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A STUDY ON INDIVIDUAL AND COMBINED EFFECTS OF SUPER DISINTEGRANTS IN PRESENCE OF BETA-CYCLODEXTRINS IN ACECLOFENAC ORAL DISPERSIBLE TABLETS

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ABSTRACT

The objective of present investigation was concerned with design and characterization of oral dispersible tablets of aceclofenac, in order to improve efficacy and better patient compliance, oral dispersible tablets were prepared by the wet granulation method with individual and combination of super disintegrants namely Croscarmellose Sodium and Microcrystalline cellulose in presence and absence of Beta-cyclodextrins, using 1% starch as a binding agent. In vitro release studies were performed by using USPXXIII type II apparatus (paddle method). Compatability of drug with components individually and in combination was also studied. Dissolution study revealed that the formulation F-3 with the equimolar proportions of Croscarmellose Sodium and Microcrystalline Cellulose with Beta-Cyclodextrins showed better release of drug due to its synergistic effect when compared to other formulations. The formulation F-3 also showed the maximum release of drug when compared to the conventional commercial formulation.

Keywords:-Aceclofenac, Beta-Cyclodextrins, Croscarmellose Sodium, Micro Crystalline Cellulose and In-vitro studies.

INTRODUCTION

A drug can be administered via many different routes to produce a systemic pharmacologic effect. The oral route of administration is considered the most widely used route (about 90% of all drugs used to produce systemic effects) due to manifold advantages it provide to the patient like easy of ingestion, avoidance of pain, versatility, patient compliance and accurate dosing (Mahaveer Pr *et al.,* 2010; Sunita Kumari *et al.,* 2010) . But the most evident drawback of the commonly used oral dosage forms like tablet s and capsules is difficulty in swallowing. This difficulty in swallowing or dysphagia is currently affecting approximately 35% of the general population particularly pediatrics and geriatrics.

The pain is symptomatic of some form of dysfunction and resultant inflammatory processes in the body. A survey conducted for the WHO reported that one adult in five suffers from chronic non-malignant pain, which mostly occurs in the back, head, joints and limbs. More than 15% of the worldwide population suffers for instance from some form of osteoarthritis, and this incidence is even higher in the elderly. As the world population is grows older, this incidence will continue to rise. Orally administered NSAIDS plays an important role in symptomatic management of Osteoarthritis,

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Rheumatoid arthritis and Ankylosing spondylitis and other acute pain conditions.

Aceclofenac is an orally administered phenyl acetic acid derivatives with effects on a variety of inflammatory mediators In general, they produce their anti-inflammatory and analgesic effects by inhibiting cyclooxygenase and this preventing the production of prostaglandins from arachidonic acid.

Many techniques have been used in the formulation of oral dispersible tablets with the usage of super disintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate, for the DP formulations of different drugs (Susijit Sahoo *et al.,* 2010). The super disintegrants selected for the present study are croscarmellose sodium and micro crystalline cellulose along with the macromolecular inclusion complex namely beta-cyclodextrins for increasing the dissolution rate as well as bioavailability. It was essential to include super disintegrants individually and in combination, hence in the present work an attempt has been made to formulate oral dispersible tablets of aceclofenac with and without using macro molecular inclusion complex (Beta-cyclodextrins) in individual and combination with super disintegrants (Croscarmellose sodium, Microcrystalline cellulose).

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Amoli organics Pvt.ltd, Mumbai. Beta-cyclodextrins was obtained as a gift sample from Signet chemical corporation, Pvt.ltd, Mumbai. Croscarmellose sodium and microcrystalline cellulose were purchased from Loba chemie Pvt.ltd, Mumbai. All other chemicals and solvents were used are of analytical grade.

Methods

The Manufacturing procedure to formulate aceclofenac oral dispersible tablets 200mg consists of the following Table (Someshwara Rao B *et al.,* 2010):

EVALUATION PARAMETERS AND PROCEDURES

(Milind P wagh *et al.,* 2010)

Drug-Excipients Compatibility Studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage form.

Fourier Transform Infrared Spectroscopic Studies

FT-IR study was carried out by using FT-IR Spectrophotometer to find out if there is any possible chemical interaction of aceclofenac with beta-cyclodextrins, croscarmellose sodium and microcrystalline cellulose. To study the compatability of various formulation excipients with aceclofenac, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and stored in air tight containers at **40^0C/75%RH and 60^0C/90%RH**. The solid admixtures were characterized by using Fourier transform infrared spectroscopy (FT-IR).

EVALUATION OF GRANULES **(**D Bhowmik *et al.,* 2009; Chopra *et al.,* 2009)

Density (g/ml)

Granule density, True Density, Bulk density may influence compressibility, tablet porosity, flow property, and other properties. Higher compression load is required in case of dense and hard granules which in turn increase the tablet disintegration and drug dissolution time. Density is usually determined by Pycnometer.

Bulk density

Weighed quantity of Aceclofenac granules was transferred into a 50 ml measuring cylinder without tapping. During transfer the volume occupied by granules was measured. Bulk density was measured by using formula.

Pi = m/Vo

Where,

m - Mass of the blend, Vo - Untapped Volume

Tapped Density

Weighed quantity of Aceclofenac granules was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USP II) According to USP, the blend was subjected for 500 taps the % Volume variation was calculated by following formula.

P_t = m/V

Where,

m - Mass of the blend, V_i - Tapped Volume

Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that obtained from density determination.

Weighed quantity of Aceclofenac granules was transferred to 50 ml graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USP II) the difference between two tabs should be less than 2%. The percentage of compressibility Index is calculated by using formula (James L *et al.,* 1985; Carri.R.L *et al,* 1965)

CI=Vo-WV*100

Where,

V_o - Untapped density V_i - Tapped density

Hausner's Ratio

It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 -1.5. It was determined by the ratio of tapped density to bulk density.

Hausner's Ratio = V_o/V_i

Where,

V_o - Untapped density V_i - Tapped density

Angle of Repose

Angle of Repose (O) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the Flow ability of powder /granules.

Aceclofenac granules were passed through a funnel kept at a height of 2 cm from the base. The granules were passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the formula.

$\Theta = \tan^{-1}(h/r)$ (or) $\Theta = \tan^{-1}$(height /0.5 Base)

Where,

h - Height of the heap of pile, r - Radius of base of pile

EVALUATION OF TABLETS (Rajitha K *et al.,* 2009; Swamy PV *et al.,* 2010; Snehalatha et al., 2009)

Weight variation test

20 tablets were selected randomly from the lot and weighted individually to check for weight Variation. Weight variation specification as per I.P. Weight variation tolerance for uncoated tablets.

Thickness or dimension test

The thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of tablets was determined by using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of tablets was determined.

Limits: 4 - 6 kg/cm^2

Friability test

Friability of the tablets is determined by using Roche's Friabilator. It is expressed in %. Ten tablets were initially weighed and transferred to Friabilator. The Friabilator is operated at 25 Rpm for 4 min or run upto100 revolutions, the tablets are weighed again. The % friability of tablets was then calculated.

Limits: The Friability of tablet should not be exceed 1%.

$$F = \frac{\text{Initial wt - Final wt}}{\text{Initial wt}} \times 100$$

Drug Content Uniformity

Standard preparation

An accurately weighed amount of pure aceclofenac (100mg) and transferred into 100ml volumetric flask. It was dissolved and made upto volume with ph-6.8phosphate buffer and absorbance was measured at 275nm.

Sample preparation

Five tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered aceclofenac (100mg) was extracted in buffer. The solution was filtered through 0.45µm membrane and absorbance was measured at 275nm after suitable dilution.

Calculation

The amount of aceclofenac present in tablet can be calculated using the formula:

$A_T/A_S \times S_W/100 \times 100/S_t \times A_V$

Where,

A_T = Absorbance of sample preparation

A_S=Absorbance of standard preparation

S_W=Weight of aceclofenac working standard (mg)

S_t =Weight of aceclofenac tablet (mg)

A_V=Average weight of tablet (mg)

Disintegration test

The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for

ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

In-vitro Dissolution test

In-vitro dissolution testing of aceclofenac oral dispersible tablets was carried out by using IP/USP dissolution apparatus (paddle type and apparatus-II) with 900ml of pH-6.8 phosphate buffer as dissolution medium, which is maintained at 37 ± 0.5^0C. The basket was rotated at a fixed rpm of 100 at specified interval time, required volume of sample (1ml) was pipetted or withdraws out and diluted to 10ml in volumetric flask with pH-6.8 phosphate buffer, then finally, the absorbance of the sample solution in each flask was measured at 284 nm against pH-6.8 phosphate buffer used as blank.

RESULTS AND DISCUSSION

Drug-Excipients Compatability Studies

Fourier Transform Infrared spectroscopic studies

There is no appearance or disappearance of any characteristic peaks. This shows that there is no chemical interaction between the drug and excipients. The presence of peaks at the expected range confirms that the materials taken for the study are confirmed.

EVALUATION OF GRANULES

Bulk density

The bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the result it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the tablets. Values showed Table 3.

Tapped density

The tapped density was determined by cylindrical method. The tapped density values indicate good flow characteristics of the tablets. Values showed Table 3.

Compressibility Index or Carr's Index

The Carr's Index for various batches of the tablets is found to be less than 37; it indicates good flow properties of the tablets. Values showed Table 3.

Hausner's Ratio

Hausner's Ratio can be observed from Table 3 that the Carr's Index for various batches of the tablets is found to be less than 1.35; it indicates good flow properties of the tablets.

Angle of Repose

Angle of repose can be observed from Table 3 that the angle of repose for various batches of the tablets is found to be less than 40^0, it indicates good flow properties of the tablets.

Evaluation of Oral Dispersible Tablets of Aceclofenac

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the tablets. Values showed Table 4.

Thickness Test

The tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.3mm. Values showed Table 4.

Friability Test

The tablets Friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table 4.

Weight variation test

All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table 4.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. Values showed Table 4.

Disintegration time

The disintegration time of the all the batches values are within the acceptable range. Values showed Table 4.

Invitro Disintegration Test

The invitro disintegration time of the aceclofenac tablets when compared with commercial tablets, so that the results are found aceclofenac tablets (within 24 sec) when compared with commercial tablets (within 58 sec) immediately disintegrated. Values showed Table 4.

Table 1. Comparative formula of 200mg Aceclofenac Oral Dispersible Tablets

S.No	Ingredients (in mg)	F1	F2	F3	F4	F5	F6
1.	Aceclofenac	100	100	100	100	100	100
2.	Beta-cyclodextrins	5	5	5	5	5	---
3.	Croscarmellose sodium	10	2.5	5	7.5	---	5
4.	Micro crystalline cellulose	---	7.5	5	2.5	10	5
5.	Mannitol	80	80	80	80	80	85
6.	Talc	3	3	3	3	3	3
7.	Magnesium stearate	2	2	2	2	2	2

Table 2. Drug excipients compatability for Aceclofenac

S.No	Drug+ Excipients	Parameter	Initial value of parameters	Conditions			
				40^0C/75%RH		60^0C/90%RH	
				2 Week	4 Week	2 Week	4 week
1	Aceclofenac	Any colour change	No colour change	No colour change	No colour change	No colour change	No colour change
2	Aceclofenac + beta-cyclodextrins	Any colour change	No colour change	No colour change	No colour change	No colour change	No colour change
3	Aceclofenac + croscarmellose sodium	Any colour change	No colour change	No colour change	No colour change	No colour change	No colour change
4	Aceclofenac + microcrystalline cellulose	Any colour change	No colour change	No colour change	No colour change	No colour change	No colour change
5	Aceclofenac + beta-cyclodextrins+ CMS:MCC (1:1)	Any colour change	No colour change	No colour change	No colour change	No colour change	No colour change

Table 3. Evaluation of granules of all formulations

S.No	Formulation Code	volume before tapping (v_0)	Volume After tapping (v_i)	Loose bulk density	Tapped bulk density	Compressibility index	Hausner's ratio	Angle of repose
1	F1	6.1	5.4	0.327	0.370	11.47	1.129	39.72
2	F2	5.9	5.5	0.338	0.363	6.77	1.072	40.13
3	F3	5.3	4.6	0.377	0.434	13.20	1.15	39.24
4	F4	6.1	5.2	0.327	0.384	14.75	1.173	40.19
5	F5	5.5	4.7	0.363	0.425	14.54	1.170	39.42
6	F6	5.6	5.3	0.382	0.454	13.89	1.19	39.73

Table 4. Evaluation of Oral Dispersible Tablets of Aceclofenac

S.No	Formulations	Hardness (kg/cm2)	Thickness (cm)	Friability (%w/w)	Weight Variation	Drug content uniformity	Disintegration time (min)
1	**F1**	5.8	0.3	0.18	201.0	99.89	3.1 min
2	**F2**	6.1	0.3	0.23	200.29	99.30	1.03 min
3	**F3**	5.3	0.3	0.25	200.04	99.31	24 sec
4	**F4**	5.7	0.3	0.19	200.7	98.86	5min
5	**F5**	5.8	0.3	0.24	200.13	98.62	7 min
6	**F6**	5.4	0.3	0.23	200.02	99.42	35 sec

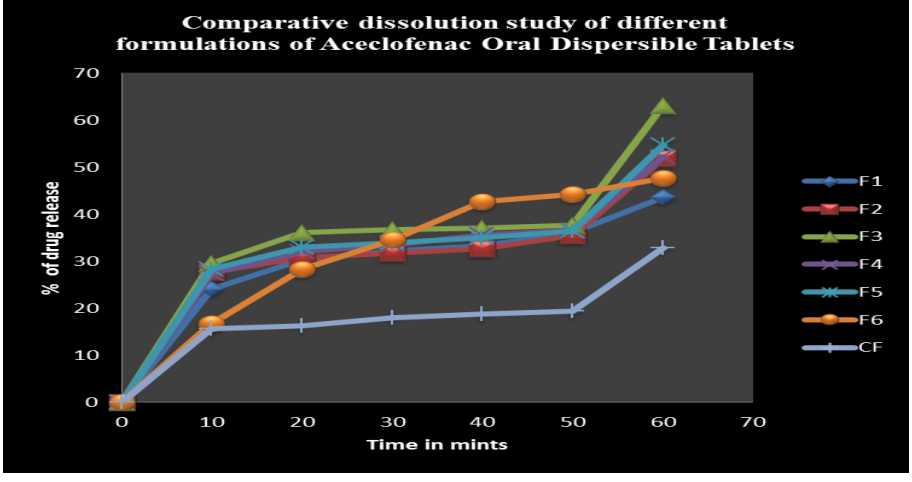
Table 5. Invitro Disintegration Test

S.No	Formulations	Disintegration time (min)
1	**F1**	3.1
2	**F2**	1.03
3	**F3**	24 sec
4	**F4**	5
5	**F5**	7
6	**F6**	35 sec
	CF	58 sec

Table 6. Comparative dissolution study of different formulations of Aceclofenac Oral Dispersible Tablets

Time in (min)	% Cumulative percent drug release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**CF**
0	**0**	**0**	**0**	**0**	**0**	0	**0**
10	24.048	27.585	29.448	27.306	28.242	16.6	15.561
20	30.294	30.754	36.072	31.968	32.994	28.3	16.308
30	32.247	31.689	36.630	33.363	33.930	34.5	17.982
40	33.273	32.715	36.999	35.604	34.947	42.6	18.729
50	36.072	35.415	37.656	36.540	36.351	44.2	19.386
60	43.524	51.921	63.099	52.101	54.711	47.6	32.805

Fig 1. Comparative dissolution study of different formulations of Aceclofenac Oral Dispersible Tablets



DISCUSSION

Super disintegrant which are used for the purpose of improving the solubility and Dissolution of oral solid dosage form by means of appreciable disintegration ultimately resulting a well-designed disintegrating tablet. Though a wide range of Super disintegrant materials are available, there is a continues need to develop new and more efficient Oral disintegrating tablets (ODT) using various effective Super disintegrant combinations. The combination of croscarmellose sodium and microcrystalline cellulose proved to be effective in reducing disintegration time in presence of beta-cyclodextrins, the presence of characteristic peaks in entire spectrum indicates stable form of aceclofenac in solid admixture. The evaluation properties of granules revealed good flow properties, post formulation studies weight variation, hardness, friability, drug content uniformity values are within the acceptable limits of Indian pharmacopoeia. The invitro disintegration and dissolution studies revealed that the formulation-3 showed the better release of drug when compared to other and marketed formulation.

CONCLUSION

Though various combinations of super disintegrant agents were tried but at the end 1:1 ratio super disintegrant combination found to be appreciable in terms of disintegration time and drug release. Aceclofenac release from the ODT tablets formulated employing croscarmellose sodium and micro crystalline cellulose in the presence of β-Cyclo dextrin was found to be more rational. Disintegration time and drug release from the ODT tablets (F3) formulated employing 1:1 ratio super disintegrant combination in the presence of β-Cyclo dextrin was appreciable. The order of increase in enhancement in disintegration time of aceclofenac observed with various ratios of super disintegrants combinations was F3>F6>F4>F1>F2>F5. The order of increase in drug release observed with various Super disintegrant combinations from various ODTs was F3(1:1)> F5(1:0) > F4(2.5:7.5) > F2(7.5:2.5) > F6(1:1)>F1(0:1). To evaluate the influence of β-Cyclo dextrin on super disintegrant combination a separate formulation (F6) was prepared omitting β-Cyclo dextrin and results declared that β-Cyclo dextrin is playing a significant role in improving disintegration and release of Aceclofenac from F3- ODT. Among all the designed formulations F-3 was found to be a better ODT when compared to all other super disintegrant combinations ODTs. Aceclofenac ODT s with makeable disintegration and drug release profile could be designed employing combination disintegrating agents namely croscarmellose sodium and micro crystalline cellulose in 1:1 ratio containing β-Cyclo dextrin.

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