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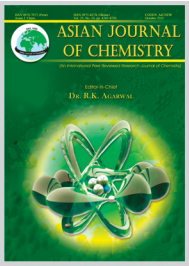

Formulation Development of Nimesulide Tablets by Wet Granulation and Direct Compression Methods Employing Starch Citrate

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Nimesulide, a widely prescribed antiinflammatory analgesic drug belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor solubility and dissolution rate. The objective of the present study is to develop nimesulide rapidly dissolving tablet formulations by wet granulation and direct compression methods employing starch citrate, a new modified starch. As per FDA guidelines on biowaivers, drug products containing weakly acidic BCS class II drugs with a dissolution of > 85 % in 0.5 h are eligible for biowaiver. Hence a dissolution of > 85 % in 0.5 h is taken as target dissolution to achieve in the formulation development of nimesulide tablets. Starch citrate prepared by reacting potato starch with citric acid at elevated temperatures was insoluble in water and has good swelling (1500 %) property without pasting or gelling when heated in water. In the micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of starch citrate prepared. All the physical properties studied indicated that starch citrate is a promising pharmaceutical excipient in tablets. Nimesulide rapidly dissolving tablets with >85 % dissolution in 0.5 h could be formulated employing starch citrate as directly compressible vehicle by direct compression method (BF3) and also employing nimesulide-starch citrate (1:2) solid dispersion by wet granulation method (BF4). Formulations BF3 and BF4 respectively gave 90.25 % and 99.73 % dissolution in 0.5 h fulfilling the target dissolution requirement for biowaiver.

Key Words: Nimesulide tablets, Starch citrate, Direct compression, Solid dispersion.

INTRODUCTION

Nimesulide, a widely prescribed anti inflammatory analgesic drug belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor solubility and dissolution rate. Achieving higher dissolution rate is a key factor in its formulation development especially solid dosage forms like tablets. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs, which exhibit high solubility, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersions in water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Wing[2] has reported reaction of starch with citric acid to yield starch citrate, a biodegradable product possessing high ion-exchange capacity. Wepner *et al.*[3] have described a process for the synthesis of citrate derivatives of starch. Starch citrate is investigated as resistant starch in food industry. We reported[4] starch citrate, a new modified starch, as an efficient carrier in solid dispersions for enhancing the dissolution rate of poorly soluble drugs.

Direct compression is the preferred method for the preparation of tablets[5]. It offers several advantages[6,7]. Notable among them are (i) It is economical compared to wet granulation since it requires fewer unit operations (ii) More suitable for moisture and heat sensitive APIs since it eliminates wetting and drying steps (iii) Changes in dissolution profiles are less likely to occur in tablets made by direct compression method on storage than in those made from granulations[8]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms[9]. Disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. Starch citrate, a new modified starch, was also reported[10] to be a promising directly compressible vehicle for the preparation of tablets by direct compression method.

The objective of the present study is to develop nimesulide rapidly dissolving tablet formulations by wet granulation and direct compression methods employing starch citrate, a new modified starch. As per FDA guidelines[11] on biowaivers, drug products containing weakly acidic BCS class II drugs with a dissolution of > 85 % in 0.5 h in phosphate buffer pH 6.8-7.4 are eligible for biowaiver. Hence a dissolution of > 85 % in 0.5 h is taken as target dissolution to achieve in the formulation development of nimesulide tablets. In the present study starch citrate was prepared, characterized and used in the formulation development of nimesulide tablets with > 85 % dissolution in 0.5 h.

EXPERIMENTAL

Nimesulide was gift sample from M/s Natco Pharma Pvt. Ltd, Hyderabad., Starch citrate was prepared in the laboratory, Citric acid (Qualigens), Dichloromethane (Qualigens), potato starch (S.D. Fine Chemicals), Methanol (S.D. Fine Chemicals), crospovidone lactose, talc, magnesium stearate and acacia were procured from commercial sources.

Preparation of starch citrate: Citric acid (40 g) was dissolved in 100 mL of water and pH of the solution was then adjusted to 3.5 with 10 M sodium hydroxide. Starch citrate was prepared based on the method of Klaushfer *et al.*[12] with some modifications. Citric acid (20 g) was dissolved in 20 mL of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made upto 50 mL by adding water. The citric acid solution (50 mL) was mixed with 50 g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28 ºC). The tray was then placed in forced air oven and dried at 60 ºC for 6 h. The mixture obtained was ground and further dried in a forced air oven at 130 ºC for 2 h. The dry mixture was repeatedly washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50 ºC to remove the water/ moisture completely. The product obtained was ground and sized.

Characterization of starch citrate: The starch citrate prepared was evaluated for the following:

Solubility: Solubility of starch citrate was tested in water, aqueous buffers of pH 1.2, 4.5 and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.

pH: The pH of a 1 % w/v slurry was measured.

Melting point: Melting point was determined by using melting point apparatus.

Viscosity: Viscosity of 1 % dispersion in water was measured using Ostwald viscometer.

Swelling index: Starch citrate (200 mg) was added to 10 mL of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes were allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$S.I.(\%) = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100$$

Test for gelling property: The gelling property (gelatinization) of the starch and starch citrate prepared was evaluated by heating a 7 % w/v dispersion of each in water at 100 ºC for 0.5 h.

Moisture absorption: The hygroscopic nature of starch citrate was evaluated by moisture absorption studies in a closed desiccator at 84 % relative humidity and room temperature.

Particle size: Particle size analysis was done by sieving using standard sieves.

Density: Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Bulk density[13]: Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

Angle of repose[14]: Angle of repose was measured by fixed funnel method.

Compressibility index[15]: Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tapings of a sample of starch citrate in a measuring cylinder. Compressibility index was calculated using the following equation.

$$\text{Compressibility index (CI)} = \frac{V_0 - V}{V_0} \times 100$$

Estimation of nimesulide: An UV spectrophotometric method based on the measurement of absorbance at 230 nm in phosphate buffer pH 7.4 was used for estimation of nimesulide. The method obeyed Beer- Lambert's law in the concentration range of 0-10 µm/mL. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.65 % and 1.4 % respectively. No interference from excipients used was observed.

Formulation of nimesulide tablets: Four different batches of tablets each containing 50 mg of nimesulide were formulated and evaluated. The formulae of tablets prepared are given in Table-1. In batch BF1 the tablets were formulated employing nimesulide alone and dicalcium phosphate as diluent and prepared by wet granulation method using water as granulating fluid. In batch BF2 the tablets were formulated employing nimesulide alone and lactose as diluent and prepared by wet granulation method using water as granulating fluid. In batch BF3 the tablets were formulated employing starch citrate as directly compressible vehicle and prepared by direct compression method. In batch BF4 the tablets were formulated employing nimesulide-starch citrate (1:2) solid dispersion and the tablets were prepared by wet granulation method employing water as granulating fluid. In all the batches acacia (2 %) as binder, crospovidone (5 %) as disintegrant, talc (2 %) and magnesium stearate (2 %) as lubricants were used. In each batch 100 tablets were prepared.

Preparation of solid dispersions of nimesulide in starch citrate: Solid dispersions of nimesulide and starch citrate were prepared in 1:2 ratio of drug: carrier by solvent evaporation method. Nimesulide (1 g) was dissolved in dichloromethane (10 mL) in a dry mortar to get a clear solution. Starch citrate (2 g) was then added and mixed. The thick slurry was kneaded for 15 min for complete evaporation of dichloromethane and then dried at 55 ºC until dry. The dried mass was pulverized and sieved through mesh no. 100.

Preparation of nimesulide tablets by wet granulation method: Compressed tablets each containing 50 mg of

nimesulide were prepared by wet granulation method employing nimesulide alone(BF1 and BF2) and its solid dispersions in starch citrate (BF4). The required quantities of nimesulide or nimesulide-starch citrate (1:2) solid dispersion, diluent (DCP or lactose) and acacia were mixed thoroughly in mortar by following geometric dilution technique. The granulating fluid, water was added and mixed thoroughly to form dough mass. The mass was passed through mesh No 12 to obtain wet granules. The wet granules were dried at 60 ºC for 2 h. The dried granules was passed through mesh No 16 to break the aggregates. Crospovidone and the lubricants (TALC and magnesium stearate) were passed through mesh No 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a Cadmach 16-station rotary tablet punching machine (M/s Cadmach Engineering Co. Pvt. Ltd., Mumbai) to a hardness of 6 kg/cm^2 using 9 mm concave punches.

TABLE-1
FORMULAE OF NIMESULIDE TABLETS FORMULATED EMPLOYING STARCH CITRATE BY WET GRANULATION AND DIRECT COMPRESSION METHODS

Ingredient (mg/Tablet)	Formulation			
	BF1	BF2	BF3	BF4
Nimesulide	50	50	50	-
Starch citrate	-	-	140	-
Nimesulide-starch citrate (1:2) solid dispersion	-	-	-	150
DCP	145.8	-	-	45.8
Lactose	-	45.8	5.8	-
Crospovidone	11	11	11	11
Acacia	4.4	4.4	4.4	4.4
Talc	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4
Total weight of tablet (mg)	220	220	220	220

BF1: tablets formulated employing nimesulide alone and using DCP as diluent; BF2: tablets formulated employing nimesulide alone and using lactose as diluent; BF3: Nimesulide tablets formulated by direct compression employing starch citrate as DCV. BF4: Nimesulide tablets formulated employing nimesulide-starch citrate (1:2) solid dispersion

Preparation of nimesulide tablets by direct compression method: Compressed tablets each containing 50 mg of nimesulide were prepared by direct compression method (BF3) employing starch concave punches as directly compressible vehicle. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd) to a hardness of 6 kg/cm^2 using 9 mm concave punches. In each case 100 tablets were compressed.

Evaluation of tablets: All the tablets prepared were evaluated for content of active ingredients, hardness, friability, disintegration time and dissolution rate as per official (IP) methods. Hardness of tablets was tested using Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time was determined in a Labindia tablet disintegration test machine (Model: DT 1000) using water as test fluid.

Estimation of drug content in the tablets: From each batch of tablets prepared 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of drug was taken for assay into a 100 mL conical flask and extracted with 3 × 20 mL quantities of methanol. The methanolic extracts were filtered and collected into a 100 mL volumetric flask and the volume was made upto 100 mL with methanol. The solution was then suitably diluted with phosphate buffer of pH 7.4. The absorbance of the solution was measured at 230 nm. Drug content of the tablets was calculated using the standard calibration curve.

Dissolution rate study: Dissolution rate of nimesulide from the tablets prepared was studied in phosphate buffer pH 7.4 (900 mL) employing USP 8 station dissolution rate test apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. One tablet containing 50 mg of nimesulide was used in each test. A temperature 37+1 ºC was maintained throughout. Samples of dissolution medium (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals and assayed for nimesulide at 230 nm. For comparison, dissolution of nimesulide from one commercial brand was also studied. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Starch citrate was prepared by reacting starch with citric acid at elevated temperatures. When citric acid is heated, it will dehydrate to yield an anhydride. The citric anhydride can then react with starch to from starch citrate. The reactions involved are shown in Fig. 1. Starch citrate prepared was found to be white, crystalline, non hygroscopic powder and can easily be ground to different sizes. Powder that passes through mesh no.80 and retained on mesh no.120 was collected. This powder has an average particle size of 152 µm. The starch citrate prepared was characterized by determining various physical properties. The properties of starch citrate are summarized in Table-2.

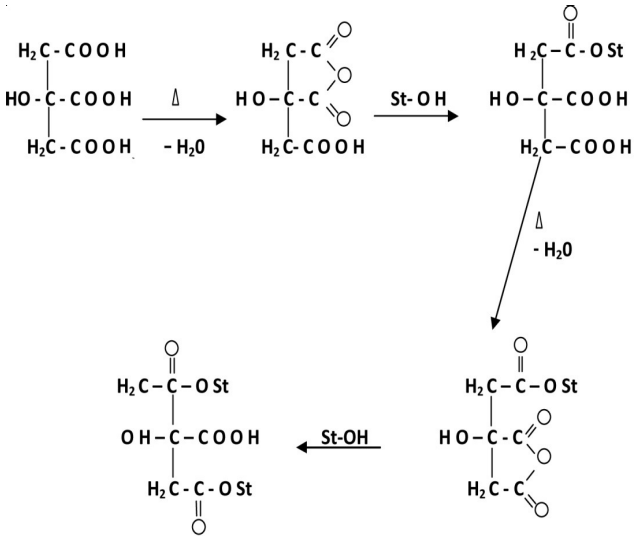

Fig. 1. Starch-citric acid reaction

When tested for m.p. it was charred at 220 ºC. Starch citrate prepared was insoluble in water, aqueous fluids of acidic and alkaline pH and several organic solvents tested. In water it exhibited good swelling (1500 %). No gelling/pasting was observed with starch citrate when its aqueous dispersion was heated at 100 ºC for 0.5 h, where as potato starch formed a

paste/gel during the above heat treatment. In the micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of starch citrate prepared. All the physical properties studied indicated that starch citrate is a promising pharmaceutical excipient in tablets. We have earlier reported[4,10] starch citrate as an efficient carrier[4] for solid dispersions to enhance dissolution rate of poorly soluble drugs and also as a promising directly compressible vehicle[10].

TABLE-2
PHYSICAL PROPERTIES OF THE STARCH CITRATE

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1 % w/v aqueous dispersion)	7.72
Melting point	Charred at 210 ºC
Viscosity (1 % w/v aqueous dispersion)	1.01 cps
Swelling index	1500
Gelling property	No gelling and the swollen particles of starch citrate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
Moisture absorption	4.5 %
Particle size	152 µm (80/120 mesh)
Density	0.645 g/cc
Bulk density	0.834 g/cc
Angle of repose	21.04º
Compressibility index	8.81 %

Four different batches of nimesulide tablets were formulated and prepared by wet granulation and direct compression methods as per the formulae given in Table-1. The physical properties of the prepared tablets are summarized in Table-3. All the nimesulide tablets prepared were found to contain the nimesulide with in 100 ± 2 % of the labeled claim. Hardness of the tablets was in the range 6-8 Kg/sq cm. Percentage weight loss in the friability test was less than 0.68 % in all the cases. Tablets formulated employing starch citrate (BF3 and BF4) disintegrated rapidly within 2-10 min. Tablets formulated employing nimesulide alone (BF1 and BF2) disintegrated within 5-6 min. All the four batches of tablets prepared fulfilled the official (IP) specification for weight variation. As such all the nimesulide tablets prepared were of good quality with regard to drug content, friability, hardness and disintegration time and fulfilled the official (IP) specifications of uncoated tablets.

Dissolution rate of nimesulide tablets prepared and one commercial brand was studied in phosphate buffer of pH 7.4. The dissolution profiles of the tablets prepared are shown in Fig. 2. The dissolution parameters of the prepared tablets are given in Table-4. Dissolution of nimesulide from all the tablets prepared followed first order kinetics with correlation coefficient 'R' values > 0.912. Dissolution efficiency (DE_{30}) values were calculated as described by Khan[16]. All the dissolution parameters (PD_{30}, T_{50}, DE_{30}, K_1) indicated rapid and higher dissolution of nimesulide from tablets formulated employing starch citrate as directly compressible vehicle (BF3) and nimesulide-starch citrate (1:2) solid dispersion (BF4) when

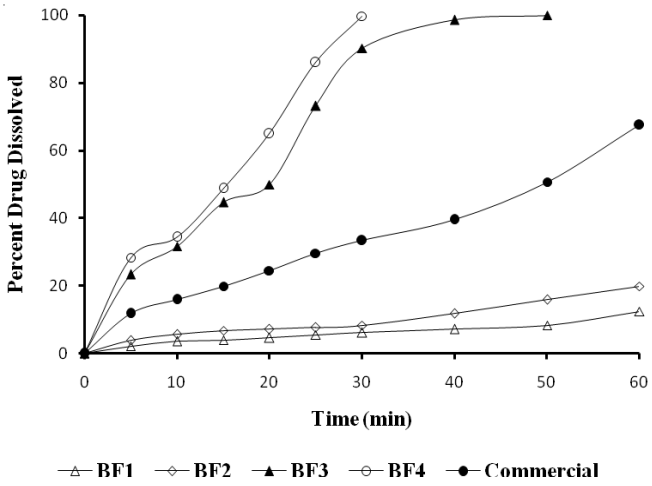

Fig. 2. Dissolution profiles of nimesulide tablets formulated employing starch citrate by wet granulation and direct compression methods

TABLE-3
DRUG CONTENT, HARDNESS, FRIABILITY, DISINTEGRATION TIME AND WEIGHT VARIATION OF NIMESULIDE TABLETS FORMULATED EMPLOYING STARCH CITRATE BY WET GRANULATION AND DIRECT COMPRESSION METHODS

Formulation	Drug content (mg/tab)	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration time (min-sec)	Weight variation (maximum % deviation)
BF1	49.1	7.0	0.68	4-30	1.5
BF2	49.5	8.0	0.25	5-10	2.5
BF3	49.0	8.0	0.48	2-10	1.8
BF4	50.15	8.0	0.42	1-55	1.2
Commercial	51.0	6.0	0.88	5-30	-

TABLE 4
DISSOLUTION PARAMETERS OF NIMESULIDE TABLETS FORMULATED EMPLOYING STARCH CITRATE BY WET GRANULATION AND DIRECT COMPRESSION METHODS

Formulation	PD_{30} (%)	T_{50} (min)	DE_{30} (%)	Increase in DE_{30} (No of folds)	K_1 (min^{-1})	Increase in K_1 (No of folds)
BF1	6.16	> 60	3.79	-	0.0018	-
BF2	8.24	> 60	5.86	1.55	0.0032	1.76
BF3	90.25	20.0	44.63	11.78	0.132	72.02
BF4	99.73	16.0	52.05	13.74	0.154	84.79
Commercial	33.34	50.0	19.72	5.20	0.012	6.57

PD_{30} : percent dissolved in 30 min; T_{50}: time for 50 % dissolution; DE_{30}: dissolution efficiency upto 30 min; K_1: first order dissolution rate

compared to tablets formulated employing nimesulide alone (BF1 and BF2) and commercial brand tested. Tablets formulated employing lactose as diluent (BF2) gave relatively higher dissolution rate and DE_{30} values when compared to those formulated employing DCP as diluent (BF1).

Tablets formulated employing starch citrate as directly compressible vehicle (BF3) and nimesulide-starch citrate (1:2) solid dispersion (BF4) gave much higher dissolution rates and DE_{30} values when compared to formulation BF1 (control). A 72.02 and 84.79 fold increase in the dissolution rate (K_1) was observed with formulations BF3 and BF4 respectively when compared to formulation BF1. A 2.14 and 4.82 fold increase in the dissolution rate (K_1) was observed with these formulations when compared to commercial formulation. Formulations BF3 and BF4 respectively gave 90.25 % and 99.73 % dissolution in 0.5 h fulfilling the target dissolution requirement for biowaiver. Formulations BF1, BF2 and commercial brand could not fulfill the target dissolution requirement.

Conclusion

Starch citrate prepared by reacting potato starch with citric acid at elevated temperatures was insoluble in water and has good swelling (1500 %) property without pasting or gelling when heated in water. In the micromeritic evaluation, the angle of repose and compressibility index values revealed the excellent flow characteristic of starch citrate prepared. All the physical properties studied indicated that starch citrate is a promising pharmaceutical excipient in tablets. Nimesulide rapidly dissolving tablets with >85 % dissolution in 0.5 h could be formulated employing starch citrate as directly compressible vehicle by direct compression method (BF3) and also employing nimesulide-starch citrate (1:2) solid dispersion by wet granulation method (BF4). Formulations BF3 and BF4 respectively gave 90.25 % and 99.73 % dissolution in 0.5 h fulfilling the target dissolution requirement for biowaiver.

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