Comparative Design and Evaluation of Nimesulide Dispersible TabletsUtilizing Natural and Synthetic Polymers

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Abstract:

Objectives: The aim of the present work was to prepare and evaluate dispersible tablets of Nimesulide with a view to enhancing patient compliance and minimizing the side effects.

Methodology: In this study, dispersible tablets of nimesulide were formulated by direct compression method using such as pectin of mango peel (Mangifera indica), Hibiscus rosa sinensis was used as natural disintegrants and crospovidone as a synthetic super disintegrant in different ratios. The prepared formulations were evaluated for hardness, friability, drug content, in vitro dispersion time, wetting time, water absorption ratio, in vitro drug release studies.

Results: Among all the formulations, the formulation (F4) mango peel pectin is the overall best formulation based on in vitro drug release studies. Stability studies on the formulations indicated that there are no significant changes in drug content.

Conclusion: From the above studies, it can be concluded that dispersible tablets of Nimesulide can be prepared using different natural super disintegrants for faster dispersion.

Keywords: Dispersible tablets, Nimesulide, Superdisintegrants, Hibiscus rosa sinensis, Mango peel pectin.

Introduction:

Oral drug delivery is a widely used route for administering medications due to its convenience, ease of administration, and high patient acceptance. It involves the delivery of drugs through the mouth, where they are absorbed into the bloodstream through the gastrointestinal (GI) tract.

However, the effectiveness of oral drug delivery depends on various factors, which includes the physicochemical properties of the drug, formulation, and the patient's GI physiology. One of the primary challenges in oral drug delivery is achieving adequate drug absorption. Many drugs have low solubility-y or stability in the acidic environment of the stomach, leading to poor absorption in the small intestine. To overcome this, various formulation strategies have been developed, such as using prodrugs, lipid-based formulations, and nanocarriers to enhance drug solubility and bioavailability.

Another challenge is achieving targeted drug delivery to particular regions of the GI tract. This is particularly important for drugs that are absorbed in such particular regions or have adverse effects on certain regions. To address this, various delivery systems, such as enteric coatings, pH-sensitive polymers, and macro nano particles, have been developed to control drug release and improve site-specific targeting. Tablets are a solid dosage form of medication that are designed to be taken orally. They are one of the most commonly used forms of medication and are widely used for their convenience, ease of use, and stability. Tablets are typically composed of active pharmaceutical ingredients (APIs) and other excipients, such as binders, fillers, and lubricants, which help to maintain the tablet's structural integrity and aid in the tablet's dissolution and absorption.

Tablets can be designed to release their active ingredients in different ways. Immediate-release tablets release their active ingredients quickly, whereas sustained-release or extended-release tablets release their active ingredients for a longer duration, often through a specialized coating or formulation. [1,2]

Dispersible Tablet:

According to European Pharmacopoeia Dispersible tablets are a type of tablet that dissolves in water or other liquids to form a homogeneous solution or suspension. These tablets are designed to disintegrate quickly when added to a liquid, allowing the active ingredient to be rapidly released and absorbed into the body.[3]

Nimesulide is chemically N-(4-nitro-2- phenoxyphenyl) methane sulphonamide (Figure 1). It belongs to selective COX-2 inhibitors, with a potent analgesic activity. The pKa values of Nimesulide ranges from 5.9- 6.56. It is freely soluble in organic polar solvents, but is sparingly soluble in aqueous solution (0.01mg/ml) and so has low bioavailability. It belongs to BCS class II drugs. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods such as micronization, complexation and solid

dispersion. The rate of dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution. Nimesulide is used for painful inflammatory conditions as antipyretic, analgesic, antiinflammatory agent.

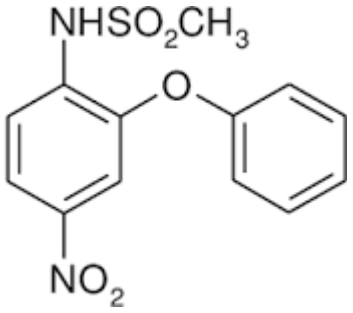

Fig. 1 N-(4-nitro-2-phenoxyphenyl) methanesul fonamide.

Fast-Dissolving Tablets Containing Nimesulide Micropellets were formulated and evaluated. Nimesulide fast-dispersible tablets have been prepared by direct compression method. Fast disintegrating tablet is solid unit dosage form that is placed in mouth, pharynx and esophagus as saliva passes down into stomach so bioavailability is greater. Mouth dissolving tablets of nimesulide were formulated using vacuum drying technique. Theconcept of fast dissolving tablets has emerged from the desire to provide patients with a more convenient means of taking their medication. polyvinylpyrrolidone (Polyplasdone) etc. These provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.

The benefits of this approach include: the drug gets faster into suspension so absorption is quicker and ultimate onset of clinical effect. Hence, a fast-dissolving dosage form may be particularly suitable for conditions such as fever, pain, Inflammation etc. where a fast onset of clinical effect is required. This fast-disintegrating technology of Nimesulide is convenient for administrationand 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 be avoided. These dosage forms dissolve in the oral cavity within a minute without the need of water or chewing [4]

Materials and methods

Drug and reagents: Nimesulide as obtained as gift sample from Swapnroop drugs& pharmaceuticals Aurangabad Maharashtra, India crospovidone, microcrystalline cellulose, D-

mannitol, Talc and magnesium stearate of analytical grade was procured from space chemicals Nashik, India.

Instruments: Shimadzu UV-1800 UV/VIS spectrophotometer, USP XXIV dissolution testing apparatus II (paddle method), electronic balance (Shimadzu, AX200, Japan), Pfizer hardness tester and the Roche friabilator.

Methods:

All the ingredients were passed through sieve #60. The drug, diluents, superdisintegrant and sweetener were mixed. All the above ingredients were properly mixed together (in a poly-bag). Talc and magnesium stearate were passed through sieve #80, mixed, and blended with initial mixture in a poly-bag. The ingredients were directly compressible. The powder blend was compressed into single punch tablet machine according to the formulations tabulated in Table 1. Superdisintegrant Mango peel pectin, Hibiscus rosa sinensis mucilage and crospovidone were used in varying concentration ranging from 4 mg, 8mg, 16 mg were used to prepare the tablets.

Preparation of mango peel powder:

Peel was removed from fully ripe mango. The peels were cut into small pieces, washed with tap water, blanched with hot water at 95 °C for 10 min, drained and left cooled at room temperature, prior to drying at 60 ± 1 °C until the moisture content of 4%–6% was reached. The dried peel was ground to a fine powder in a high-speed food processor and passed through a sieve.

Extraction of mango peel pectin:

Twenty grams of mango peel powder was suspended in 600 mL of diluted acidic solution (distilled H_2O adjusted to pH 1.5 with 2 M HCl) and soaked for 20 min at room temperature. The slurry was heated in a microwave oven followed by recooling to room temperature. The solution was filtered and pressed manually using a nylon cloth. The filtrates were centrifuged at 5000× *g* for 20 min to eliminate any remaining coarse particles. Pectin was precipitated from this clear supernatant by adding the same volumes of ethanol (95%); mixed and stored in a refrigerator at 4 °C for 30 min. The separation was achieved by vacuum filtration.

The obtained pectin was dried in a hot air-oven at 40 °C until constant weight. [5-8]

Extraction of *Hibiscus rosa sinensis*:

Hibiscus rosasinensis (China rose) was procured from the local area. Collected leaves were carefully washed and dried under shade for 24 h and then further dried in the oven at 30-40°C. The size was reduced with the help of a grinder. Powdered leaves were passed through sieve no. #22 and then used for further evaluation.

Extraction of Mucilage:

Powdered leaves of Hibiscus rosasinensis were used for the extraction of mucilage. The powdered leaves are placed in 1000 ml beaker containing 500ml of distilled water and allowed it to boil for at least 3-4 h with continuous stirring and heating at 60°C for sufficient release of mucilage in water. The concentrated solution was then filtered through muslin cloth in order to separate marc from the filtrate and refrigerated for cooling (3-4°C). To the extract, acetone was added to the quantity, three times the volume of filtrate for the precipitation of mucilage to occur. The precipitated mucilage was washed with acetone and then collected through filtration by muslin cloth. Mucilage was further dried in a hot air oven at a temperature less than 40°C. The obtained dried mucilage was grinded and passed through sieve #80 and finally stored in airtight container. [9]

Determination of λ_{max}:

Derivation of drug spectrum: Five mg of Nimesulide was accurately weighed and dissolved in 100 ml of ethanol to obtain a stock solution of concentration 50 µg/ml. The solution was analyzed in UV spectrophotometer using ethanol as a blank. The λmax (peak point denoting maximum wavelength) of this stock solution and the absorbance at that point was noted from the formed wavelength vs absorbance graph. The standard λmax for Nimesulide should be between 296-299 nm.

Preparation of calibration curve of Nimesulide in Ethanol: From the previously prepared stock solution of 50 µg/ml, dilutions of concentrations 10, 20, 30,40 and 50 µg/ml were prepared in ethanol. The absorbances of dilutions from 10-50 µg/ml concentrations were measured in UV spectrophotometer at the λmax obtained from the drug spectrum using ethanol as blank. The graph was plotted between concentration (x-axis) and corresponding absorbance values (y-axis).

Pre-compression Studies: Pre-compression or pre-formulation studies were performed on all batches of drug-excipient blends. Studies performed involved powder flow properties (angle

of repose, bulk density, tapped density, Carr's index, and Hausner's ratio) which are discussed as follows: -

Table 1: Formulation used in the preparation of tablet

Ingredients used	**Formulation code and quantity (mg)**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Nimesulide	100	100	100	100	100	100	100	100	100
Hibiscus rosa sinensis	4	8	16	-	-	-	-	-	-
Mango peel pectin	-	-	-	4	8	16	-	-	-
Crospovidone	-	-	-	-	-	-	4	8	16
Methyl crystalline cellulose	50	50	50	50	50	50	50	50	50
Talc	4	4	4	4	4	4	4	4	4
Mannitol	36	32	24	36	32	24	36	32	24
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight of each tablet = 200 mg									

Angle of repose: The angle of repose for the powder blends of all batches was found to exhibit good flow properties as all the values (Ɵ i.e., angle of repose) were in the range 30-35º. The values obtained are given in Table-2 along with bulk density, tapped density, Hausner's ratio, and Carr's index values.

Bulk Density, Tapped Density, Hausner's Ratio, and Carr's Compressibility Index: Carr's compressibility index and Hausner's ratio were calculated from the values obtained from bulk and tapped densities. Hausner's ratio was found to be less than 1.18 for all batches of powder blends and the Carr's index was found to be below 15% for all batches of powder blends, hence, the flow property was good. The results predicted in the flow property studies are given in Table-2 [10-17]

Table 2: Precompression studies of Nimesulide

Formulation code	Angle of repose (º)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
F1	31.02±0.7	0.758±0.03	0.868±0.01	12.67±0.3	1.15±0.1
F2	32.13±0.3	0.755±0.01	0.850±0.03	11.17±0.7	1.13±0.4
F3	32.32±0.4	0.689±0.03	0.768±0.03	10.29±0.2	1.12±0.6
F4	30.88±0.2	0.747±0.02	0.832±0.02	10.21±0.1	1.11±0.3
F5	33.77±0.3	0.802±0.05	0.904±0.04	11.28±0.6	1.13±0.7
F6	32.24±0.8	0.751±0.03	0.847±0.06	11.44±0.9	1.13±0.5
F7	30.61±0.6	0.820±0.01	0.917±0.06	10.58±0.6	1.12±0.4
F8	30.54±0.5	0.774±0.06	0.881±0.01	12.15±0.7	1.14±0.3
F9	31.14±0.1	0.802±0.03	0.832±0.02	10.21±0.4	1.12±0.2

Post-compression Studies:

Organoleptic characters: The tablets from all the batches were evaluated for their organoleptic characters like appearance, color, odor, and shape by simply through observation and sensory capabilities.

Thickness and diameter: The thickness and diameter of tablets were measured using vernier calipers. Five tablets were taken from each batch, calculated average, and results were expressed in millimetres.

Hardness: The hardness of the tablets was determined using Monsanto Hardness tester. Three tablets were randomly picked from each formulation and average values were noted. Hardness values are expressed in Kg/cm^2.

Friability: The friability of the tablet was determined using the Roche friabilator as per the standards of I.P. The Friabilator was operated at 25 rpm for 4 minutes. The % Friability (F) of tablets from every batch was then calculated as follows:

$F = [(Wi-Wf / Wi) \times 100] \%$

According to USP, IP and BP, friability should not be more than 1.0 %

Table: 3 Post compression parameters of formulated tablets

Formulation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	202±1.32	199±1.19	198±2.33	201±1.56	200±2.27	201±1.54	202±1.36	200±1.53	198±2.33
Thickness(mm)	2.25±0.12	2.61±0.31	2.68±0.24	2.50±0.19	2.23±0.04	2.56±0.07	2.22±0.08	2.69±0.06	2.51±0.04
Hardness (kg/cm^2)	3.0±0.14	3.2±0.15	3.6±0.35	3.7±0.46	2.5±0.19	3.2±0.1	3.7±0.4	3.0±0.1	3.7±0.4
Friability (%)	0.54±0.018	0.48±0.028	0.43±0.028	0.52±0.058	0.49±0.022	0.57±0.086	0.63±0.022	0.39±0.051	0.32±0.014
Wetting time	47±1.20	46±0.90	49±2.70	38±1.35	79±2.20	46±0.9	47±1.2	79±2.2	47±1.2
Water absorption ratio (%)	90.81±1.29	92.47±1.26	91.17±1.24	93.58±1.31	57.81±2.26	91.17±2.38	90.82±1.17	90.88±1.08	92.17±1.25
Disintegration time (sec)	36±2.8	35±3.2	34±2.4	28±4.4	69±2.5	35±2.7	36±2.5	36±2.4	69±2.5

Content of active ingredient: Five tablets from each batch were weighed and crushed with a pestle in a mortar. The fine powder was weighed to obtain 100mg and transferred to 250 ml conical flask containing 100 ml of ethanol buffer stirred for 45 min in a sonicator. The solution was filtered dilutions were prepared and analyzed by UV spectrophotometer at 296 nm and drug content was determined. As per I.P., out of 10 tablets, not more than one tablet should deviate outside range 90-110% and none outside 85-115% of average value.

Weight variation: Twenty tablets (pre-weighed) were selected from each batch, individually weighed, and then average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P., not more than two of individual weights should deviate from average weight by more than 5% and none by more than twice that percentage.

% Deviation = [(wt. of each tab.- avg. wt. of tabs) / avg. wt. of tabs) x 100]

Uniformity of dispersion: Two tablets were placed in 100 ml of water and stirred gently until completely dispersed. The dispersion obtained was passed through a sieve screen with a

nominal mesh aperture of 710 µm (sieve number 22). The tablets were considered to pass the test if no residue remained on the screen.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of water. 3 tablets from each batch were put on the tissue paper and allowed to wet completely. The wetted tablets were then reweighed. The water absorption ratio, R was determined using the following formula: -

$$R = 100\ (Wa - Wb)/Wb$$

Wa = wt. of tablet after water absorption and Wb = wt. of tablet before water absorption.

Wetting time: A piece of tissue paper (12cm x 10cm) folded twice was placed in a Petri dish (6.5 cm internal diameter) containing 10 ml of water containing Eosin, a water-soluble dye, was added to petri dish. 3 Tablets from each batch were carefully placed separately on the surface of the tissue paper and allowed to wet completely. The time required for water to reach upper surface of the tablets was noted as wetting time.

Wetting volume: Three tablets from each batch were placed in the centre of the petri dish and with the help of a 5 ml pipette, distilled water was added dropwise on the tablets. The volume required to completely disintegrate the tablets was noted as the wetting volume. The average of three values was calculated.

In-vitro dispersion time: Three tablets from each formulation were randomly selected and dispersion time study was performed. Tablets were separately added to 10 ml of water and time required for complete dispersion was measured.

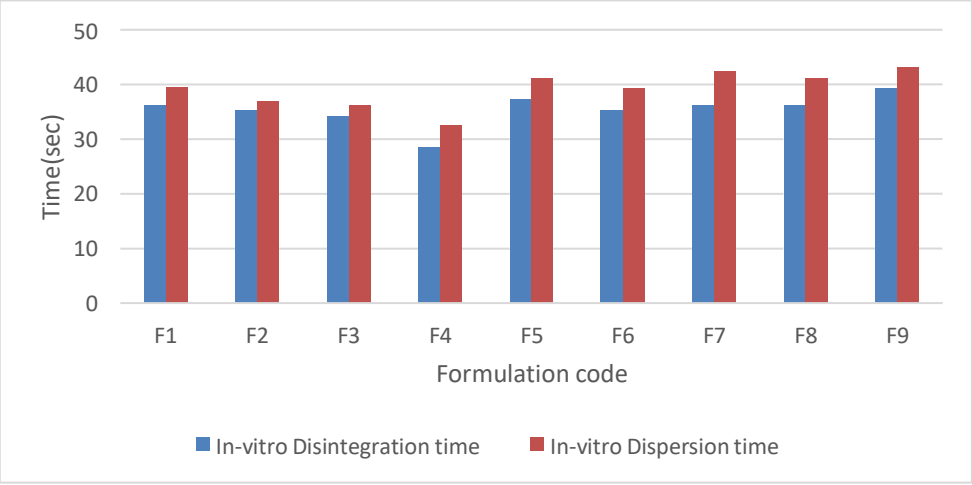

Fig.2 In-vitro Disintegration and In-vitro Dispersion time of Nimesulide

Table: 4 Dissolution data of all batch

Formulation code	Time (Min)					
	2	4	6	8	10	12
F1	40.16±1.7	55.25±0.3	60.55±1.5	73.12±1.6	80.27±1.8	85.88±1.9
F2	31.16±1.7	46.24±0.6	52.58±1.8	65.15±1.5	69.15±1.5	87.25±1.8
F3	33.15±1.7	47.26±0.6	50.56±1.8	69.13±1.5	79.28±1.8	88.29±1.2
F4	42.12±1.5	55.24±0.5	62.53±1.4	73.17±1.5	81.29±1.8	95.23±1.7
F5	43.15±1.7	57.26±0.6	60.56±1.8	79.13±1.5	88.29±1.2	92.16±1.7
F6	49.67±1.9	65.82±1.8	71.65±1.5	87.31±0.5	89.88±0.3	90.67±1.2
F7	47.10±0.6	52.82±1.3	64.54±1.9	75.12±1.6	79.37±1.4	89.34±1.7
F8	35.10±0.2	46.82±1.1	58.54±1.9	67.12±1.2	78.37±1.4	89.34±1.7
F9	47.10±0.2	58.82±1.1	69.54±1.9	72.12±1.2	77.37±1.4	88.34±1.7

In-vitro disintegration time: The disintegration time of the tablet was measured in water (37 ± 2^0 C) according to USP Disintegration test apparatus. Six tablets from each batch were placed and one litre of distilled water was used as the disintegration medium. The time required to obtain complete disintegration of all six tablets was noted. Ideally, all tablets are required to disintegrate within 3 minutes. If more than one tablet fails the test, then the study is performed again for 12 tablets. Not more than 2 tablets out of 18 tablets should deviate from the standard disintegration test limits.

In-vitro dissolution studies: The release rate of Nimesulide tablets was determined using USP Dissolution type II apparatus (paddle type). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium previously maintained at 37 ± 0.5ºC and at 50 rpm. After completion of each specified time interval, aliquots of 5ml were withdrawn from the dissolution media and the samples were replaced with fresh dissolution medium. Samples were filtered and dilutions were prepared and analyzed for absorbance spectrophotometrically at 296 nm for the drug content against the respective buffer blank.

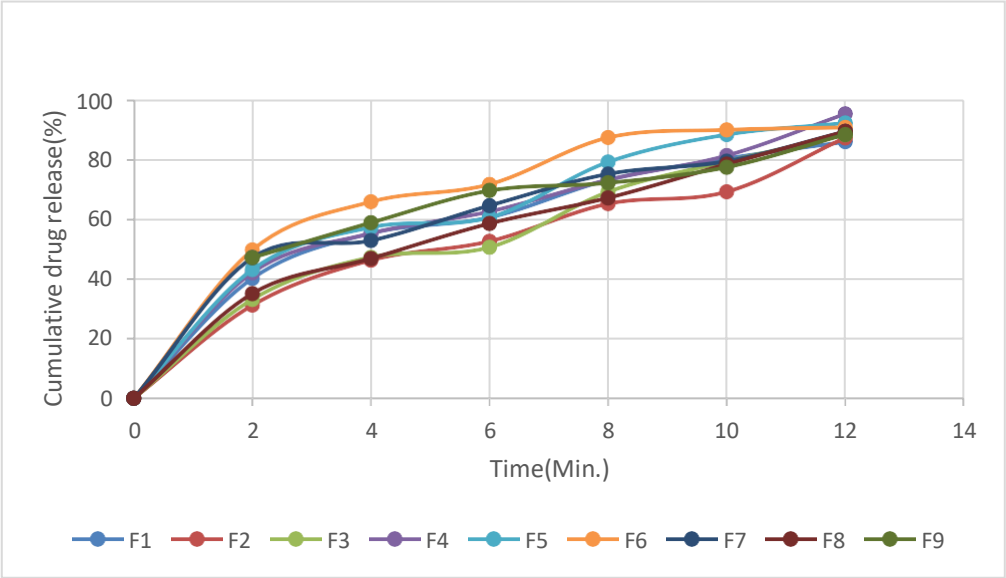

Fig.3 Comparative In-vitro Dissolution profile of all formulation

Results:

The use of superdisintegrants for the preparation of Dispersible 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 and disintegration time (Table 3). Using the same excipients, the tablets were prepared, without these superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb alarge 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. The prepared dispersible tablet gets dispersed quickly and releases the drug early as compared to its formulated conventional tablet. Fig. 3 show the cumulative percentage of Nimesulide released from formulated tablet with different concentration of Hibiscus Rosa Sinensis, Mango peel pectin and crospovidone. It is clear that the dissolution of Nimesulide has improved considerably in formulation F4 as compared to formulation F1, F2, F3, F5, F6, F7, F8 and F9. The tablets of the batch F4 showed good dissolution efficiency and rapid dissolution.

Conclusion:

In the present study the superdisintegrant property of Mango peel pectin has been explored. The tablets disintegrated much faster and more consistently when mango peel pectin *was* used as a superdisintegrant compared with Hibiscus rosa sinensis and crospovidone. It could be

concluded that Mango peel pectin could be used as natural super disintegrant in the formulation of dispersible tablets.

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