Research Article

FORMULATION DEVELOPMENT OF ACECLOFENAC TABLETS BY WET GRANULATION AND DIRECT COMPRESSION METHODS EMPLOYING STARCH PHOSPHATE

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ABSTRACT

Aceclofenac, 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. The objective of the present study is to develop aceclofenac rapidly dissolving tablet formulations by wet granulation and direct compression methods employing starch phosphate, a new modified starch. As per FDA guidelines on biowaivers, drug products containing weakly acidic BCS class II drugs with dissolution of > 85% in 30 min are eligible for biowaiver. Hence a dissolution of > 85% in 30 min is taken as target dissolution to achieve in the formulation development of aceclofenac tablets. Starch phosphate prepared by reacting potato starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures was insoluble in water and has good swelling (400%) 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 phosphate prepared. All the physical properties studied indicated that starch phosphate is a promising pharmaceutical excipient in tablets. Aceclofenac rapidly dissolving tablets with >85% dissolution in 30 min could be formulated employing starch phosphate as directly compressible vehicle by direct compression method (BF3) and also employing aceclofenac-starch phosphate (1:2) solid dispersion by wet granulation method (BF4). Formulations BF3 and BF4 respectively gave 86.51% and 99.37% dissolution in 30 min fulfilling the target dissolution requirement for biowaiver.

Keywords: Aceclofenac Tablets, Starch Phosphate, Direct Compression, Solid Dispersion, Biowaiver.

INTRODUCTION

Aceclofenac, 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 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[1]. Among the various approaches, solid dispersions in water dispersible excipients are simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs. We reported starch phosphate, a new modified starch, as an efficient carrier in solid dispersions for enhancing the dissolution rate of poorly soluble drugs[2].

Direct compression is the preferred method for the preparation of tablets[3]. It offers several advantages[4-5]. 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[6]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms[7]. 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.

The objective of the present study is to develop aceclofenac rapidly dissolving tablet formulations by wet granulation and direct compression methods employing starch phosphate, 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 30 min in phosphate buffer pH 6.8 are eligible for biowaiver. Hence a dissolution of > 85% in 30 min is taken as target dissolution to achieve in the formulation development of aceclofenac tablets[8]. In the present study starch phosphate was prepared, characterized and used in the formulation development of aceclofenac tablets with >85% dissolution in 30 min.

MATERIALS AND METHODS

Materials

Aceclofenac was gift sample from M/s Natco Pharma Pvt. Ltd, Hyderabad., Starch phosphate was prepared in the laboratory, 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.

the initial volume (V_o) and final
tapings of a sample of starch
linder. CI was calculated using

$$\text{dex (CI)} = \frac{V_o - V}{V_o} \times 100$$

tric method based on the
nce at 275 nm in phosphate
estimation of aceclofenac. The
bert's law in the concentration
hen the standard drug solution
(n=6), the relative error
t of variation (precision) were
% respectively. No interference
observed.

ac Tablets

ablets each containing 50 mg of
ulated and evaluated. The
ed are given in Table 1. In batch
mulated employing aceclofenac
osphate (DCP) as diluent and
ation method using water as
atch BF2 the tablets were
eclofenac alone and lactose as
wet granulation method using
. In batch BF3 the tablets were
starch phosphate as directly
prepared by direct compression
the tablets were formulated
tarch phosphate (1:2) solid
lets were prepared by wet
oying water as granulating fluid.
(2%) as binder, crospovidone
(2%) and magnesium stearate
sed. In each batch 100 tablets

y Wet Granulation and Direct

mg/Tablet)	
BF3	BF4
50	-
140	-
-	150
-	45.8
5.8	-
11	11
4.4	4.4
4.4	4.4

Preparation of Solid Dispersions of Aceclofenac in Starch Phosphate

Solid dispersions of aceclofenac and starch phosphate were prepared in 1:2 ratio of drug: carrier by solvent evaporation method. Aceclofenac (1 g) was dissolved in dichloromethane (10 ml) in a dry mortar to get a clear solution. Starch phosphate (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^{o}C until dry. The dried mass was pulverized and sieved through mesh no. 100.

Preparation of Aceclofenac Tablets by Wet Granulation Method

Compressed tablets each containing 50 mg of aceclofenac were prepared by wet granulation method employing aceclofenac alone (BF1 and BF2) and its solid dispersions in starch phosphate (BF4). The required quantities of aceclofenac or aceclofenac-starch phosphate (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^{0}c for 2h. The dried granules were 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.

Preparation of Tablets by Direct Compression Method

Compressed tablets each containing 50 mg of aceclofenac were prepared by direct compression method (BF3) employing starch phosphate 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 Cadmach 16-station rotary tablet punching machine (M/s Cadmach Machinery Co. Pvt. Ltd) to a hardness of 6 kg/cm^{2} using 9 mm round and flat 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 3x20 ml quantities of methanol. The methanolic extracts were filtered and collected into a 100 ml volumetric flask and the volume was made up to 100 ml with methanol. The solution was then suitably diluted with phosphate buffer of pH 6.8. The absorbance of the solution was measured at 275 nm. Drug content of the tablets was calculated using the standard calibration curve.

Dissolution Rate Study

Dissolution rate of aceclofenac from the tablets prepared was studied in phosphate buffer pH 6.8 (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 aceclofenac was used in each test. A temperature 37$\pm$1^{o}C was maintained throughout. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for aceclofenac at 275 nm. For comparison, dissolution of aceclofenac from one commercial brand was also studied. All the dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Starch phosphate was prepared by reacting potato starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. The reactions involved are shown in Figure 1.

Starch phosphate prepared was found to be white, crystalline, non hygroscopic powder and can easily be ground to different sizes. Powder which 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 phosphate prepared was characterized by determining various physical properties. The properties of starch phosphate prepared are summarized in Table 2.

Table 2: Physical Properties of the Starch Phosphate Prepared

Property	Result
Solubility	Insoluble in all aqueous and organic solvents tested
P^{H} (1% w/v aqueous dispersion)	7.25
Melting Point	Charred at 210^{o}c
Viscosity (1% w/v aqueous dispersion)	2.11 cps
Swelling Index	400
Gelling Property	No gelling and the swollen particles of starch phosphate separated from water. Whereas in the case of starch, it was gelatinized and formed gel.
Moisture Absorption	< 4.0 %
Particle Size	152 µm (80/120 mesh)
Density	1.667 g/cc
Bulk Density	0.534 g/cc
Angle of Repose	20.04^{0}
Compressibility Index	11.01 %

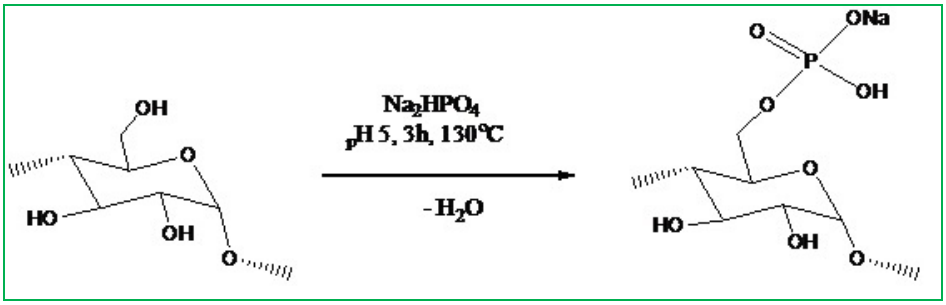

Figure 1: Phosphorification of Potato Starch to Produce Starch Phosphate

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Bulk Density	0.534 g/cc
Angle of Repose	20.04^0
Compressibility Index	11.01 %

Table 3: Drug Content, Hardness, Friability, Disintegration Time and Weight Variation of Aceclofenac Tablets Formulated Employing Starch Phosphate by Wet Granulation and Direct Compression Methods

Formulation	Drug Content (mg/tab)	Hardness (Kg/cm2)	Friability (% weight loss)	Disintegration Time (min-sec)	Weight Variation (maximum % deviation)
BF1	49.0	7.0	0.88	6-30	2.5
BF2	49.4	8.0	0.35	7-00	1.5
BF3	49.1	7.0	0.28	1-00	1.9
BF4	48.9	8.0	0.42	0-50	1.2
Commercial	99.1	6.0	0.58	6-00	--

Table 4: Dissolution Parameters of Aceclofenac Tablets Formulated Employing Starch Phosphate 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	20.03	> 60	11.22	-	0.0069	-
BF2	40.56	45.0	24.30	2.17	0.014	2.07
BF3	86.51	12.0	55.02	4.90	0.097	14.66
BF4	99.37	7.0	68.81	6.13	0.148	21.59
Commercial	54.52	24.0	31.42	2.80	0.025	3.63

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

When tested for m.p., it was charred at 210°C. Starch phosphate prepared was insoluble in water, aqueous fluids of acidic and alkaline pH and several organic solvents tested. In water it exhibited good swelling (400%). No gelling/pasting was observed with starch phosphate when its aqueous dispersion was heated at 100°C for 30 min, 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 phosphate prepared. All the physical properties studied indicated that starch phosphate is a promising pharmaceutical excipient in tablets. We have earlier reported starch phosphate as an efficient carrier for solid dispersions to enhance dissolution rate of poorly soluble drugs[2].

Four different batches of aceclofenac 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 aceclofenac tablets prepared were found to contain the aceclofenac with in 100±2% of the labeled claim. Hardness of the tablets was in the range 7-8 Kg/sq.cm. Percentage weight loss in the friability test was less than 0.88% in all the cases. Tablets formulated employing starch phosphate (BF3 & BF4) disintegrated rapidly within 1-00 min-sec. Tablets formulated employing aceclofenac alone (BF1 & BF2) disintegrated within 6-7 min. All the four batches of tablets prepared fulfilled the official (IP) specification for weight variation. As such all the aceclofenac 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 aceclofenac tablets prepared and one commercial brand was studied in phosphate buffer of pH 6.8. The dissolution profiles of the tablets prepared are shown in Figure 2. The dissolution parameters of the prepared tablets are given in Table 4. Dissolution of aceclofenac from all the tablets prepared followed first order kinetics with correlation coefficient 'R' values > 0.910. Dissolution Efficiency (DE_{30}) values were calculated as described by Khan *et al*[14]. All the dissolution parameters (PD_{30}, T_{50}, DE_{30}, K_1) indicated rapid and higher dissolution of aceclofenac from tablets formulated employing starch phosphate as directly compressible vehicle (BF3) and aceclofenac-starch phosphate (1:2) solid dispersion (BF4) when compared to tablets formulated employing aceclofenac alone (BF1 & 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).

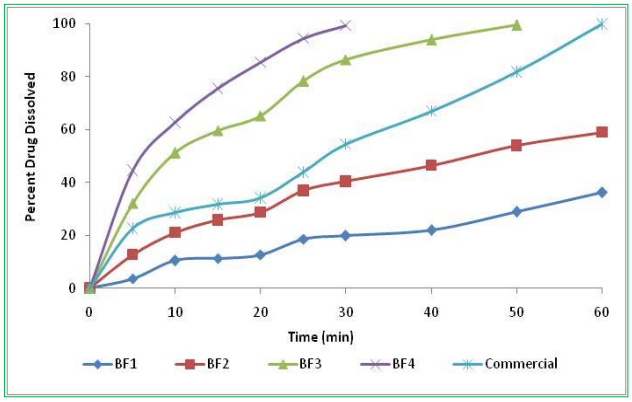

Figure 2: Dissolution Profiles of Aceclofenac Tablets Formulated Employing Starch Phosphate by Wet Granulation and Direct Compression Methods.

Tablets formulated employing starch phosphate as directly compressible vehicle (BF3) and aceclofenac-starch phosphate (1:2) solid dispersion (BF4) gave much higher dissolution rates and DE_{30} values when compared to formulation BF1 (control). A 14.06 and 21.59 fold increase in the dissolution rate (K_1) was observed with formulations BF3 and BF4 respectively when compared to formulation BF1. A 3.9 and 6.0 fold increase in the dissolution rate (K_1) was observed with these formulations when compared to commercial formulation. Formulations BF3 and BF4 respectively gave 86.51% and 99.37% dissolution in 30 min fulfilling the target dissolution requirement for biowaiver. Formulations BF1, BF2 and commercial brand could not fulfill the target dissolution requirement.

CONCLUSION

Starch phosphate prepared by reacting potato starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures was insoluble in water and has good swelling (400%) 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 phosphate prepared. All the physical properties studied indicated that starch phosphate is a promising pharmaceutical excipient in tablets. Aceclofenac rapidly dissolving tablets with >85% dissolution in 30 min could be formulated employing starch phosphate as directly compressible vehicle by direct compression method (BF3) and also employing aceclofenac-starch phosphate (1:2) solid dispersion by wet granulation method (BF4). Formulations BF3 and BF4 respectively gave 86.51% and 99.37% dissolution in 30 min fulfilling the target dissolution requirement for biowaiver.

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