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Enhancement of Dissolution Rate of Aceclofenac Tablets by Solid Dispersion in Superdisintegrants

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Aceclofenac, a widely prescribed non-steroidal antiinflammatory drug is practically insoluble in water and aqueous fluids, because it exhibits poor and variable dissolution rate and oral bioavailability. The objective of the study is to investigate the feasibility of enhancing the dissolution rate of aceclofenac by solid dispersion in superdisintegrants, a new class of tablet excipients. Solid dispersions of aceclofenac in four superdisintegrants namely croscarmellose sodium, crospovidone, prosolve and primogel were prepared and evaluated for dissolution rate. The dissolution rate of aceclofenac could be enhanced markedly upto 32 fold by solid dispersion in superdisintegrants. The order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > prosolve > primogel. The solid dispersions of aceclofenac in crospovidone and croscarmellose sodium could be formulated into tablets by both wet granulation and direct compression methods and the resulting tablets also gave much higher dissolution rates and DE_{30} values when compared to plain tablets.

Key Words: Aceclofenac, Dissolution rate, Solid dispersion, Superdisintegrants.

INTRODUCTION

Aceclofenac is an orally administered non-steroidal antiinflammatory drug used in a variety of painful conditions[1,2]. Aceclofenac is practically insoluble in water and aqueous fluids. Its aqueous solubility was found to be 0.53 mg/mL. As such its oral absorption is dissolution rate limited. The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms and leads to poor and variable dissolution rate and oral bioavailability. Among the various methods of enhancement of the dissolution rate and oral bioavailability, solid dispersion technologies were found to be very successful with a number of drugs[3-6]. Studies were carried out on solid dispersion of aceclofenac in water dispersible superdisintegrants as carriers with an objective of enhancing the dissolution rate of aceclofenac

from tablets. A new class of tablet excipients called superdisintegrants were evaluated as carriers for solid dispersions and for enhancing the dissolution rate of aceclofenac. The feasibility of formulating the solid dispersions developed into compressed tablets was also investigated.

EXPERIMENTAL

Aceclofenac (gift sample from M/s Suyaash Labs, Chennai), primogel, crospovidone, croscarmellose sodium, prosolve (gift sample from M/s Orchid Health Care Ltd., Chennai), dichloromethane GR (Qualigens), lactose I.P., potato starch I.P., talc I.P., magnesium stearate I.P and acacia (Loba Chemie) were used. All other materials were used of pharmacopoeial grade.

Preparation of solid dispersions in superdisintegrants: Solid dispersions of aceclofenac in superdisintegrants (primogel, crospovidone, croscarmellose sodium and prosolve) were prepared by solvent evaporation method. The required quantity of drug was dissolved in dichloromethane to get a clear solution in a dry mortar. The superdisintegrant (passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50 ºC for 4 h in an oven. The dried product was powdered and shifted through mesh No. 100. In each case solid dispersions were prepared at three different ratios of drug: carrier namely 3:1, 1:1 and 1:2 or 25, 50 and 66 % concentration of the carrier (superdisintegrants).

Preparation of aceclofenac tablets: Tablets each containing 100 mg of aceclofenac were prepared by wet granulation and direct compression methods employing its solid dispersions in crospovidone (1:1) and croscarmellose (1:1). In the case of wet granulation method, acacia (2 %) as binder, potato starch (15 %) as disintegrant, lactose (q.s) as diluent, talc (2 %) and magnesium stearate (2 %) as lubricants were also included in the formulations. The tablet granulations were compressed into tablets to a hardness of 5-6 kg/cm^2 on a 16-station 'Cadmach' tablet machine.

In the case of direct compression method, prosolve, a directly compressible vehicle (30 %), potato starch (15 %), lactose (q.s), talc (2 %) and magnesium stearate (2 %) were also included in the formulations. All the ingredients were blended thoroughly in a closed high density polyethylene bottle and were directly compressed into tablets to a hardness of 5-6 kg/cm^2 on a 16-station 'Cadmach' tablet machine.

Evaluation of tablets: Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a Thermonic tablet disintegration test machine using distilled water as fluid.

Estimation of aceclofenac: An UV spectrophotometric method based on the measurement of absorption at 275 nm in a phosphate buffer of pH 6.8 was used for the estimation of aceclofenac. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 1-10 µg/mL. When a standard drug solution was repeatedly assayed (n = 6), the relative error and coefficient of variation were found to be 0.80 and 1.2 %, respectively. No interference by the excipients used in the study was observed.

Dissolution rate study: Dissolution rate of aceclofenac as such and from various solid dispersions and tablets formulated was studied using Disso-2000 (Labindia) 8 station dissolution rate test apparatus with a paddle stirrer. The dissolution rate was studied in 900 mL phosphate buffer of pH 6.8. Aceclofenac (50 mg) or its solid dispersion equivalent to 50 mg of aceclofenac or one tablet containing 100 mg of aceclofenac, a speed of 50 rpm and a temperature of 37 ± 1 ºC were used in each test. Samples of dissolution medium (5 mL) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted and assayed for aceclofenac by measuring absorbance at 275 nm. The dissolution experiments were conducted in triplicate.

X-ray powder diffraction patterns of aceclofenac and its solid dispersions were obtained using X-ray powder diffractometer (Phillips model No. PW 1729) employing F_c-K_∞ radiation. The diffractograms were run at 2.4 ºC/min in terms of 2θ angle. The FT-IR spectra were recorded by using KBr disc as reference on a FTIR spectrophotometer (Model: NP-602378-14.002, instrument serial No. 72425).

RESULTS AND DISCUSSION

Solid dispersions of aceclofenac in four water dispersible super-disintegrants namely prosolve, primogel, crospovidone and croscarmellose sodium were prepared by solvent evaporation method employing dichloromethane as solvent for the drug. All the solid dispersions prepared were found to be fine and free flowing powders. There was no loss of drug during the preparation and all the solid dispersions contained the drug equal to the theoretical drug content based on the proportion drug and carrier taken. Low s.d and c.v (< 2.0) in the per cent drug content values indicated that the drug content was uniform in a batch of solid dispersion prepared in all the cases.

The dissolution of aceclofenac from all solid dispersions was rapid and several times higher than the dissolution of aceclofenac as such. The dissolution data were fitted into zero order and first order kinetic models to assess the kinetics and mechanism of dissolution. The kinetic model that best fits the dissolution data was evaluated by comparing the correlation

coefficient (r) values obtained in various models. The model that gave higher 'r' value is considered as the best fit model. The 'r' values were found to be higher in the first order model than those in zero order models with all the solid dispersions as well as the pure drug indicating that the dissolution of aceclofenac as such and from all solid dispersions followed first order kinetics. The DE_{30} values were calculated in each case as reported by Khan *et al.*[7]. The dissolution parameters of various solid dispersions prepared are given in Table-1.

TABLE-1
DISSOLUTION PARAMETERS OF ACECLOFENAC AND ITS SOLID DISPERSIONS IN SUPERDISINTEGRANTS

Solid dispersion	Carrier and concentration (%)	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Increase in K_1 (no. of folds)
Aceclofenac	–	65	0.0086	20.06	–
SDF 1	Prosolve (25)	3.5	0.0441	72.13	5.13
SDF 2	Prosolve (50)	3.0	0.0497	77.05	5.78
SDF 3	Prosolve (66)	3.5	0.0453	69.07	5.27
SDF 4	Primogel (25)	3.6	0.0297	64.83	3.45
SDF 5	Primogel (50)	3.7	0.0276	66.50	3.20
SDF 6	Primogel (66)	3.0	0.0511	80.68	5.94
SDF 7	Crospovidone (25)	3.2	0.0420	77.82	4.88
SDF 8	Crospovidone (50)	3.0	0.1689	86.93	19.63
SDF 9	Crospovidone (66)	3.0	0.1776	84.37	20.66
SDF 10	Croscarmellose sodium (25)	3.5	0.0420	68.56	4.88
SDF 11	Croscarmellose sodium (50)	3.2	0.2740	88.67	31.86
SDF 12	Croscarmellose sodium (66)	3.0	0.0613	78.10	7.13

Among the superdisintegrants tested croscarmellose sodium and crospovidone gave much higher enhancement in the dissolution rate of aceclofenac. A 31.86 and 19.63 fold increase in the dissolution rate of aceclofenac was observed with these solid dispersions at 1:1 ratio of drug: carrier, respectively. At 1:1 ratio of drug:carrier, the order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > prosolve > primogel. In each case the dissolution rate was increased as the concentration of carrier was increased from 25 to 50 %. At 66 % carrier concentration (a drug:carrier ratio of 1:2), there was no further increase in the dissolution rate in majority of the dispersions. Hence a drug: carrier ratio of 1:1 is considered optimum for enhancing the dissolution rate in the case of water dispersible super disintegrants.

The observed increase in the dissolution rate of aceclofenac from its solid dispersions is due to the possible reduction in particle size and deposition of the drug in 'miniscular' form on the surface of the water dispersible superdisintegrants used as carriers during the process of preparation by solvent evaporation. The easy and rapid dispersibility of superdisintegrants might have also contributed to the increased dissolution rate. As the superdisintegrants used as carriers remain suspended in the dissolution medium the drug particles deposited on them are continuously exposed to the solvent action and undergo rapid dissolution.

The X-ray diffractogram of aceclofenac exhibited characteristic diffraction pattern indicating its crystalline nature. Three strong peaks were observed at 25.9148, 18.4424 and 24.4414 (2θ degrees) with integrated intensity counts of 26791, 11624 and 11015, respectively. Several diffraction peaks were observed with varying intensity counts. The poor dissolution rate of aceclofenac is due to its crystalline nature. In the X-ray diffractograms of solid dispersions though several diffraction peaks were observed, their intensities were much reduced. For comparison, the intensities of strongest peaks observed in the X-ray diffractograms of aceclofenac and its selected solid dispersions are given in Table-2. The reduced peak intensities observed in the case of X-ray diffractograms of solid dispersions indicated a reduction in the crystallinity of the drug in the solid dispersions. This change in the physical state of the drug in the solid dispersions might have also contributed to the enhanced dissolution rate of aceclofenac from its solid dispersions.

TABLE-2
INTENSITIES OF STRONGEST PEAKS OBSERVED IN THE X-RAY DIFFRACTOGRAMS OF ACECLOFENAC AND ITS SOLID DISPERSIONS

Product	2θ (deg.)	Integrated intensity (counts)
Aceclofenac	25.9148	26791
	18.4424	11624
	24.4414	11015
Aceclofenac-crospovidone (1:1) solid dispersion	25.8476	24527
	18.3839	6790
	24.3856	6615
Aceclofenac-croscarmellose (1:1) solid dispersion	25.8390	15166
	18.3950	4614
	24.3812	4396

The FTIR spectra of aceclofenac and its solid dispersions showed its characteristic IR absorption peaks at 3319 cm^{-1} (NH stretching), 1771 cm^{-1}

(CO stretching), 1716 cm^{-1} (COOH stretching), 1567 cm^{-1}, 1578 cm^{-1} and 1589 cm^{-1} (aromatic ring), 1149 cm^{-1} (COC stretching) and 899 cm^{-1} (CCl) indicating no interaction between aceclofenac and the carriers used in the solid dispersions.

Solid dispersions in crospovidone (1:1) and croscarmellose sodium (1:1) were formulated into tablets by wet granulation and direct compression methods. All the tablets prepared contained aceclofenac within 100 ± 5 % of the labeled content. Hardness of the tablets was in the range 5-6 kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was less than 0.95 in all the tablet formulations prepared. All the tablets formulated disintegrated rapidly within 7 min. Overall tablets formulated employing direct compression method, disintegrated more rapidly when compared to those tablets formulated with wet granulation method. The dissolution parameters of aceclofenac tablets formulated are given in Table-3. All the tablets formulated employing solid dispersions gave rapid and higher dissolution of aceclofenac when compared to that of aceclofenac plain tablets (*i.e.* tablets formulated employing aceclofenac and lactose as diluent TF1 and TF4). Aceclofenac dissolution from all the tablets followed first order kinetics with correlation coefficient 'r' above 0.898. Aceclofenac tablets formulated employing its solid dispersions and prepared by direct compression method gave rapid and higher dissolution of aceclofenac when compared to the corresponding tablets prepared by wet granulation method. In the wet granulation method, a 5.53 and 12.85 fold increase in the dissolution rate (K_1) of aceclofenac was observed with the tablets formulated employing

TABLE 3
DISSOLUTION PARAMETERS OF ACECLOFENAC TABLETS FORMULATED EMPLOYING ITS SOLID DISPERSIONS

Formulation	T_{50} (min)	K_1 (min^{-1})	DE_{30} (%)	Increases in K_1 (no. of folds)
Wet granulation method				
TF 1	61.0	0.0141	22.73	–
TF 2	6.0	0.0779	69.97	5.52
TF 3	3.5	0.1812	80.53	12.85
Direct compression method				
TF 4	24.0	0.0232	38.58	–
TF 5	3.0	0.2911	85.63	12.55
TF 6	3.0	0.3337	85.80	14.38

TF1 and TF4 are plain tablets formulated employing aceclofenac as such; TF2 and TF5 are tablets formulated employing aceclofenac-crospovidone (1:1) solid dispersion; TF3 and TF6 are tablets formulated employing aceclofenac-croscarmellose (1:1) solid dispersion.

solid dispersions in crospovidone (1:1) and croscarmellose sodium (1:1) respectively. Whereas in the direct compression method a 12.55 and 14.38 fold increase in the dissolution rate (K_1) of aceclofenac was obtained with the tablets formulated employing the corresponding solid dispersions, respectively.

Conclusion

The dissolution rate of aceclofenac could be enhanced markedly upto 32 fold by solid dispersion in water dispersible superdisintegrants. The order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone > prosolve > primogel. The solid dispersions of aceclofenac in crospovidone and croscarmellose sodium could be formulated into tablets by both wet granulation and direct compression methods and the resulting tablets also gave much higher dissolution rates and DE_{30} values when compared to plain tablets.

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