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RESEARCH ARTICLE

INFLUENCE OF CO-CRYSTALLIZER IN PRESENCE OF SOLUBILIZER ON THE DISSOLUTION OF ACECLOFENAC

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Abstract: Aceclofenac (BSC class II drug) is a novel non-inflammatory drug (NSAID) having anti-inflammatory and analgesic properties. One of the major drawbacks with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The present study was aimed to develop an oral formulation of aceclofenac with chitosan and polysorbate-80 to improve the dissolution using high shear homogenizer. The homogenized microparticles of Aceclofenac were obtained using various concentration of 1% solution of chitosan in acetic acid (10-70mg) and polysorbate-80 (1-5 mg) per tablet. The homogenized particles were kept in oven for 6 hours at 60^0C, and the paste was adsorb on Neusilline and microcrystalline cellulose. These was granulated and compressed to form the tablets. The maximum dissolution 92.20% was observed at the drug:chitosan: polysorbate-80 ratio (1:0.5:0.025).

Key words: Aceclofenac, Chitosan, Polysorbate-80, solubility, High shear homogenizer.

INTRODUCTION:

Aceclofenac (2-[(2, 6-diclorophenyl) amine] phenylacetoxyacetic acid) is an orally effective Non-Steroidal Anti-Inflammatory Drug (NSAID) of phenyl acetic group, which possesses analgesic properties. It is well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. Unfortunately, it has low aqueous soluble (0.058µg/ml), but slightly solubility in basic pH conditions leading to poor dissolution and insufficient oral bioavailability. It is weakly acidic drug (pKa = 4-5). Aejaz A. et al. various compositions of Aceclofenac solid dispersions were prepared by physical mixing, fusion and solvent evaporation methods using. PVP, PEG 6000, mannitol and urea as carrier to enhance the solubility of drug [1]. Milind P. Wagh et al. Fast dissolving tablet of aceclofenac were prepared by direct compression method after incorporating super disintegrants croscarmellose sodium, crosspovidone and sodium starch glycolate [2]. K.P.R. Chowdary et al. modified starch as a carrier in solid dispersions for enhancing the dissolution rate of aceclofenac [3]. Bhupendra Kumar Tiwari et al. Aceclofenac solid dispersions were prepared by using carriers (i.e., lactose and urea) in .The drug and carrier was dissolved in dichloromethane and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained [4]. K. Gowthamarajan et al. prepared Solid dispersion of Aceclofenac was tried with PEG- 6000, β-Cyclodextrin, gelatin hydrolysate, SLS and Croscarmellose. It was found that the aceclofenac, croscarmellose complex has given the best solubility results [5]. Kiroj Rajbanshi et al. was carried out to the dissolution of Aceclofenac (BCS –II), by solid dispersion technique using different carrier and super disintegrant by Kneading method [6]. Reddy B. V. et al. was to enhance the oral bioavailability and dissolution rate of aceclofenac by solid dispersions using polyethylene glycol (PEG-6000) as a carrier to study the effect of carrier on dissolution rate. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by fusion technique using dropping method [7]. Mutalik et al. demonstrated the use of natural polymers in preparing co-crystals that improve the pharmacokinetics and pharmacodynamics properties in animal model [8].

Chandel et. al. research study was to explore the possibility of employing co crystallization technique in the two drug i.e. aceclofenac and paracetamol and characterization of co crystal [9]. Aceclofenac dispersion in chitosan solution was prepared and co-crystallized and the effect of dissolution was observed. The literature review on 'Co-crystal' reveals that most of the research work has been done to elucidate the mechanism of co crystallization. Also, some research work has been carried out in this field to develop the aqueous solubility of few poorly water-soluble drugs using 'co crystallization' technique. Co-crystals having advantages like stable crystalline form (as compared to amorphous solids), no needs to make or break covalent bonds, theoretical capability of all types of API molecules.

Materials and Methods:

Materials

Aceclofenac (Nutraplus India limited, Mumbai), Chitosan (Elppe chemical Pvt. Ltd. Raigad), polysorbate-80 (Visuaat chemical ltd. Ambernath), Neusilline (Fuji chemical industry co. ltd. Japan), microcrystalline cellulose (Ankit Pulps & Boards,Nagpur),povidone (Nanhang Industrial co. ltd. china), cross carmellose sodium (Gujrat microwax,Ahmedabad), colloidal anhydrous silica (Wacker chemi AG,Germany), magnesium stearate (VASA pharma chem.,Beharmpura), purified talc (Ankit Pulps & Boards,Nagpur). All other chemicals and reagents used were of analytical grade.

Methods

Development of Calibration curve

A Stock solution of Aceclofenac (1mg/ml) was prepared by dissolving 100 mg of drug in 100 ml of methanol. From this 5,10,15,20 and 25 µg/ml dilutions were prepared. The wavelength of maximum absorbance (λmax) was determined by scanning one of the dilutions from 400 to 200 nm in the spectrophotometer and the spectrum was recorded. The absorbance of all the dilutions were measured at the λmax 274 nm and a standard curve between the concentration and their respective absorbance was plotted. This standard curve was used to estimate the concentration of the drug released from the Aceclofenac formulations.

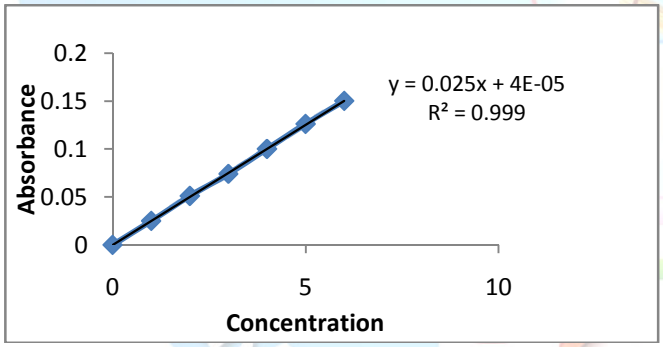

Fig.1: Standard curve of Aceclofenac

Preparation of Aceclofenac Dispersion

The 1% chitosan solution was prepared in 0.1 N acetic acid by soaking overnight. The Aceclofenac was dispersed in the weight quantity of chitosan solution after addition of polysorbate-80 the dispersion was homogenized using high shear homogenizer for 30 minutes at 9000 rpm to produce microparticles of aceclofenac. This was kept in oven 6 hours at 60°C. The thick paste was adsorb on the mixture of neusilline and microcrystalline cellulose and passed through 30 mesh. The granules were further dried and granulated using povidone as binder. The granules were blended with lubricants and super disintegrants and compressed to produce tablets. (Table 1)

Evaluation and Characterization of the high shear Aceclofenac microparticles

Particle size measurement

The particle size were analyze on SEM.

Pre compression parameter

All the batches were evaluated for various parameters like bulk density, tapped density, Carr's compressibility index and Hausner ratio by conventional methods. [10] (Table 2).

Post compression parameter

All the batches were evaluated for various parameters like weight variation, hardness, drug content and in - vitro dissolution test (Table 3).

Content uniformity test

Aceclofenac particles equivalent to 10 mg was weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 274 nm by UV spectrophotometer.

In-Vitro Dissolution test

The dissolution studies were conducted in a United States Pharmacopeia dissolution apparatus II (paddle method, ELECTROLAB Dissolution tester TDT-08L). The dissolution medium was maintained at 37°C ±0.5 °C and stirred at 50 rpm by means of an adjusted constant speed motor.*In-vitro* Dissolution studies were performed in phosphate buffer pH 7.5. Samples (5 mL) were withdrawn at respective time interval and filtered. The absorbance of the sample was measured at 274 nm after suitable dilution if necessary; using appropriate blank and the drug release was estimated. (Table 3).

Results and Discussion

In this study, Aceclofenac microparticles were developed using the high shear homogenization with the solubilizer and co-crystallizer, strategy is to exploit the carboxylic acid dimer with exofunctional which acts as either a hydrogen bond donor or acceptor. So this chosen API renders itself to be amenable for the synthesis of co-crystals. In the F3 formulations average particles size was 88µm, while the average particle size of formulation F1 was 156 µm. The formulation F2 containing 2.5 mg Polysorbate-80 having average particle size as 116µm. The particle size of F4, F5 and F6 having similar quantity of Polysorbate-80 but varying quantity of chitosan showed average particle size was 123 µm. reduction in particle size of aceclofenac is due to high shear imparted by high shear homogenizer and the particle size was also dependant on the Polysor-

bate-80 concentration, as the concentration of Polysorbate-80 as increased, the particle size was reduced. This could be due to the emulsification and dispersion properties of Polysorbate-80. The presence of Polysorbate-80 also helps in enhancing the wetting property of aceclofenac particles. The presence of higher quantity of Polysorbate-80 in formulation F3 has resulted in the formation of sticky granules; which were difficult to compress. Hence, it was excluded from further studies.

Table 1 Formulations of Aceclofenac Tablet

Ingredients	F1	F2	F3	F4	F5	F6
Dry mixing Stage	**Quantity in mg**					
Aceclofenac	100	100	100	100	100	100
Chitosan(Dried basis)	10	10	10	30	50	70
Polysorbate- 80	1.0	2.5	5.0	2.5	2.5	2.5
Neusilline	82	85	90	70.5	50.5	30.5
Microcrystalline cellulose	30	25.5	18	20	20	20
Binding Stage						
Povidone	10.0	10.0	10.0	10.0	10.0	10.0
Lubrication Stage						
Cross carmellose sodium	12.0	12.0	12.0	12.0	12.0	12.0
Colloidal anhydrous silica	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0
Purified talc	2.0	2.0	2.0	2.0	2.0	2.0

Table 2: Physical Parameter of Aceclofenac Granules

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner ratio	Compressibility index (%)
F1	0.664	0.751	1.13	11.58
F2	0.651	0.737	1.13	11.66
F3	0.650	0.744	1.14	12.63
F4	0.653	0.741	1.13	11.87
F5	0.653	0.732	1.12	10.79
F6	0.655	0.740	1.13	11.48

Table 3: Evaluation Parameter of Aceclofenac Tablets

Formulation		F1	F2	F4	F5	F6
Drug Release (%)	10 minute	44.98	47.24	54.67	58.16	55.32
	20 minute	50.86	53.66	68.22	71.69	70.05
	30 minute	57.65	60.53	80.50	83.26	85.28
	45 minute	64.28	68.36	83.22	92.20	94.12
Drug content (%)		99.01	98.28	100.03	99.98	99.58

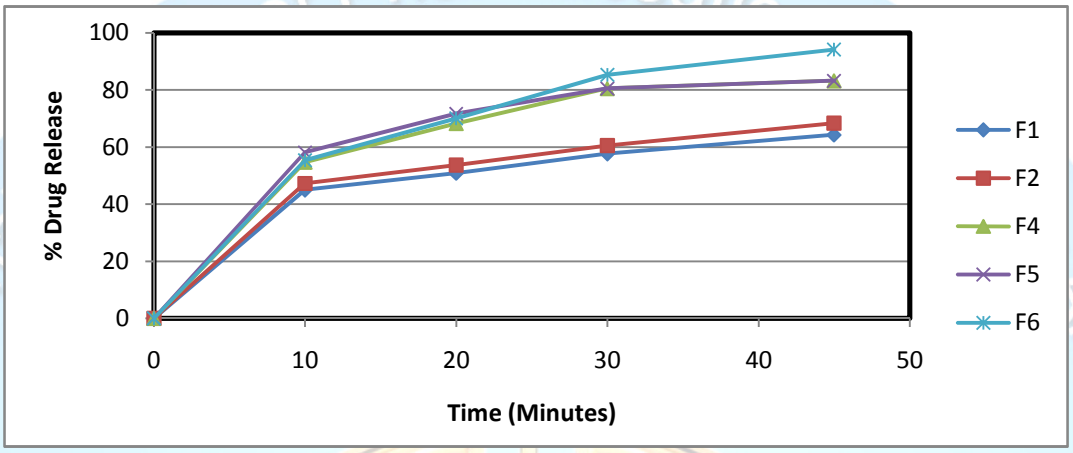

Fig. 2: Cumulative Aceclofenac release from Tablets

All the batches of Aceclofenac were evaluated for their pre compression parameters (i.e. bulk density, tapped density, Carr's compressibility index and Hausner ratio) were observed to have the good flow property.

These batches were futher evaluated for their post compression parameters (i.e. weight variation, hardness, thickness and disintegration test). These parameters were found to be within acceptable limit.

Drug content of all the batches were about 99-100%. The dissolution studies of aceclofenac tablets prepared using different concentration of Polysorbate-80 (F1 to F3) as solubilizer showed different percentage of drug release depending upon the concentration of polysorbatee-80. Formulation F2 showed 68.36 % drug release in 45 minute, when the Polysorbate-80 concentration was 2.5 mg/tab as compared to 64.28 % drug release from F1 when the concentration was 1.0 mg/tab.

The dissolution pattern of the aceclofenac was improved further by using chitosan use as co-crystallizing agents, in different ratio (F4 to F6). Increase in concentrations of chitosan favorably reflected on dissolution pattern, the drug release was increased from 83.22 % to 92.20 % in 45 min by incorporating the 30 mg/tab and 50mg/tab of chitosan respectively. This increase in dissolution by the increasing the concentration of chitosan could be, due to the formation of co-crystals of aceclofenac from the dissolution pattern of formulation F4 and F5 the optimum ratio for co-crystallization of aceclofenac may be in the ratio of aceclofenac: chitosan (1:0.5) because the further increase in the chitosan concentration has produced slight improvement in dissolution.

CONCLUSION

High shear Aceclofenac microparticles were developed using chitosan and Polysorbate-80. The particle size was reduce due to the high shear and the wetting property of further improved with Polysorbate-80. The presence of chitosan has played the important role by forming co-crystal which has the high dissolution rate the optimum ratio of aceclofenac: chitosan: Polysorbate-80 was formed to be (1:0.5:0.025).

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REFERENCE:

1. Aejaz A. et al., Studies on Aceclofenac Solid Dispersion In Corporate Gels: Development, Characterization And In Vitro Evaluation, IJPPS, 2010; Vol 2, Suppl 1.
2. Milind P. Wagh et al., Formulation And Evaluation Of Fast Dispersible Tablets Of Aceclofenac Using Different Superdisintegrant, IJPPS, 2010; Vol 2, Suppl 1.

3. K.P.R. Chowdary et al., Formulation Development of Aceclofenac Tablets Employing Starch Phosphate -A New Modified Starch, International Journal of Pharma Sciences and Research (IJPSR)Vol.2 (3), 2011, 124-129
4. Bhupendra Kumar Tiwari et al. Enhancement of solubility of aceclofenac by using different solubilization technique, Int. J. of Pharm. & Life Sci., Vol. 2(3), 2011, 620
5. K. Gowthamarajan et al. Dissolution Enhancement of Poorly Soluble Aceclofenac by Solid Dispersion Technique and Its Comparison with Marketed Formulations, International Journal of PharmTech Research, Vol.2,(4), 2010, 2347-2356.
6. Kiroj Rajbanshi et al. Dissolution enhancement of aceclofenac tablet by solid dispersion technique, International Journal of Pharma Sciences and Research, Vol 5 (4), 2014.
7. Reddy B. V. et al. Enhancement of oral bioavailability and dissolution rate of aceclofenac using solid dispersions by dropping method, Indian Drugs 49 (12), 2012.
8. S.Mutalik, P. Anju, K. Manoj and N. Usha, Int. J. Pharm., 2008, 350,279.
9. Chandel et. al. Co-crystalization of aceclofenac and paracetamol and their Characterization, International journal of pharmacy & life sciences, 2(8): Aug., 2011.
10. Rockville MD.The Unit States Pharmacopeial Convention. United States of Pharmacopeia-National Formulary, USP 30–NF 25., 2007:1:634-645.