

FORMULATION AND EVALUATION OF FAST DISSOLVING NIMESULIDE TABLETS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The aim of this study was to prepare fast dissolving tablets of Nimesulide by employing solid dispersion technique. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and hausner's ratio. Tablets were subjected to post compressional analysis for the parameters such as hardness, friability, in- vitro disintegration time, wetting time and dissolution. Stability studies were carried out as per ICH guidelines for three months. The results revealed that tablets prepared by solid dispersion having drug to PVP ratio of 1:3 (P3), yielded the best result in terms of dissolution rate. Stability studies revealed that upon storage tablets prepared by solid dispersion with PVP did not show any change in disintegration time after stability studies.

KEYWORDS: Nimesulide, Fast dissolving tablets, Croscarmillose sodium, Solid dispersion.

INTRODUCTION

The Oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. Therefore, oral solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. Among the pharmaceutical dosage forms, the conventional tablets seem to be most popular, because of its ease of transportability and comparatively lower manufacturing cost. There are several factors other than physicochemical properties of the drug that may influence the dissolution rate and hence, bioavailability of the drugs forms the solid dosage forms. It has shown that, the dissolution rate of pure drugs can be altered significantly by the proper selection of formulation components as well as processing methods¹.

Clinically, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed by physicians for inflammatory disorders. NSAIDs exert their effect through inhibition of cyclooxygenase-II, the main form of isozyme associated with inflammation. But the simultaneous inhibition of cyclooxygenase- I and the resulting gastric and renal dysfunction limit their frequent use.² Nimesulide, a model active pharmaceutical ingredient acts specifically on

cyclooxygenase-II and does not affect cyclooxygenase-I.³ Hence, Nimesulide exerts its anti-inflammatory action while showing a marked increase in gastrointestinal tolerability and minimal incidences of renal dysfunction. Because of its additional action of inhibiting respiratory burst of phagocytosing neutrophils, Nimesulide is also well tolerated by asthmatic patients.⁴ Thus, it is one of the most commonly prescribed NSAIDs for the treatment of various inflammatory conditions such as tonsillitis, pharyngitis, stomatitis, rheumatoid arthritis, osteoarthritis, low back pain, etc. Nimesulide results in poor bioavailability when administered in the form of conventional tablets because of its high hydrophobicity and poor aqueous solubility.⁵ This fast Dissolving technology of Nimesulide is convenient for administration and patient compliance for disabled, bedridden patient and for travelers and busy people, who do not always have access to water. And also the risk of choking or suffocation can also be avoided. These dosage forms dissolve in the oral cavity within a minute without the need of water or chewing. This technology also offers new business opportunity like product differentiation, product promotion, and patent extension.⁶ The fast dissolving tablets of Nimesulide contains superdisintegrants, which accelerates the disintegration of tablets by virtue of their ability to absorb large amount of water when exposed to aqueous environment. This

rapid disintegration of FDTs is due to penetration of saliva into the pores, which lead to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablets. This increase bioavailability / rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.⁷ The objective of this study was to enhance the efficacy of drug molecule, achieve better compliance, enhance onset of action, and provide stable dosage form.

MATERIALS AND METHODS

Nimesulide was gifted from Zydus Hetero drugs Ltd. (Hyderabad, India). Croscarmellose sodium Gift sample from Maple biotech Pvt. Ltd, Pune, Microcrystalline cellulose, PVP, Talc and Magnesium stearate were purchased from S.D. Fine chemicals Pvt. limited, Mumbai and all other materials were of analytical grade.

METHODS

Preparation of solid dispersions of Nimesulide

Solid dispersions of Nimesulide were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier (PVP) was added in ratio of 1:1, 1:2, and 1:3. The solvent was evaporated at room temperature and dried in hot air oven at 50^o C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in desiccator.

Preparation of tablets containing solid dispersions of Nimesulide

The solid dispersions equivalent to 100 mg of drug were taken. Then mixed with directly compressible diluent and superdisintegrant in a plastic container. Magnesium stearate and aerosil were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend (Table 1)

Evaluation of Nimesulide tablets

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time, drug content and stability studies. Pfizer hardness tester was used for the determination of the hardness of the tablets. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded (Fig.1). The thicknesses of tablets were recorded during the process of compression using Calipers (Mitotoyo; Japan). The friability of the tablets was determined using a Roche by taking two tablets from each batch and accurately weighed and placed in the friabilator then operated for 100 revolutions. Then the tablets were dedusted and reweighed. Percentage friability was calculated using the formula, % Friability = 100 (W_o - W) / W_o. In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the

disintegration apparatus was positioned into a 1-litre beaker containing 900ml of distilled water and time of disintegration was recorded at 37± 0.5^oC. In the wetting time study, a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For drug content analysis a total 10 tablets were weighed and powdered. The powder equivalent to 100 mg of Nimesulide was taken and dissolved in phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (A PG instrument UV-spectrophotometer T₈₀ model) at 254 nm. The stability study of the tablets was carried out according to ICH guidelines. The formulations were stored at 40 ±2^oC / 75 ±5%RH for 4 weeks in a stability chamber (Labcare, Mumbai, India)

In-vitro release studies

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 6.8) was taken in vessel and the temperature was maintained at 37 ± 0.5^oC. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with Phosphate buffer pH 6.8 prior to analysis in the UV Spectrophotometer (A PG instrument UV-spectrophotometer T₈₀ model) at 254 nm.

RESULTS AND DISCUSSIONS

The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Results are shown in Table 2. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, and drug content are shown in Table 3. In all the formulations, the hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥ 101.55 %) and uniform in all the formulations. The tablets were subjected for evaluation of *in-vitro* disintegration time and it was observed that formulations P1, P2, P3 disintegrated rapidly while P did not disintegrated in the specified limit of time for fast dissolving tablets. Wetting time of formulations P were significantly higher than other formulations. The dissolution of Nimesulide from the formulations is shown in Fig 2. The results were compiled in Table 3. The dissolution rate of tablets prepared with solid dispersion in the ratio 1: 1, 1:2, 1:3

(P1, P2, P3) with PVP increased significantly ($P < 0.05$) than formulation P (control). This may be due to the use of Croscarmellose sodium, which causes swelling to 4-8 folds in 10 seconds⁸ and due to particle size reduction and improved wettability⁹. In addition to micronization, conversion of drug to amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions¹⁰. In practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted^{11,12}. This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which effect results in a decreased effective surface area for dissolution¹³. The stability study for all the formulations were carried out according to the ICH guidelines at $40 \pm 2^\circ \text{C} / 75 \pm 5\% \text{RH}$ for 4 weeks, by storing the tablets in a stability chamber. No significant change in the thickness observed in all formulations and drug content of all formulations was within the acceptable limits. Results are shown in Table 4.

CONCLUSION

The major problem of Nimesulide is poor bioavailability when administered in the form of conventional tablets because of its high hydrophobicity and poor aqueous solubility. The results revealed that it is possible to enhance the dissolution rate of Nimesulide by increasing the surface area of the drug by solid dispersion method.

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Table 1: Formulae used in the preparation of tablets using PVP solid dispersion

Ingredients (mg)	P	P1	P2	P3
Amount of solid Dispersion equivalent to 100 mg of drug	100	205	301	408
Lactose	391	256	160	53
MCC	--	20	20	20
Croscarmellose Sodium	--	10	10	10
Aspartame	3.0	3.0	3.0	3.0
Aerosil	3.0	3.0	3.0	3.0
Magnesium Stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Tablet Weight (mg)	500	500	500	500

Table 2: Precompressional Parameters

Formulation	Angle of Repose (θ)	Compressibility (%)	Hausner's Ratio
P	24.18 \pm 0.71	10.53 \pm 1.40	1.23 \pm 0.07
P1	23.25 \pm 1.53	11.39 \pm 2.10	1.21 \pm 0.08
P2	22.13 \pm 0.67	14.49 \pm 0.70	1.12 \pm 0.05
P3	25.37 \pm 0.44	13.11 \pm 0.35	1.09 \pm 0.05

Note: Values in parenthesis are standard deviation (\pm SD)

Table-3: Post compression parameters of tablets

Formulation	Drug content (%)	Thickness (mm)	Friability (%)	Hardness test (kg/cm^2)	Weight variation (%)	Wetting time (sec)	Disintegration time (sec)
P	99.33 \pm 0.27	3.9 \pm 0.10	0.63	4.2 \pm 0.18	498 \pm 1.14	498 \pm 6.13	401 \pm 4.07
P1	96.78 \pm 0.19	4.0 \pm 0.16	0.61	4.1 \pm 0.27	501 \pm 1.25	59 \pm 3.11	47 \pm 2.19
P2	98.38 \pm 1.26	3.8 \pm 0.11	0.84	4.3 \pm 0.29	503 \pm 1.61	57 \pm 1.30	48 \pm 2.49
P3	101.55 \pm 0.67	3.9 \pm 0.21	0.57	4.0 \pm 0.33	497 \pm 1.54	51 \pm 2.27	40 \pm 2.10

Note: Values in parenthesis are standard deviation (\pm SD)

Table 4: Tablet parameters after stability studies

Formulation	Disintegration Time (sec)	Thickness (mm)	Drug content (%)
P	417±9.15	3.8±0.25	98.14±1.30
P1	50±3.18	4.1±0.15	96.01±1.48
P2	46±2.07	3.9±0.12	97.19±0.29
P3	45±2.24	3.9±0.33	99.95±1.27

Note: Values in parenthesis are standard deviation (±SD)

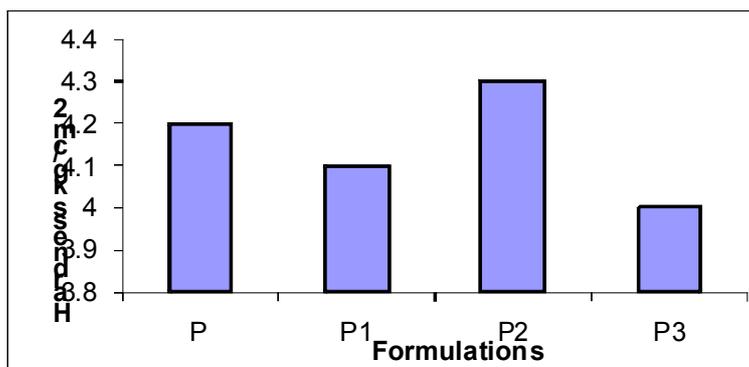


Fig. 1: Hardness of tablets prepared with PVP (P1, P2, P3) solid Dispersion

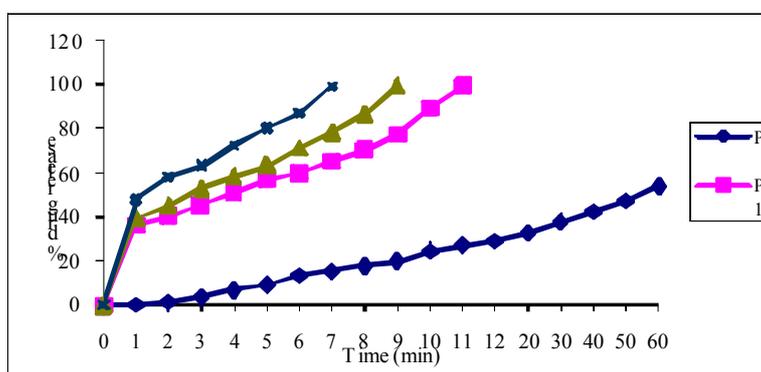


Fig. 2: Dissolution profiles of formulations containing PVP solid dispersions

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