



Formulation, Evaluation and Comparison of Fast-Dissolving Tablet of Nimesulide by Using Crospovidone as Superdisintegrant

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ABSTRACT

Fast dissolving tablets (FDT) of Nimesulide were prepared by direct compression method. The study was performed by incorporating the superdisintegrant (crospovidone) in 2 %, 4 %, 8 %, 12 % concentration respectively. Four formulations were prepared to assess their efficiency. The optimized batch (Formulation 4) was compared with the available marketed preparation. The optimized batch (Formulation 4) showed excellent in vitro/in vivo dispersion time and drug release as compared to marketed preparation.

Keywords: Nimesulide, direct compression, superdisintegrant.

INTRODUCTION

Nimesulide, N-(4-Nitro-2-phenoxyphenyl) methane sulfonamide a derivative of p-nitro phenyl methane sulfonamide is a selective COX-2 non-steroidal anti-inflammatory drug. It belongs to selective COX-2 inhibitors, with a potent analgesic activity, when administered orally, rectally or topically. Its main impurities are C (2-phenoxyaniline) and D (2-phenoxy-4-nitroaniline). The literature survey suggests P_{ka} values ranges from 5.9-6.56 of Nimesulide. This compound is freely soluble in organic polar solvents, but is sparingly soluble in aqueous solution (0.01mg/ml) and so has low bioavailability and thus classifying it into BCS class II (Biopharmaceutical classification system).^[1-2] FDT of nimesulide is partially absorbed through the oral mucosa directly enters the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism of the liver, which may result to increase the fraction of drug to reach the systemic circulation. 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. 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 rapid disintegration of FDT is due to penetration of saliva into the pores, which lead to the swelling of superdisintegrant

to create enough hydrodynamic pressure for quick and complete disintegration of tablets. This increases bioavailability / rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down. This technology also offers new business opportunity like product differentiation, product promotion, and patent extension. The objective of this work is to enhance the efficacy of drug molecule, achieve better compliance, and enhance onset of action as compared to the marketed preparation.^[3]

MATERIALS AND METHODS

Nimesulide, Crospovidone, D-mannitol, MCC, Talc, Magnesium stearate, Aspartame, was supplied as a gift sample by Ranbaxy laboratories Ltd, Dewas (M.P.). All ingredients and solvents used were of analytical grade.

Blending and tableting

The superdisintegrant (Crospovidone) in varying concentration (2 %, 4 %, 8 %, and 12 %) was used to develop the tablets. The drug, diluents, superdisintegrant, and sweetener were passed through #36 while talc and magnesium stearate were passed through # 60, (as shown in Table 1) All the ingredients were co-ground in mortar pestle for 5 min. the mixed blend of excipients was compressed using multiple tooling twenty station single rotary with single punch on cadmach (CDMIV) machine to produce biconvex shaped tablets (plane on both sides), weighing 200 mg each with thickness of 4.40 ± 0.20 mm and diameter of 7.0 mm (Fig. 1) for all formulations. Approximate 100 tablets were compressed.^[4]

Physical evaluation of blend

In solid dosage form the physicochemical properties of blend rules the tablet quality. The mixing step if not properly

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optimized can affect the characteristics of blend and thereby tablet produced. The blends were characterized by mass-volume relationship (bulk density, tapped density, Hauser's ratio, compressibility index) and flow properties (static angle of repose).^[3-4]

Evaluation of formulated tablets

Prepared tablets were evaluated for hardness (Schulzner hardness tester), thickness (digimatic vernier caliper; Mitutoya, Model CD-6 CS, Japan), friability (Roche friabilator), Weight variation, disintegration time, *in vitro* dispersion time, wetting time of tablet, water absorption

ratio, *in vivo* disintegration time, I. R. studies, dissolution study and drug content.^[2-4]

Table 1: Formulation of fast-dissolving tables of Nimesulide

Ingredients(mg)	F1	F2	F3	F4
Nimesulide	100	100	100	100
Crospovidone	4	8	16	24
MCC	50	50	50	50
D-manitol	30	26	18	10
Aspartame	10	10	10	10
Talc	4	4	4	4
Mg.stearate	2	2	2	2

Table 2: Evaluation of fast dissolving tablets of Nimesulide

S. No.	Evaluation Test	F1	F2	F3	F4	API	Marketed
1	Bulk Density (gm/cm ³)	0.571	0.6	0.572	0.533	0.444	
2	Tapped Density (gm/cm ³)	0.8	0.8	0.71	0.727	0.571	
3	Carr's Index (%)	28.62	25	19.43	26.68	22.24	
4	Hausner Ratio	1.4	1.33	1.24	1.36	1.28	
5	Angle of Repose (°)	29°43'	28°52'	30°00'	29°40'	30°40'	
6	Weight Variation (mg)	201 (SD±1.716)	200 (SD±1.486)	201.1 (SD±2.403)	199.85 (SD±1.424)		250.55 (SD±3.11)
7	Hardness (kg/cm ²)	6.375 (SD±0.28)	5.375 (SD±0.25)	6.25 (SD±0.3)	4.975 (SD±0.54)		6.95 (SD±0.191)
8	Thickness (mm)	4.613 (SD±0.041)	4.666 (SD±0.011)	4.643 (SD±0.03)	4.78 (SD±0.02)		3.92 (SD±0.087)
9	Friability (%)	0.32	0.43	0.39	0.25		0.357
10	Disintegration Time (sec)	15 (SD±0.577)	12 (SD±0.577)	11 (SD±0)	7 (SD±0.577)		12 (SD±0.577)
11	In-Vitro Dispersion Time (sec)	50 (SD±0.577)	41 (SD±0.577)	38 (SD±0.577)	22 (SD±0)		35 (SD±0.577)
12	Wetting Time (sec)	60 (SD± 0.577)	56 (SD± 0)	50 (SD± 1.527)	12 (SD±0)		23 (SD±0.577)
13	Water Absorption Ratio (%)	48 (SD±0.456)	66.16 (SD±0.029)	72.26 (SD±0.6)	109.5 (SD±0)		110.56 (SD±0.42)
14	In Vivo disintegration Time (sec)	15	13	11	8		22
15	Assay (%)	94.15	102.47	101.09	103.57		

In weight variation test 20 tablets were selected at random and average weight was determined using an electronic balance (Mettler Toledo X8403S, Switzerland), tablets were weighed individually and compared with the average weight. Disintegration time was determined using USP tablet disintegration test apparatus (ED 2L, Electrolab, India)) in 900 ml distilled water without disk at 37°C ± 0.5 °C, Wetting time was carried out by using the method given by Bi et al. (1996) , in this method a piece of tissue paper folded twice was kept in a small Petri dish (internal diameter-6.5 cm) containing 6 ml of water. A tablet was carefully placed in the centre of the Petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The wetted tablet is then weighed and the water absorption ratio was calculated using eq.1

$$R=100(Wb-Wa)/Wa.....1$$

Where Wa and Wb are the weights of tablet before and after water absorption.

For the determination of *in vitro* dispersion time, (Fig. 2a and 2b), one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C and the time required for complete dispersion was recorded.^[3-4]

In vivo disintegration time was evaluated in three human volunteers by placing a tablet on the tongue and immediately the time was recorded. They were allowed to move the tablet against the upper palate of the mouth with their tongue. Immediately after the last noticeable mass had disintegrated, the time was recorded. The subjects were asked to spit out the content of the oral cavity after tablet disintegration and

rinse their mouth with distilled water. The swallowing of saliva was prohibited during the test.^[4]

In vitro dissolution study of all the formulations (F1, F2, F3, and F4) and marketed tablets were performed by using USP type II paddle apparatus in 6.8 pH phosphate buffer (900 ml) at 37°C±0.5°C at speed 50±5 rpm.^[4]

For assay mobile phase used was, methanol: ACN in 60:40 ratio. Column used was C18 4.6×250 mm (5 mm packing) at flow rate 1.0 ml/min. The UV detection was performed at 254 nm. Injected volume was 20µl. IR study was done by preparing dried Kbr and tablet powder in 100:1 ratio. The IR spectra of tablet and standard drug were obtained.^[2, 5-8] (Fig 3)

RESULT AND DISCUSSION

Fast dissolving drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. This dosage form is designed for dysphagic, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations, as they dissolve/disintegrate very fast when placed in the mouth.

The superdisintegrant (Crospovidone) was used in different concentration to formulate FDT of Nimesulide and the optimized batch was compared with the marketed preparation.

Since the properties of the powder mixture are important for the uniformity of the mass of tablets, the flow of powder blend was analyzed before compression of tablets.

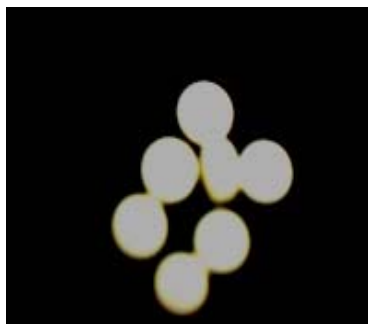


Fig.1:Nimesulide FDT's.



Fig 2(a):In vitro dispersion time (before)



Fig2(b):In vitro dispersion time (After)

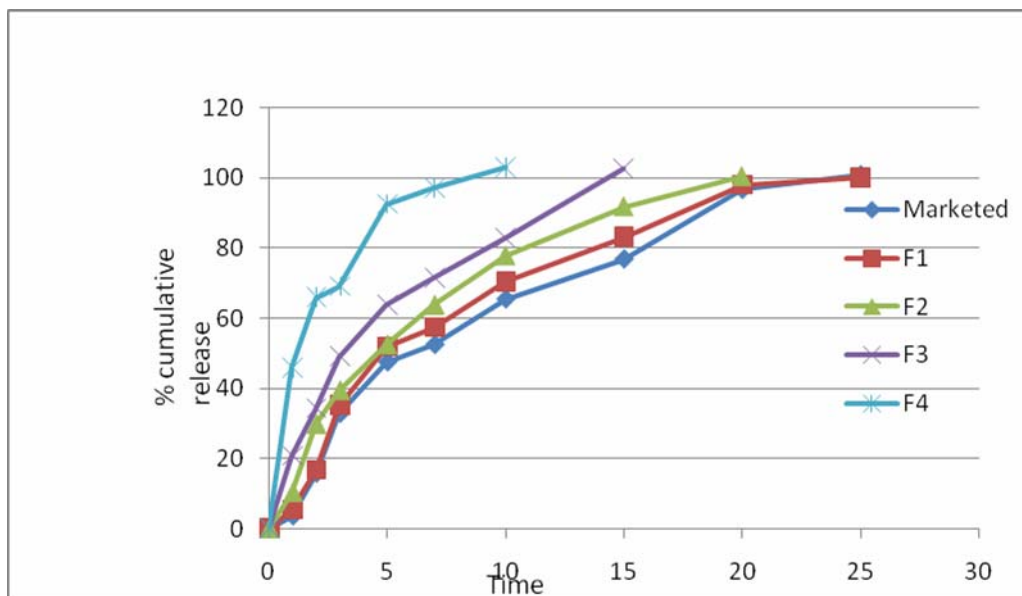


Fig 3:In vitro dissolution profile

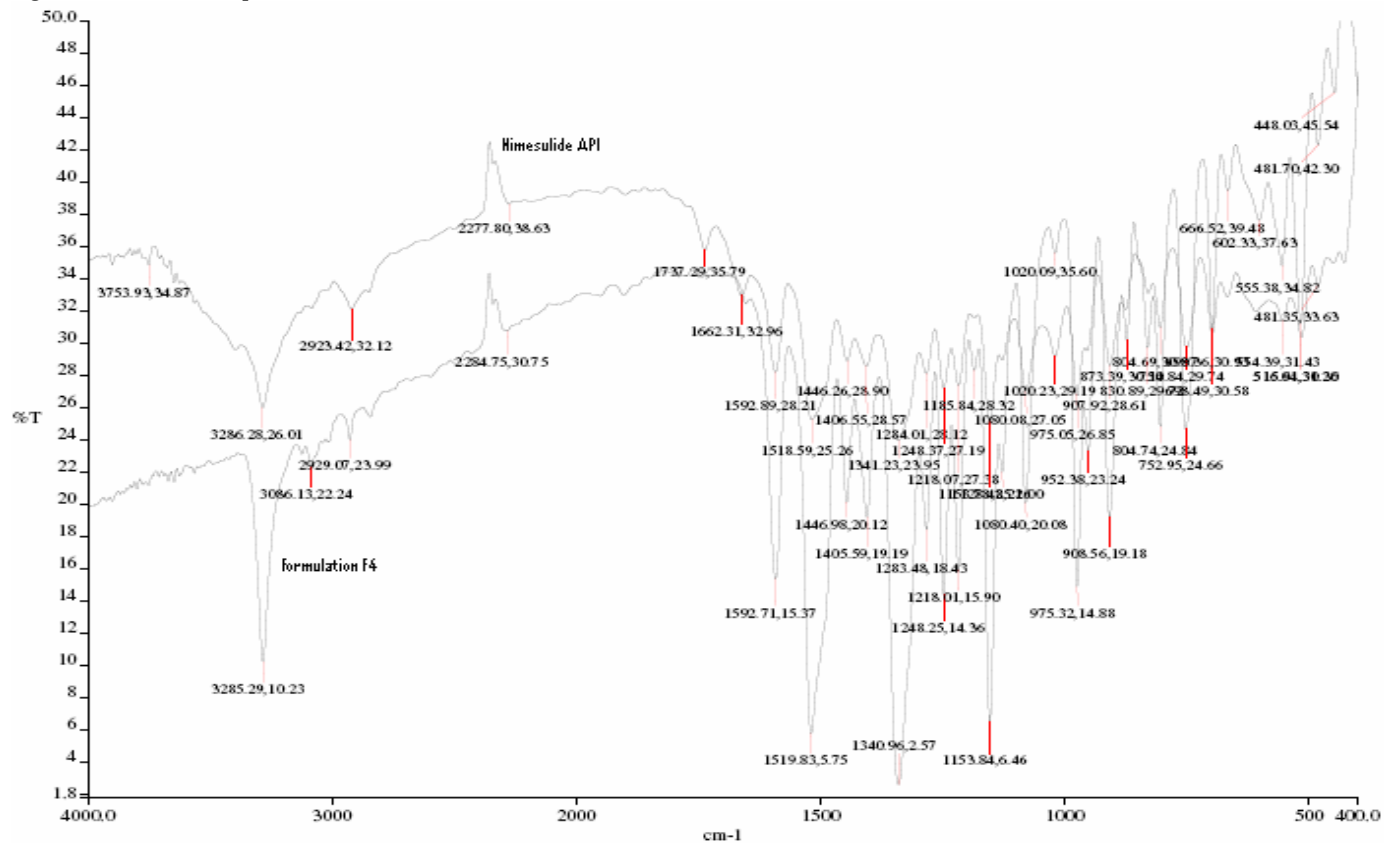


Fig 4:Overlap IR profile of API (Nimesulide) vs formulation F4

All the formulation was evaluated for bulk density, tapped density, Hauser's ratio, compressibility index and angle of repose, (Table 3). As the powder was free flowing tablets produced were of uniform weight with acceptable weight variation ($\leq 1.19\%$) due to uniform die fill. Thus the observation of the study can be summarized as

- Tablets prepared by direct compression method were found to be good, without any chipping, sticking and capping.
- Most important parameter of fast dissolving tablets is disintegration time. In the present study all tablets disintegrated in ≤ 15 seconds fulfilling official requirements (≤ 3 min), for dispersible tablets. Formulation F4 showed disintegration of ≤ 7 second, where as marketed preparation showed ≤ 12 second.
- The hardness was found to be in the range of 4.9-6.4 kg/cm².
- The friability was found to be less than 1 % was indication of good mechanical resistance of tablets.
- Drug content was found to be in the range of 94 % - 103.5 % (Limit 90 %-110 %).
- The water absorption ratio which indicate faster swelling ability of the superdisintegrant in presence of little amount of water; for F4 it was 109.5 % where as that of marketed preparation it was 110.56 %.
- The formulation F4 showed in vivo dispersion time in 8 second, showing faster dispersion in mouth; where as for market preparation it was 22 seconds.
- The dissolution study of formulation F4 showed that complete drug was release in 10 minutes while marketed formulation showed drug release in 25 min (Fig. 3).

Thus it can be concluded by the research study that the disintegration of Nimesulide can be enhance by direct compression technique with addition of croscopovidone.

REFERENCES

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res.* 1995; 12: 413-420.
2. Ali Raguia, Shoukri, Ahmed IS, Shamma RN. In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets. *European journal of pharmaceutics and biopharmaceutic.* 2009; 73: 162-171.
3. Shukla Dali, Chakraborty S, Singh S, Mishra B. Mouth Dissolving Tablets II : An Overview of Evaluation Techniques. *Scipharma*, 2009; 77: 327-341.
4. Setty CM, Prasad DVK, Gupta VRM. Development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrants. *IJPS*, 2008; 70: 180-185.
5. Biscarini L, Patoia L, Favero AD. Nimesulide – A new non-steroidal anti-inflammatory agent. *Drugs Today*, 1988; 70: 23-27.
6. Chopra VS, Singhai SK. Formulation and characterization of fast dissolving tablets of nimesulide. *IJPCR*, 2009; 1(2): 82-84.
7. Zade PS, Kawtikwar PS, Sakarkar DM. Formulation, evaluation and optimization of fast dissolving tablet containing Tizanidine Hydrochloride. *International Journal of PharmTech Research*, 2009; 1: 34-42.
8. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. *IJPPS*, 2009; 1:219-223.