paddle stirrer. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals with a pipette containing prefilter. The samples were filtered through 0.45 μm millipore filter. The samples were suitably diluted and assayed spectrophotometrically at 240 nm. Each dissolution rate test is repeated for three times and the average values were reported. The percent of drug dissolved at various time intervals was calculated and plotted against time. Dissolution efficiency (DE) from the dissolution data is calculated by the method proposed by Khan[14] and DE_{30} values were calculated from the dissolution data.

Statistical analysis:

The differences between in solubility values as well as DE values of the solid mixtures in comparison with NM/NM_1 were statistically evaluated using analysis of variance (ANOVA). In the case of normal distributed results 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

The DSC thermograms of co-grinding mixtures of NM and GK/MGK in comparison with pure NM, ground NM and the physical mixtures are shown in fig. 1. The thermograms of the pure drug showed two endothermic peaks at 115 and 125.9° respectively corresponding to the melting of its two polymorphs[15]. NM_1 also exhibited two endothermic peaks at 114 and 125.5° similar to NM. The DSC thermograms of physical mixtures as well as co-grinding mixtures of NM and GK/MGK also showed two endothermic peaks with reduced peak intensity indicating that the absence of a well defined chemical interaction between NM and GK/MGK. However, the decrease of the thermal features of the drug in co-grinding mixtures could be attributed to the conversion of most of the crystalline form of drug to amorphous form. These results are further confirmed by XRD results.

Fig. 2 showed the comparative XRD patterns of pure NM, NM_1, physical mixtures and co-grinding mixtures of NM and GK/MGK. XRD pattern of NM exhibited characteristic diffraction peaks and NM_1 also showed all the peaks showed by pure NM, however, the intensity of peaks were slightly
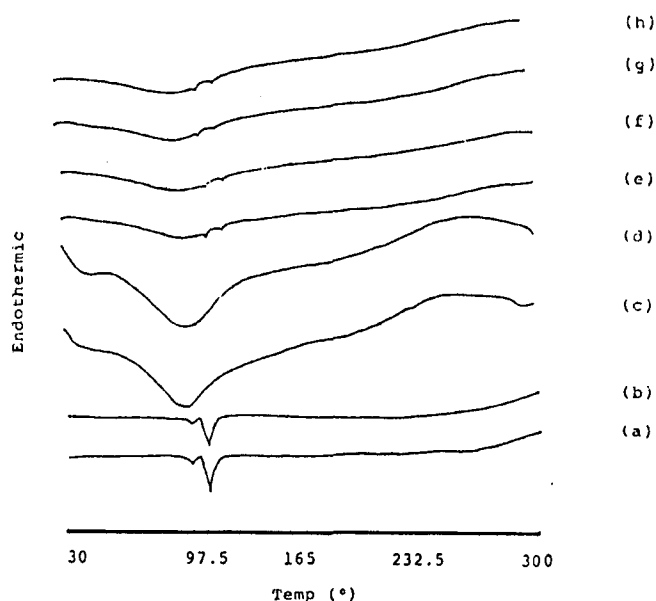
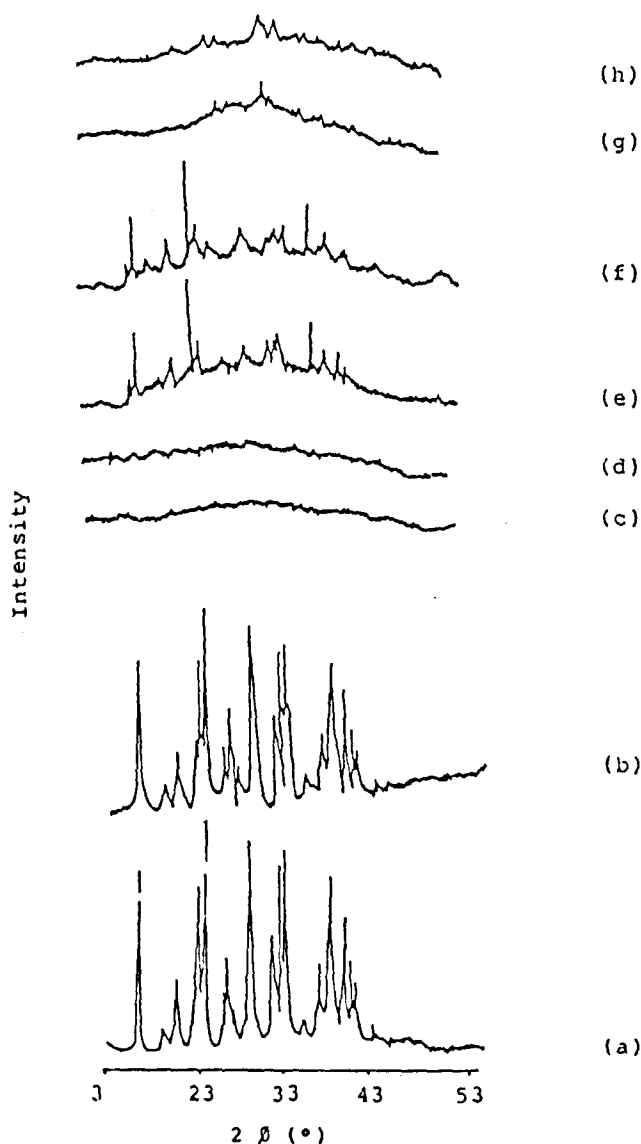Fig. 1: DSC thermograms of solid mixtures of NM and GK/MGK.

DSC thermograms of a) Pure NM, b) NM_1, c) GK, d) MGK, e) PM-GK, f) PM-MGK, g) CM-GK and h) CM-MGK were taken to investigate the changes occurred to thermal properties of NM in solid mixtures in comparison with pure NM, ground NM and both the carriers.

reduced when compared to that of NM. The physical mixtures of NM and GK/MGK also showed some of the peaks observed in XRD pattern of NM supposedly due to the presence of crystalline NM. Thus, the mere presence of GK/MGK in the physical mixtures does not interfere with the characteristics of the co-existing NM. On the other hand, the 1:9 w/w ratio of NM-GK/MGK ground mixtures did not show any peaks of NM. This result implies that NM is present in the amorphous form, both in the CM-GK and CM-MGK.

An improvement in the solubility of NM in both the prepared co-grinding mixtures was observed as shown in Table 1. However, solubility of NM and NM_1 not differed significantly indicating grinding of NM alone not changed the solubility characteristics. It was also found that there was no statistically significant difference between the solubility of NM from CM-MGK and CM-GK indicating that GK and MGK have similar effect on improving the solubility of NM. Though the solubility of NM from both the co-grinding mixtures increased significantly (P<0.001), the solubility of NM from both of the physical mixtures was not significantly increased.

The dissolution behavior of pure NM, NM_1 in comparison with physical mixtures and co-grinding mixtures are

shown in fig. 3. The depicted dissolution profiles of the six types of samples can be assigned with the following rank order basing on their DE_{30} values (Table 1) being CM-MGK>CM-GK>PM-MGK>PM-GK>NM/NM$_1$ Less than 30 % of pure NM/NM$_1$ was dissolved in 120 min. Both the physical mixtures had slightly improved the dissolution rate of NM compared with that of NM powder. The PM-MGK however, showed more improvement in NM dissolution, when com-

TABLE 1: SOLUBILITY AND DISSOLUTION EFFI-CIENCY VALUES OF NIMODIPINE.

Product	Solubility (μg/ml) (Mean±s.d.)	DE_{30} (%) (Mean±s.d.)
NM	2.8±0.4	9.0±0.92
NM$_1$	2.8±0.6	9.4±0.99
PM-GK	3.4±0.4	11.8±1.27
PM-MGK	3.5±0.6	16.3±1.41
CM-GK	11.9±1.7	38.8±1.58
CM-MGK	12.2±1.2	74.8±1.87

Samples of pure NM or NM$_1$ or solid mixtures were taken in conical flask with teflon-lined screw caps containing water and were kept on a shaker incubator maintained at 37±0.5° for 24 h. After set aside for 12 h the solution was filtered and the filtrate was assayed for NM content. In vitro dissolution studies were also performed to all the solid mixtures in comparison with pure NM or NM$_1$ and DE_{30} values were calculated.

Fig. 2: XRD patterns of solid mixtures ofNM and GK/MGK. XRD patterns of a) Pure NM, b) NM$_1$, c) GK, d) MGK, e) PM-GK, f) PM-MGK, g) CM-GK and h) CM-MGK were taken to investigate the changes occurred to crystallinity of NM in solid mixtures in comparison with pure NM, ground NM and both the carriers.

pared to PM-GK. The improvement of NM dissolution rate from both the physical mixtures may arise from the higher hydrophilic potency of GK/MGK, one contributing factor to the increase of wettability of the particles of NM[16]. The differences in dissolution profiles of NM from physical mixtures might be due to the differences in viscosity. It was reported that the lower the viscosity of the carrier, higher the dissolution rate of co-existed drug[17]. Among all the solid mixtures, CM-MGK improved the dissolution rate of NM to the maximum. This result indicated that grinding of drug along with the hydrophilic carrier improved the dissolution rate of poorly water-soluble drug. The differences in dissolution rate of NM from solid mixtures containing GK or MGK due to the differences in their viscosities. The viscosity of 1% w/v of MGK at 28° was found to be 550 cps, which was about 3 times less than that of GK[13]. Higher the viscosity of the carrier results in the formation of thick and stagnant gel layer around the drug particles during dissolution process resulted in reduced diffusion/dissolution of drug[17].

All the parameters except the disintegration time for all the tablets prepared were satisfactory (Table 2). All the tablets were found to contain NM within 100±3% of the labeled claim. Hardness of the tablets was found to be with in the range of 4-5 kg/sq.cm under satisfactory. Friability of tablets was less than 1% w/w. Though the tablets prepared using NM-MGK solid mixtures disintegrated within 5 min, the tab-
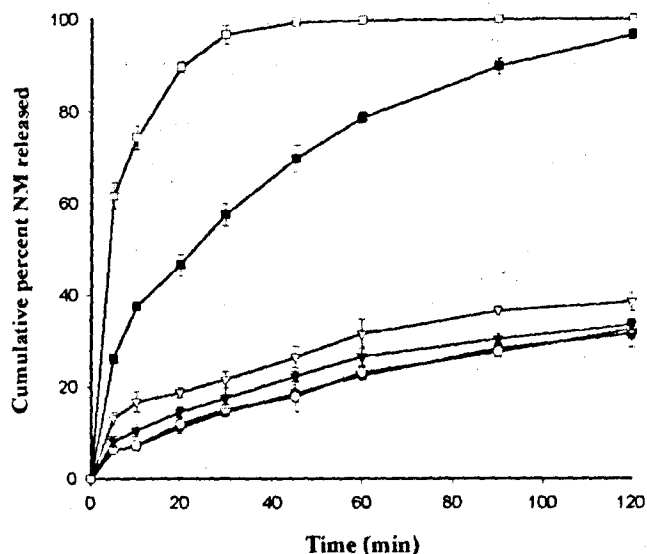
Fig. 3: *In vitro* dissolution profiles of NM from solid mixtures.

In vitro dissolution profiles of nimodipine from pure NM (-●-), ground NM (-O-), solid mixtures containing GK as carrier (PM-GK (-▼-), CM-GK(-■-)) and MGK as carrier (PM-MGK (-▽-), CM-MGK (-□-)) were studied in 900 ml of 0.2 % w/v SLS, samples drawn at regular time intervals and nimodipine content was measured spectrophotometrically at 240 nm.

lets of NM-GK solid mixtures were not disintegrated even up to 30 min. This may be due to high viscous nature of GK resulted in formation of cohesive mass of NM and GK during compression into tablets[18]. It was demonstrated that the decreased viscosity of matrix resulted in the faster dug diffusion[19]. The high swelling ability and low viscosity nature of MGK attributed to the rapid disintegration of tablets containing NM-MGK solid mixtures. This result is in the line of our

previous results[12]. The dissolution profiles of NM from prepared tablets containing MGK as carrier are found to be similar with that of powder samples and confirmed by the DE_{30} values given in Table 2. However, the dissolution rate of NM from tablets prepared with GK containing solid mixtures further decreased, when compared to corresponding powder mixtures (Table 2). This is due to the high viscosity nature of GK for which it has been used as release retardant in the development of oral controlled release formulations[20].

The results of the present investigation clearly indicated the suitability of MGK-NM co-grinding mixtures for the preparation of tablets with improved dissolution rate and efficiency of NM. The proposed tablet formulation with co-grinding mixture of NM and MGK should ensure a good bioavailability of NM.

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TABLE 2: TABLETTING AND DISSOLUTION CHARACTERISTICS OF PREPARED TABLETS.

Tablet	Weight[a] (mg)	Drug Content[b] (%)	Hardness[b] (kg/cm²)	Friability[c] (%)	D.T.[d] (Min)	DE₃₀[d] (%)
PM-GK	304.0±2.63	99.2±1.37	4.56±0.67	0.49	>30	5.2±1.96
PM-MGK	304.2±2.33	100.0±2.03	4.19±0.42	0.59	3.5	15.7±1.84
CM-GK	303.6±2.89	99.6±1.49	5.10±0.51	0.51	>30	12.1±2.56
CM-MGK	305.2±2.67	99.8±1.67	4.33±0.34	0.76	4	72.0±2.45

Prepared tablets were evaluated for various tabletting characteristics. The dissolution studies were performed in 900 ml of 0.2% w/v SLS in water using USP dissolution test apparatus II. Samples were withdrawn at predetermined time intervals and assayed spectrophotometrically at 240 nm. a Mean ± S.D., n = 20 tablets, b Mean ± S.D., n = 5 tablets, c n = 10 tablets and d n= 3 tablets.

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