ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of mouth dissolving tablets of nimesulide by new coprocessed technique

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ABSTRACT

Attempts were made to prepare mouth dissolving tablets of Nimesulide by direct compression method with a view to enhance patient compliance. The two superdisintegrants used in this study were Croscarmillose sodium and Sodium starch glycolate. The prepared batches of tablets were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. Using the same excipients, the tablets were prepared, without disintegrants and were evaluated in the similar way. From the results obtained, it can be concluded that the tablet formulation (P4) showed the promising formulation. Also the hardness, friability, disintegration time and dissolution rate of prepared tablets were found to be acceptable according to standard limits.

Keywords: Nimesulide, Mouth dissolving tablets, In vitro evaluation, Superdisintegrants.

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ISSN: 0975-8585

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self- administration, compactness, and ease in manufacturing. For the past one decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[1].

However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as " melt in mouth" or " mouth dissolve (MD)" or sometimes " dispersible" tablets. These are novel types of tablets that disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bed- ridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [2].

Nimesulide (4-nitro-2-phenoxymethanesulfoanilide) is a selective COX-2 non-steroidal anti-inflammatory drug. This compound, a derivative of p- nitrophenylmethanesulfonamide, is structurally a unique non-steroidal anti-inflammatory drug. It belongs to selective COX-2 inhibitors, with a potent anti-inflammatory and analgesic activity, when administered orally, rectally, or topically. Due to its analgesic and antipyretic properties, Nimesulide is widely used for the treatment of various inflammatory processes. Besides, its better tolerated and causes fewer adverse effects than other currently used nonsteroidal anti-inflammatory drugs. It also shows less severe gastrointestinal side effects. This compound is structurally different from other new classes of COX-2 inhibitors named coxibes. The literature data suggests pKa values, (from 5.9 to 6.56) of Nimesulide. This compound is freely soluble in organic polar solvents, while its solubility in water was reported to be 0.01 mg ml but it depends on the pH of the aqueous solution [3].

Clinically, non-steroidal 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 [4]. Nimesulide, a model active pharmaceutical ingredient acts specifically on cyclooxygenase-II and does not affect cyclooxygenase–I [5]. 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 [6]. 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 [7]. In the present study, an attempt was made to develop mouth-dissolving tablets of Nimesulide and to improve its bioavailability.

MATERIALS AND METHODS

Nimesulide was a gift from Mann Pharmaceutical Industries (Mehsana, India). Croscarmellose sodium used was analytical reagent grade procured from Loba Chemicals, Mumbai and Sodium Starch Glycolate used was procured from Merck Limited, Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of mouth dissolving tablets of Nimesulide

All the materials were passed through 60 # screens prior to mixing. Nimesulide, Croscarmellose sodium, Sodium Starch Glycolate, and Mannitol were mixed using a glass mortar and pestle. All the materials were directly compressible so this uniformly mixed blend was compressed into tablets using concave face round tooling on a 16-station rotary tablet machine (Table 1).

Evaluation of Nimesulide mouth dissolving tablets

Weight variation test [8]

Weight variation test was done by weighing 20 tablets individually, by using Sartorious balance (Model CP- 224 S). Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness [8]

The thickness was measured by placing tablet between two arms of the Varnier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness [8]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability [8]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_o) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = 100 (W_o - W) / W_o$$

Wetting time [9]

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water- containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio (%) [10,11]

A piece of tissue paper folded twice was placed in a small petridish (Internal Diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where, W_b is the weight of the tablet before water absorption and W_a is the weight of the tablet after water absorption.

In-vitro disintegration test [8]

The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

In-vitro dissolution study [12]

The release rate of Nimesulide from mouth dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 as a dissolution medium, at 37±0.5^{0}C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35 and 40min. The samples were filtered

through a 0.45μ membrane filter. Absorbance of these solutions was measured at 254 nm using a Shimadzu UV-1700 UV/VIS spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

The use of superdisintegrants for preparation of mouth dissolving tablets is highly effective and commercially feasible. The results of tablets were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study (Table 2). Using the same excipients, the tablets were prepared, without these superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well. Prepared mouth-dissolving tablet gets dispersed in the mouth quickly and releases the drug early as compared to its formulated conventional tablet. Figure 1 show the cumulative percentage of Nimesulide released from formulated tablet with different concentration of Crosscarmellose sodium and Sodium starch glycolate. It is clear that the dissolution of Nimesulide has improved considerably in formulation P4 as compared to formulation P1, P2, P3 and P5 (Control). The tablets of the batch P4 showed good dissolution efficiency and rapid dissolution.

Table 1: Formulation of Nimesulide MDT

Ingredients	Formulation Code				
	P1	P2	P3	P4	P5
Nimesulide	100	100	100	100	100
Sodium starch glycolate	10	20	10	20	--
Crosscarmellose sodium	40	40	45	45	--
Lactose	44	34	39	29	194
Mannitol	94	94	94	94	94
Aspartame	6	6	6	6	6
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Total (mg)	300	300	300	300	300

Table 2: Evaluation of Nimesulide MDT

Formulation parameters	Formulation Code				
	P1	P2	P3	P4	P5
Weight variation (%)	302±1.32	299±2.19	298±2.33	301±1.56	300±2.27
Thickness (mm)	4.2	4.1	4.3	4.1	4.5
Hardness (kg/cm2)	3.0±0.14	3.2±0.15	3.6±0.35	3.7±0.46	2.5±0.19
Friability (%)	0.41	0.38	0.33	0.32	0.39
Wetting time (sec)	47±1.20	46±0.90	49±2.70	38±1.35	79±2.20
Water absorption ratio (%)	90.81	92.47	91.17	93.58	57.81
Disintegration time (sec)	36±2.8	35±3.2	34±2.4	28±4.4	69±2.5

ISSN: 0975-8585

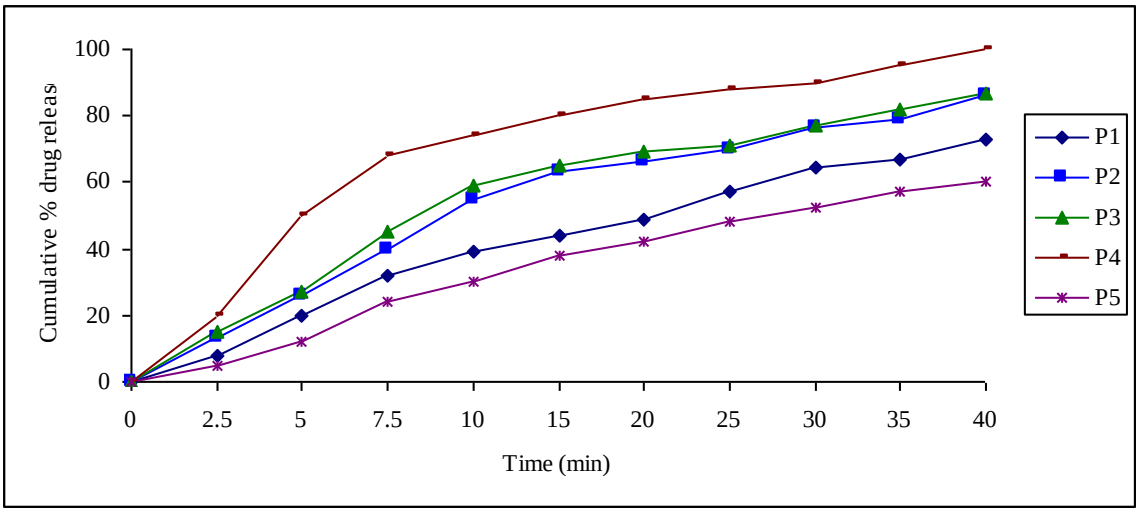

Fig. 1: Drug release profile of Nimesulide MDT from various batches

CONCLUSION

It can be concluded that disintegration time and dissolution rate of Nimesulide can be enhanced to a great extent by direct compression technique with the addition of combination of superdisintegrants. Further investigations are needed to confirm the *in-vivo* efficiency.

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