International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 910-914, Oct-Dec 2009

Formulation, Evaluation and Optimization of Fast-Dissolving Tablets Containing Nimesulide Micropellets

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Abstract: The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Fast dissolving tablets (FDTs) are solid unit dosage form, which disintegrate or dissolve rapidly without chewing or water. FDTs provide an advantage particularily for pediatric, geriatric, and bedridden or mentally disabled patients. Nimesulide is a crystalline and poor bioavailable drug because of its high hydrophobicity and poor aqueous solubility. Spherical micropelletization technique is a possible approach which provides maximum dissolution with enhanced wettability as well as uniform and spherical pellet size to achieve the smooth gastric transit of drug. The purpose of this research was to formulate uncoated micropellet of Nimesulide to improve its bioavailability and micromeritic properties, which would be beneficial during development of fast dissolving tablets. The formulated Nimesulide micropellets were used for the development of FDTs. All the formulations were evaluated for their general physical characteristics and in vitro dissolution study. The disintegration time and dissolution profile of the FDTs of Nimesulide micropellets were compared with the FDTs containing plain Nimesulide was concluded that FDTs prepared with Nimesulide micropellets are fast disintegrating and have improved dissolution profile than FDTs prepared with plain Nimesulide.
Keywords: Fast dissolving tablet, Micropellets, Nimesulide.

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Introduction and Experimental

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva[1]. They are also suitable for the mentally ill, the bedridden, 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. Taste masking is of critical importance in the formulation of acceptable FDTs[2-3]. 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. Nimesulide, a model active pharmaceutical ingredient acts specifically on cyclooxygenase-II and does not affect cyclooxygenase–I. 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.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.[4-5]

In the present study, Nimesulide uncoated micropellets prepared by using spherical agglomeration technique for the formulation of fast dissolving tablets[6]. FDTs were developed by using some superdisintegrants such as microcrystalline cellulose (Avicel PH-101), Crosscarmellose Sodium [Ac Di Sol], Sodium starch Glycolate, Crospovidone and dry granulation technique has been used in preparation of granules .

The main aim of the present study to develop Nimesulide uncoated micropellets to improve its bioavailability and micromeritic properties, which would be beneficial during processing of such crystalline drug. These micropellets of Nimesulide were further formulated into the FDTs. The disintegration time and dissolution rate of the Nimesulide micropellets based formulations were compared with the plain Nimesulide based formulations of FDTs.

Materials and Methods

Nimesulide was obtained as gift sample from Redson Pharmaceuticals Ahmedabad, (India). Croscarmellose sodium, sodium starch glycolate, and mannitol were obtained as gift samples from Zydus Cadila Healthcare Ltd, Ahmedabad, (India). Avicel-PH101 (Microcrystalline cellulose) was obtained as gift sample from Colorcon, Mumbai (India). Crospovidone and Magnesium stearate were gifted by Signet Chemicals Mumbai (India). All reagents and chemicals used were of AR grade.

Preparation of Nimesulide micropellets:

Nimesulide uncoated micropellets were prepared using spherical agglomeration technique. The drug solution was prepared by dissolving 1.5g of Nimesulide in 20ml acetone and poured drop by drop into 100ml of demineralised water at room temperature under continuous stirring at 400-500 rpm by using a magnetic stirrer. After 20 min of continuous stirring 6ml of bridging liquid isopropyl acetate (10%v/v) was introduced in drop wise manner into the crystallization medium to produce spherical micropellets having mean diameter of 100-200 µm. The stirring continued for 2 hrs to get stable and spherical micropellets. The spherical micropellets formed were separated by filtration and dried at 45°C for 24hrs in a hot air oven.

Preparation of fast dissolving tablets (FDTs):

FDTs of Nimesulide uncoated micropellets were prepared by dry granulation technique. The formulation of Nimesulide uncoated micropellets based FDTs is given in Table 1. All ingredients were passed through a # 100 sieve, weighed, and blended. Ethanol was used as granulating fluid and it was added slowly to the power blend, and kneading was performed for few minutes until formation of wet mass. The dried granules were re-sieved through a # 20 sieve and thoroughly mixed with the lubricants. The lubricated granules were compressed by a single station tablet punching machine, using flat faced punches. Similarly plain Nimesulide based FDTs were prepared for comparative study with FDTs of Nimesulide uncoated micropellets (Table 2).

Evaluation of tablets

All prepared FDTs were evaluated for uniformity of weight and drug content, as per I.P. method[7]. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester.Disintegration times were tested using Hicon tablet disintegration apparatus[8]. Diameter and thickness were measured by Vernier caliper.

***in vitro* drug release study of FDTs:**

in vitro drug release was studied using USP 2 apparatus, with 900 ml of dissolution medium of saline phosphate buffer pH 7.4 maintained at 37±0.5°C for 1 h, at 50 rpm. 5ml of sample was withdrawn at definite time intervals, and was replaced by an equal volume of fresh dissolution medium of same pH and the dissolved drug was estimated using UV spectrophotometer at λ_{max} 393 nm after suitable dilution of the samples.

Optimization of Formula:

The optimized formulations from prepared formulations of FDTs were selected, depending upon the several factors such as less disintegrant concentration, less disintegration time and fast dissolution rate[8].

Results and Discussion

The formulated FDTs met the pharmacopoeial requirement of uniformity of weight. All the tablets conformed to the requirement of assay, as per I.P. Hardness, % friability, disintegration time; diameter and thickness were well within acceptable limits (Table 3). For Nimesulide uncoated micropellet based formulation the drug content found in the range of 99.15-102.21% (acceptable limit) and the hardness of the tablet was found between 3.63 - 4.26 kg/cm^2. The friability of tablet was found below 1% indicating good mechanical resistance .Disintegration time of all batches was found in the range of 10.44-15.32 sec. For plain Nimesulide based formulation the drug content found in the range of 97.90-101.15% (acceptable limit) and the hardness of the tablet was found between 3.53 - 4.0 kg/cm^2. The friability of tablet was found below 1% indicating good mechanical resistance .Disintegration time of all batches was found in the range of 14.30-25.36 sec.

Batch M6 and F6 was selected as optimized batch containing crospovidone as superdisintegrant in 4% concentration. It has less disintegration time of 10.44 sec and 14.30 sec respectively. The dissolution study was carried out and 98.52% of drug release was occurring for M6 and 82.22% for F6 within 30 min.

The dissolution profile of the Nimesulide uncoated micropellet based formulation M6 showed enhanced dissolution than the plain Nimesulide based formulation F6 (Fig.1). All the formulations showed pleasant organoleptic properties, pleasant mouth feel, and no gritty feeling in the mouth.

From the results of present study it was concluded that FDTs of Nimesulide uncoated micropellet can be successfully prepared by using different superdisintegrants and it takes lesser disintegration time and show faster dissolution rate than plain Nimesulide based FDTs .

Table 1 : Formulations of Nimesulide uncoated micropellets based FDTs

Ingredients (Quantity in mg)	M1	M2	M3	M4	M5	M6
Nimesulide uncoated micropellets	100	100	100	100	100	100
Mannitol	75.00	72.50	75.00	72.50	75.00	72.50
Avicel-PH101	62.50	62.50	62.50	62.50	62.50	62.50
Croscarmellose sodium	7.50	10.00	-	-	-	-
Sodium starch glycolate	-	-	7.50	10.00	-	-
Crospovidone	-	-	-	-	7.50	10.00
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50
Aspartame	2.50	2.50	2.50	2.50	2.50	2.50
Tablet weight	250	205	250	250	250	250

Table 2 : Formulations of Plain Nimesulide based FDTs

Ingredients (Quantity in mg)	F1	F2	F3	F4	F5	F6
Nimesulide	100	100	100	100	100	100
Mannitol	75.00	72.50	75.00	72.50	75.00	72.50
Avicel-PH101	62.50	62.50	62.50	62.50	62.50	62.50
Croscarmellose sodium	7.50	10.00	-	-	-	-
Sodium starch glycolate	-	-	7.50	10.00	-	-
Crospovidone	-	-	-	-	7.50	10.00
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50
Aspartame	2.50	2.50	2.50	2.50	2.50	2.50
Tablet weight	250	205	250	250	250	250

Table 3 : Physical properties of Nimesulide uncoated micropellets based and Plain Nimesulide based FDTs

Formulation Code	Drug content (%)	Friability (%)	Hardness (kg/cm^2) ±SD	Diameter (mm) ±SD	Thickness (mm) ±SD	Disintegration time (sec)±SD
M1	99.15	0.056	4.00±0.02	9.43±0.03	4.58±0.01	15.32±0.02
M2	100.32	0.506	3.63±0.07	9.04±0.02	4.57±0.02	14.02±0.05
M3	100.90	0.20	4.26±0.05	9.28±0.02	4.88±0.02	14.52±0.02
M4	102.21	0.10	4.12±0.02	9.24±0.01	4.42±0.03	12.30±0.02
M5	99.60	0.42	4.20±0.05	9.61±0.02	4.54±0.02	12.42±0.01
M6	91.28	0.28	4.08±0.04	9.47±0.01	4.87±0.01	10.44±0.02
F1	98.77	0.10	4.0±0.03	9.09±0.02	4.86±0.02	25.36±0.01
F2	99.60	0.25	3.53±0.01	9.10±0.02	4.69±0.02	20.66±0.02
F3	97.90	0.028	3.42±0.02	9.69±0.02	4.62±0.02	18.56±0.01
F4	100.77	0.096	3.74±0.04	9.65±0.03	4.57±0.01	16.14±0.01
F5	101.15	0.14	3.78±0.01	9.60±0.02	4.65±0.02	16.25±0.01
F6	99.84	0.032	3.64±0.05	9.62±0.02	4.44±0.01	14.30±0.02

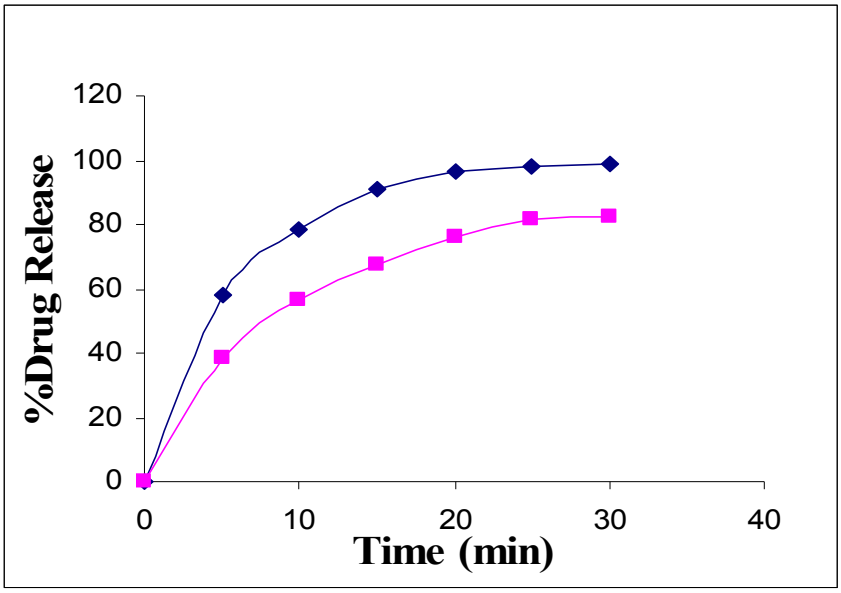

Fig.1:Comparative drug release profile of Nimesulide uncoated micropellets based FDTs (—◆— M6) and Plain Nimesulide based FDTs (—●— F6)

Acknowledgement
The authors wish to thank Redson Pharmaceuticals Ahmedabad, (India), Zydus Cadila Healthcare Ltd, Ahmedabad, (India), Colorcon, Mumbai (India) and Signet Chemicals Mumbai (India) for providing gift samples to carry out this research.

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