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Formulation and evaluation of oral dispersible tablet of nimesulide by direct compression method

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Abstract

Based on Biopharmaceutics Classification System (BCS), nimesulide is a class II drug, characterized by low solubility and high permeability. Thus, its dissolution represents a limiting step in the drug absorption process which directly affects the bioavailability of the drug. Oral Dispersible tablets (ODTs) of nimesulide overcome the problem related to dissolution by enhancing the rate of dissolution by decreasing the disintegration time and making it easy to administer to patients who refuse to swallow a tablet. In the present study, different formulations of nimesulide were prepared to vary the concentration of superdisintegrants: crospovidone, croscarmellose sodium, sodium starch glycolate along with other excipients: PVP K-30, Aerosil, Mannitol, and Magnesium stearate by direct compression method. Precompression and post-compression parameters were evaluated and also the effect of different concentrations of superdisintegrants on the release profile of Nimesulide ODT was studied. The final data revealed that a combination of 10% crospovidone and 8.33% SSG i.e. formulation B4 was found best combination with the lowest dispersion time of 40 seconds, lowest disintegration time of 19.16 seconds, and lowest wetting time of 15 seconds as compared to other formulations. All other studied parameters were found to be satisfactory for all ODT formulations for Nimesulide. It was concluded that Nimesulide can be successfully formulated as oral dispersible tablets using various superdisintegrants in different concentrations by direct compression method. The optimized batch can be subjected to real-time and accelerated stability studies to determine the shelf life for commercial use.

Keywords: Oral Dispersible Tablets; Nimesulide; Superdisintegrants; Direct Compression Method; Dispersion time

1 Introduction

The oral route is the most commonly employed route of drug administration. The popularity of the oral route is attributed to ease of administration, patient acceptance, accurate dosing, cost-effective manufacturing methods, and generally improved shelf-life of the product [1]. In oral delivery, tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease of manufacturing [2]. Tablets vary in size and weight, depending on the amount of medicinal substances and the intended mode of administration [3]. Acceptable dissolution rate, mechanically strong tablets that can handle packaging, transport, and eventually patient utilization. Moreover, the tablets must fulfill the requirements for bioavailability and bioequivalency [4]. Out of various types, Oral dispersible tablets (ODTs) are the popular patient-friendly tablet dosage form that rapidly disintegrates in the mouth without the need for water [5,6]

ODTs are commercially prepared by direct compression technology and make use of superdisintegrants, which when placed on the tongue disintegrate instantaneously and the drug gets dissolved or dispersed in saliva [7]. The basic approach used in the development of oral dispersible tablets is the use of superdisintegrants. These provide

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instantaneous disintegration of tablets after being put on the tongue, thereby releasing the drug in saliva. Usually, superdisintegrants are added to a drug formulation to facilitate the breakup or disintegration of the tablet into smaller particles that can dissolve more rapidly than in the absence of superdisintegrants [8,9]. Dispersible tablets offer advantages for patients who have difficulty swallowing. It has been reported that dysphagia is common among all age groups of patients but is more specific to pediatrics, and geriatrics along with patients with nausea, vomiting, and motion sickness complications [8]. Dispersible tablets with good taste and flavor increase the acceptability of bitter drugs by various groups of the population.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class Food and Drug Administration approved for use as antipyretic, anti-inflammatory, and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, and migraines and used as opioid-sparing agents in certain acute trauma cases [10]. Nimesulide, one of the most used NSAIDs in fever, pain, inflammation, rheumatoid arthritis, tendinitis, thrombophlebitis, and trauma has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw edema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats [11]. The analgesic potency of nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing test in rats, and acetic acid and acetylcholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin, and paracetamol (acetaminophen) in rats with yeast-induced fever [12]. Animal studies have suggested that nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam, and ibuprofen. Nimesulide appears to have little effect on renal prostaglandin synthesis in rats [13].

Tablets are usually prepared with the assistance of appropriate pharmaceutical excipients. Compressed tablets commonly contain some type of pharmaceutical excipient besides the medicinal agent [14]. According to their functionality, they can be categorized as fillers/diluents, disintegrants, glidants, sweeteners, coating agents, binders, lubricants, buffering agents, wetting agents, and matrix formers [15]. Microcrystalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) are used to manufacture rapidly dispersible tablets. Rapid disintegration can also be achieved by adding effervescent material in a tablet to generate carbon dioxide, which also helps in the taste masking of a drug. The major drawback of the effervescent form is hygroscopicity i.e., the ability to absorb atmospheric moisture. Sometimes super disintegrants are added in optimal concentration, to achieve good oral dispersibility with pleasant feeling. Common examples of super disintegrants include sodium starch glycolate, crospovidone, alginic acid, calcium silicate, and croscarmellose. They provide rapid disintegration by swelling due to water absorption [16].

Based on the Biopharmaceutics Classification System (BCS), nimesulide is considered a class II drug, characterized by low solubility and high permeability. Thus, its dissolution may represent a limiting step in the drug absorption process which will directly affect the bioavailability of the drug [17]. Dispersible tablets of nimesulide lead to overcoming the problem related to dissolution by enhancing the rate of dissolution by decreasing the disintegration time and making it easy to administer to patients who refuse to swallow a tablet, such as geriatric patients and psychiatric patients. It provides fast dissolution of tablets and enhances the rate of absorption which will lead to rapid onset of action. The study was designed to formulate and evaluate the oral dispersible tablet of nimesulide by direct compression method and evaluate the effects of superdisintegrants in different concentrations on the release profile of nimesulide dispersible tablets.

2 Material and methods

2.1 Materials

Nimesulide pure drug was gifted from Aarati Drugs Limited (NMS/10100914). Sodium starch glycolate, D-mannitol, crospovidone, PVP K-30, and Potassium dihydrogen orthophosphate were purchased from HiMedia Laboratories Pvt. Ltd. Di-sodium hydrogen orthophosphate, boric acid, sodium hydrogen pellets were purchased from Thermo Fisher Scientific India Pvt. Ltd. All reagents and chemicals used were of analytical grade.

2.2 Methods

2.2.1 Formulation design

Table 1 Formulation design

Ingredients (mg)	B1	B2	B3	B4	B5	B6	B7	B8
Nimesulide	100	100	100	100	100	100	100	100
Crospovidone	10	15	-	30	25	14.233	10.4	15
SSG	20.4	20	25	25	-	24.233	25	25
CCS	15	15	30	-	30	11.933	15	10.4
PVP K-30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Aerosil	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Mg. sterate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	140	145.4	135.4	135.4	135.4	140	140	140
Total	300	300	300	300	300	300	300	300

2.2.2 Preformulation Studies

Determination of λ_{max}

A standard solution of Nimesulide 10ppm (10µg/ml) in alkaline borate buffer of pH 8.4 was scanned in the UV range of 220-400 nm using alkaline borate buffer as blank [18].

Preparation of standard calibration curve for Nimesulide at 390 nm.

Accurately weighed 10mg Nimesulide was dissolved in 10ml alkaline borate buffer and further diluted to get a stock solution of 100µg/ml. This solution was diluted further to give standard concentrations of 2,5,10,15 and 20µg/ml. The absorbance of these solutions was measured at 390 nm using a UV-Spectrophotometer [19].

2.2.3 Precompression Studies

Bulk density (D_b)

It is a ratio of the mass of powder to bulk volume. It is expressed in g/ml. accurately weighed quantity of powder was carefully poured into a graduated measuring cylinder through the large funnel and initial bulk volume was measured [20].

$$D_b = \frac{M}{V_o}$$

Where
M is the mass of powder
V_o is the volume of the powder.

Tapped density (D_t)

It is the ratio of the mass of powder to tapped density. Ten grams of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in g/ml and is given by [20]:

$$D_t = \frac{M}{V_t}$$

Where,
M = Mass of powder
V_t = Tapped volume of powder

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. A fixed funnel method was used. A funnel was fixed with its tip at a given height 'h', above a flat horizontal surface to which graph paper was placed. The powder was carefully poured through a funnel till the apex of the conical pile just touched the tip of the funnel [21]. Then, the angle of repose was calculated using the following equation,

$$\theta = \text{Tan}^{-1}\frac{h}{r}$$

Where,
θ = Angle of repose
h = Height of pile
r = Radius of the base of the pile

iv. Carr's index:

It is an indication of the compressibility of a powder. It is expressed in percentage and is given by

$$I = \frac{Dt - Db}{Dt} * 100$$

Where,
D_b = Bulk density
D_t = Tapped density

Hausner's ratio

It is the ratio of the tapped density to the untapped density [22].

$$H = \frac{Dt}{Db}$$

2.2.4 Preparation of Tablets

All ingredients (nimesulide, crospovidone, croscarmellose sodium, Sodium starch glycolate, PVP K-30, aerosil, and mannitol) were passed through sieve no.60 and were properly mixed (in a polybag). Magnesium stearate was mixed with the initial mixture in a polybag. Trial batches were run to fix the weight of the tablet to 300 mg and desired hardness was maintained. The ingredients were directly compressed into a tablet compression machine according to the formulation table [23].

2.2.5 Evaluation of tablets

Weight variation test:

A total of 20 tablets were selected randomly and weighed individually and the average weight was determined and compared with the average weight. The tablets should be within the specified limits i.e. ±7.5% of average weight as per USP [21].

Hardness test

It was determined by using a Monsanto hardness tester. Ten tablets were selected randomly and hardness was determined in kg/cm^3 and the average hardness of tablets was calculated. A tablet hardness of about 4-5 kg/cm^3 is considered adequate for mechanical stability [24].

Friability test

20 tablets were selected randomly and the initial weight was taken and kept in a Roche friability tester and was revolved at 20 rpm for 4 minutes. The tablets were taken out, dedusted, and reweighed. The friability of the tablets was calculated as:

$$\text{Percentage friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} * 100$$

The weight loss should not be more than 1% as per USP [21].

Disintegration time

It was determined using a disintegration testing apparatus in 900 ml distilled water without disk at 37±0.5 ^{0}C [23].

In-vitro dissolution studies

The release rate of Nimesulide from the tablets was determined using USP dissolution testing apparatus II (Paddle method). The dissolution test was performed using 900ml of pH 8.4 alkaline borate buffer as a dissolution medium at 37 ± 0.5 ˚C at 100 rpm of paddle speed. A sample (10 ml) of the solution was withdrawn at 15 minutes. The sample was filtered and absorbance of the solution was measured at 390 nm using a UV-visible spectrophotometer and % drug release was calculated using the equation of the calibration curve [24].

Drug content uniformity

20 tablets were weighed and powdered. An amount equivalent to 100 mg of Nimesulide was dissolved in 100 ml of pH 8.4 alkaline borate buffer, filtered, diluted appropriately, and analyzed for drug content at 390 nm using a UV-visible spectrophotometer using the equation of calibration curve [24].

In–vitro dispersion time

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5 ^{0}C and the time required for complete dispersion was recorded [23].

Wetting time

A piece of tissue paper folded twice was placed in a culture dish(d=6.5cm) containing 6 ml of phosphate buffer pH 6.8. A tablet was carefully placed on the surface of tissue paper and the time required for phosphate buffer to reach the upper surface of the tablet was noted as the wetting time [25].

Water absorption ratio

The test was done with the same procedure as that of wetting time. In this test, the initial weight of the tablets was noted before placing them on a petri dish. After complete wetting, the wetted tablet was then weighed. The water absorption ratio (R) was determined using Equation [25],

$$R = \frac{Wa - Wb}{Wb} * 100$$

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

3 Results and discussion

Determination of λ_{max}: The λ_{max} of nimesulide was determined by scanning the 10µg/ml solution of the drug using a UV-Spectrophotometer and was found to be 390nm.

Standard Calibration Curve of Nimesulide: The absorbance of the solution 0 to 20 µg/ml was measured in a UV-Spectrophotometer at 390nm. A straight line with equation y = 0.555x – 0.0266 was obtained. The linear correlation was found to be R^2=0.9968.

Precompression parameters for the powder blend: Pre-compression evaluations were done to ensure the flow properties of the powder blend.

Table 2 Results of Pre-Compression Evaluation Parameters

Formulation Code	Angle of repose(θ)	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index (%)	Hausner's ratio
B1	32.21	0.66	0.8	17.5	1.21
B2	30.9	0.66	0.83	20.48	1.25
B3	33.7	0.6818	0.8571	20.4	1.25
B4	29.7	0.714	0.857	16.68	1.20
B5	31.25	0.714	0.882	19.04	1.23
B6	33.9	0.681	0.882	22.78	1.29
B7	31.7	0.606	0.714	15.12	1.17
B8	31.79	0.588	0.714	17.64	1.21

Angle of repose

The angle of repose was used for the measurement of frictional force in a loose powder which in turn will influence the flow properties of the powder blend. The angle of repose of B4 is 29.7 which possesses good flow while other batches' values range from 30.9 to 33.9 which possesses passable flow properties. The results of the angle of repose for all the formulations were summarized in Table 2.

Bulk density

The bulk density was determined to estimate the free-flowing property of the powder mixture. The bulk density of all formulations ranges from 0.588 to 0.714 g/ml. The results are summarized in Table 2.

Tapped density

Tapped density of all formulation were determined to analyze the powder blends for their free-flowing property. The tapped density of all the formulations ranges from 0.714 to 0.882 g/ml. The results are summarized in Table 2.

Compressibility index

The compressibility index was the simplest method to measure the free flow of the powder blends of all formulations. The ease with which material was induced to flow was given by the compressibility index of B1, B4, B7, and B8 were 17.5, 16.68, 15.12, and 17.64 which indicates good flowability while the value for B2, B3, B5, and B6 were 20.48, 20.4, 19.40 and 22.78 which indicates passable flow properties. The results of all formulations are summarized in Table 3.

Hausner's ratio

The Hausner's ratio was determined to assess the flow property of the powder blend. Hausner's ratio of powder blend of B7 was 1.17 which indicates good flow and values of B1, B2, B3, B4, B5, and B8 ranged from 1.21 to 1.25 which indicates fair flow properties while Hausner's ratio of B6 is 1.29 which indicates passable flow property. The results of all formulations are summarized in Table 2.

It was evident from the results of the pre-compression studies that the powder blends of all 8 formulations possess fair or passable flow properties, which were within the standard limits and were qualified for compression into tablets.

3.1.1 Evaluation of tablets

The tablets obtained after compression were evaluated on various parameters to determine their quality and to ensure that the resultant product meets all necessary criteria required for the oral dispersible tablets.

Table 3 Results of Post-Compression Evaluation Parameters

Evaluation Parameters	Formulation Code							
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**
Weight variation (n=20) (mg)	300.3±0.73	300.15±0.72	300.83±0.41	300.93±0.44	300.45±0.85	300.94±0.37	300.21±0.9	300.69±0.69
Hardness test (kg/cm^3) (n=10)	4.3±0.33	4.1±0.3	4.05±0.26	4.1±0.3	4.25±0.25	3.9±0.3	4.3±0.26	3.95±0.35
Friability (%)	0.7	0.69	0.67	0.89	0.722	0.67	0.76	0.53
Dissolution % release	92.35	85.49	86.62	90.74	88.12	92.94	83.51	89.35
Drug content uniformity	98.03	99.10	95	100.53	95.89	98.75	99.28	96.42
Disintegration ime(sec)	21	20.33	36.83	19.16	21	27.83	28	24.16
Dispersion time(sec)	41	44.3	93.3	40	44.3	48	49.6	46.6
Wetting time(sec)	32	33	79	15	19	20	26	22
Water absorption ratio	81.05	84.60	82.77	82.10	82.13	80.54	79.55	80.35

Weight variation

The weight variation test was carried out to ensure that the tablets of each formulation were of uniform weight, which in turn would indicate the uniform distribution of the contents of the powder blends of each formulation. The weight variation for tablets of all formulations was found to be within the US pharmacopeia limits of ±7.5%. The result indicates that all tablets of each formulation were of uniform weight and passed the test as per the US Pharmacopoeia range. The results are shown in Table 3.

Hardness

The hardness of tablets was carried out to determine their resistance to abrasion or breakage during transportation, storage, and handling before usage. The hardness for tablets of all the formulations was found in the range of 3.5 to 5 kg/cm^3. The results indicate that the tablets of all formulations have good hardness, which in turn protects them from mechanical damage. The results are summarized in Table 3.

Friability test

The friability test was carried out to ensure the mechanical strength of tablets to avoid the loss of the external surface of the tablets during the process of packing, handling, transit, and storage. Friability below 1% was an indication of good mechanical resistance. The results indicate that the friability for tablets of all formulations was below 1% and hence passed the test. The results are summarized in Table 3.

Disintegration time

The disintegration time was the time taken by the tablet to break down into small particles, in the presence of an aqueous medium. It varies with the type and concentration of the superdisintegrants incorporated in the formulation. Disintegration time is the prime criterion for oral dispersible tablets, which should be less than 3 minutes as per the standards. The disintegration time for formulations B1, B2, B3, B4, B5, B6, B7, and B8 was found to be 21, 20.33, 36.83, 19.16, 21, 27.83, 28 and 24.16 seconds respectively. The formulation B4 was disintegrated in the lowest time. It may be due to the use of the highest amount of crospovidone in formulation B4.

Drug content uniformity

The drug content of the tablets was estimated to ensure that all the tablets of a formulation contain the therapeutic dosage of the active ingredient for a particular dosage form. The drug contains tablets of all the formulations ranging from 95 to 100.5% i.e. meets the USP standard range of 85-115% which indicates that the contents for tablets were uniform and passed the test. The results are summarized in Table 3.

In vitro-dissolution studies

The dissolution studies were carried out to evaluate the release profile of the drug with the function of time. The superdisintegrants were added to the solid dosage formulations to enhance the disintegration time and thereby enhance the faster release of active drug from its dosage form, which ultimately enhances the rates of absorption and bioavailability of the drug. The desired quality of oral dispersible tablets was to have maximum release of therapeutic dose at a very minimal period. The maximum drug release at a period of 15 minutes was noted for all the formulations. The drug release for tablets of formulations B1, B4, B5, B6, and B8 was found to be above 88% in 15 minutes except for formulations B2, B3, and B7. It indicates the release rate of formulations with a high proportion of crospovidone incorporated was found to be high.

Dispersion time

The dispersion time of all formulations ranges from 40 seconds to 49.6 seconds except the dispersion time of formulation B3 with 93.3 seconds in which crospovidone was not used. It indicates that with a high proportion of crospovidone, the tablet disperses quickly.

Wetting time and Water absorption ratio

The wetting time and water absorption ratio indicates the capacity of the super disintegrants to absorb water and completely wet the tablet at the earliest time possible, which were the significant characteristics of oral dispersible tablets. The minimum wetting time and maximum water absorption ratio will enable faster disintegration of the tablets. The results are summarized in Table 3. The wetting time of formulation B4 had the lowest value of 15 seconds with the use of a high proportion of crospovidone. Formulation B2 had a maximum water absorption ratio of 84.60.

4 Conclusion

It was concluded that Nimesulide can be successfully formulated as oral dispersible tablets using various superdisintegrants in different concentrations by direct compression method. The formulation containing a high percentage of crospovidone as superdisintegrants was found to be more outstanding than other formulations in terms of disintegration time and rate of dissolution. All other studied parameters were found to be satisfactory for all formulations of Nimesulide. Oral dispersible tablet dosage form is a promising future for drug delivery with the advancement in pharmaceutical excipients such as superdisintegrants. More superdisintegrants can be further investigated with different excipients after the determination of the drug-excipients compatibility study. The optimized batch can be subjected to real-time and accelerated stability studies to determine the shelf life of the product. Comparison of similarity studies can be done on the formulation by using the brand drug available in the market.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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