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Formulation and Evaluation of Nimodipine Tablets with Nimodipine - Pregelatinized Starch

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The objective of the present study is to formulate and evaluate nimodipine tablets employing nimodipine-pregelatinized starch dispersions. Dispersions of nimodipine (NM) in pregelatinized starch (PGS) were prepared in different drug and carrier ratios and were evaluated by XRD and DSC studies. NM tablets were formulated employing NM-PGS dispersions and their corresponding physical mixtures. The compressed tablets were evaluated for various tablet characteristics including dissolution rate and efficiency. Marked increase in the dissolution rate and efficiency was observed with tablets of dispersions in comparison to tablets formulated with NM-PGS physical mixtures. Dissolution of nimodipine from these tablets obeyed first-order kinetics.

Pregelatinized starch is a modified starch that has been modified chemically or mechanically to rupture all or part of the starch granules. Though many modified starches have been studied widely for their pharmaceutical applications PGS has not been investigated thoroughly[1-4]. We have been working on the pharmaceutical applications of PGS. We have previously evaluated the application of PGS in the formulation of dispersible tablets[5]. The objective of the present investigation is to formulate and evaluate nimodipine tablets employing NM-PGS dispersions. In the present study, nimodipine, a recently introduced calcium channel blocker was used. It is highly crystalline and practically insoluble in water and aqueous fluids[6]. Because of the limited aqueous solubility it exhibits dissolution characteristics and its oral absorption is dissolution rate limited. Hence to improve the dissolution rate of NM, tablets of NM-PGS dispersions were prepared and evaluated.

METHODS

Nimodipine B.P. was obtained as a gift sample from US vitamins Limited, Mumbai. Pregelatinized starch was prepared from potato starch in the laboratory using reported method[7,8]. Methanol (Merck), acetone (Qualigens), hydrochloric acid (Ranbaxy), Lactose, I.P., polyvinyl pyrrolidone (Mol.Wt. 40,000), Talc, I.P. and Magnesium stearate, I.P. were purchased from commercial sources.

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Preparation of NM-PGS dispersions and physical mixtures:

PGS employed in the present study was subjected for official identification tests, density, bulk density, compressibility index and swelling capacity was determined by standard methods for PGS[9-10].

All experiments with NM were carried out in subdued light to prevent photodegradation of nimodipine. NM-PGS dispersions were prepared by solvent evaporation method. The required quantity of drug was dissolved in methanol to get a clear solution. PGS was then added to the clear solution and dispersed. The solvent was then removed by evaporation at 40° under vacuum. The mass obtained was crushed, pulverized and sifted through mesh no. 120. Different proportions of drug:carrier such as 1:1, 1:3 and 1:9 were used to prepare the dispersions. Physical mixtures of NM and PGS were prepared in 1:1, 1:3 and 1:9 ratio, by trituration in a mortar and sifted through mesh no. 120.

Table 1 : DISINTEGRATION AND DISSOLUTION CHARACTERISTICS OF VARIOUS NIMODIPINE TABLETS PREPARED

Tablet	D.T (min) (± sd)	First-order Dissolution rate (k_1 min^{-1})$x10^3$ (±sd)	Dissolution efficiency (%) (±sd)
Tablets prepared from Solid Dispersions			
NM:PGS (1:1)	2.83±1.26	37.70±5.85	61.81±5.60
NM:PGS (1:3)	3.17±0.76	43.72±7.62	67.79±4.35
NM:PGS (1:9)	2.17±0.76	82.14±16.93	74.02±7.20
Tablets prepared form Physical Mixtures :			
NM:PGS (1:1)	2.83±0.29	33.18±12.81	46.83±7.60
NM:PGS (1:3)	3.20±1.04	35.89±1.46	54.64±2.86
NM:PGS (1:9)	3.17±0.76	38.40±16.53	61.75±4.79

The physicochemical characteristics of dispersions were evaluated by XRD and DSC by standard techniques. Powdered diffraction technique for XRD and DSC study in an atmosphere of nitrogen by SEIKO DSC - 220 C are adopted for spectral analysis.

Preparation of Nimodipine Tablets :

Tablets each containing 30 mg of nimodipine were prepared employing its physical mixtures (1:1, 1:3 and 1:9) and dispersions (1:1, 1:3 and 1:9) in PGS by conventional wet granulation method using PVP solution in alcohol as binding agent at 2% concentration in the formula and 2% each of talc and magnesium stearate as lubricants. Sufficient quantity of lactose was also added to raise the total bulk of each tablet to 250 mg. Tablet granulations were compressed into 250 mg tablets on a Cadmach single punch tablet machine to a hardness of 5-6 kg/sq.cm. The prepared tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution rate.

Dissolution rate study of Tablets :

The dissolution rate of NM tablets was studied using USP XXI Dissolution Rate Test Apparatus employing a paddle stirrer. In 900 ml of dissolution medium (0.1 N HCl), one tablet, a speed of 100 rpm and a temperature of 37±1° were employed in each test. The dissolution medium also contained 10% methanol to maintain sink condition, in all experiments[11]. A 5 ml aliquot of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed spectrophotometrically at 358 nm for NM. Dissolution efficiency values were calculated from the dissolution data as suggested by khan[12].

RESULTS AND DISCUSSION

Pregelatinized starch, prepared from potato starch was in fine and free flowing form. The PGS prepared fulfilled the official identification tests (USP XXIII) and tests for oxidizing substances. The PGS prepared was easily dispersible in purified water. The pH of 10% w/v slurry in water was 7.4. The density (g/ccc), bulk density (g/cc), porosity (%), compressibility index (%) and swelling capacity (%) of PGS prepared were 1.276, 0.384, 69.90, 15.77 and 316.7 respectively.

X-ray diffractograms of NM exhibited characteristic diffraction patterns. Whereas, in the case of diffractograms (Figure-1) of NM-PGS (1:9) dispersion many of the sharp diffraction peaks disappeared and though a few peaks were observed their peak heights were much reduced. The absence of sharp peaks indicates that majority of drug, is present in amorphous form[13].

The DSC thermograms of NM, PGS and NM-PGS (1:9) dispersion are shown in Figure-2. The DSC thermogram of dispersion showed two endothermic peaks, a sharp peak at 126.5° corresponding to nimodipine and a broad peak at 71.4° corresponding to PGS. The sharp endothermic peak at 126.5° (corresponding to NM) in the DSC thermogram of dispersion indicate that the drug, nimodipine is present in the amorphous form in the dispersion. Further DSC thermograms of NM and NM-PGS

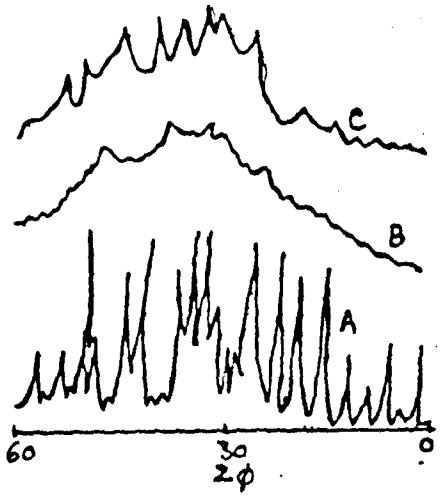

Fig.1: X-ray diffractograms of A-Nimodipine, B-Pregelatinized starch, C-Nimodipine-Pregelatinized starch dispersion (1:9)

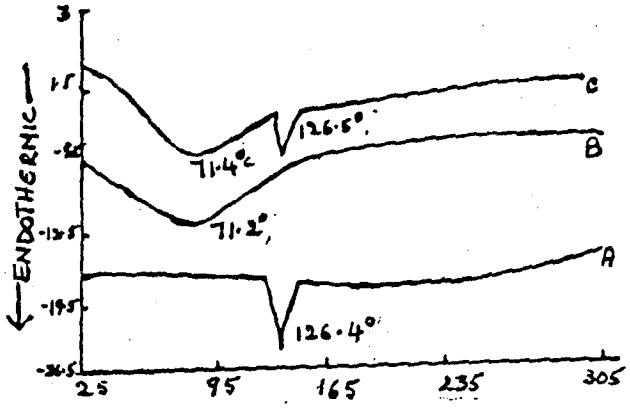

Fig.2: DSC thermograms of A-Nimodipine, B-Pregelatinized starch, C-Nimodipine-Pregelatinized starch dispersion (1:9)

dispersion are essentially similar indicating no chemical interaction between drug and PGS.

All the tablets formulated with NM-PGS physical mixtures, solid dispersions were found to contain NM within 100±5 per cent of the labeled claim. Hardness of the tablets was found to be within the range of 4-5 kg/sq. cm under satisfactory. Friability of tablets was less than 1%. All the tablets prepared disintegrated within 4 min. The tablets prepared with dispersions gave rapid and fast dissolution of NM when compared to tablets prepared with NM-PGS physical mixtures. The possible mechanisms responsible for increased dissolution rate from these tablets are (a) rapid disintegration of the tablets, due to superior swelling capacity of PGS (b) presence of drug in amorphous form in tablets of NM-PGS solid dispersions, since amorphous form is the highest energy form of a compound which produce faster dissolution. Other factors such as possible reduction in particle size, the easy and rapid dispersibility of PGS and deposition of drug in amorphous form on the surface of PGS might have also contributed to the increased dissolution rate of NM from tablets of NM-PGS solid dispersions. The dissolution rate of nimodipine from the tablets increased when the proportion of PGS increased. Hence dissolution of NM from the compressed tablets followed first-order kinetics.

Thus fast disintegrating nimodipine tablets giving rapid dissolution of the formulated drug employing nimodipine-pregelatinized starch dispersions by conventional wet granulation method in comparison to nimodipine-PGS physical mixtures could be formulated.

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