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FORMULATION AND EVALUATION OF DICLOFENAC POTASSIUM ORALLY DISINTEGRATANT TABLETS (ODT) BY USING DIFFERENT SUPERDISINTEGRANTS

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Abstract:

Diclofenac Potassium, a sparingly soluble non-steroidal anti-inflammatory drug, was taken as candidate for decreasing the onset of action time and increasing its bioavailability by overcoming its first pass metabolism. Diclofenac Potassium orally disintegrating tablet (ODT) formulations were developed using by using different ratios of superdisintegrants. The tablets were were prepared by superdisintegrants addition method using Crospovidone, Croscarmellose sodium and Sodium Starch Glycolate, evaluated from both compendial and non-compendial criteria (i.e. uniformity of weight, uniformity of content, friability, in vitro disintegration time, in vitro dissolution, wetting time, in vivo disintegration time, moisture analysis and scanning electron microscopy. The best formula results showed that ODT disintegrated within few seconds and showed significantly faster in-vitro dissolution rate of Diclofenac Potassium in comparison with commercially available immediate release tablet Diclofenac Potassium tablet (Cataflam®).

Key words: *Diclofenac Potassium, Crospovidone, Croscarmellose sodium sodium and Sodium Starch Glycolate.*

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INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing.[1-2] But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients[1] , but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.

ODTs technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid [3, 4]. Orally disintegrating tablets are known by various names such as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast or rapid dissolving tablets, porous tablets, mouth dissolving tablets and rapimelts. The excipients used in ODT, usually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties like hydrophilicity or hydrophobicity. If the active pharmaceutical ingredient is hydrophobic in nature, then dosage form is called disintegrating tablet whereas, if it is hydrophilic, then the dosage form is called fast dissolving tablet [5].

Diclofenac sodium is traditional non-steroidal anti-inflammatory (NSAIDS) affords quick relief of pain and wound edema [5,6]. The main objective behind formulation of such a dosage form will definitely get futile. Thus in the present study an attempt has been made to mask the taste of Diclofenac sodium and to formulate ODTs with good mouth feel so as to prepare a “patientfriendly dosage form”.

The study was proposed to formulate an oral delivery device, in the form of fast disintegrating tablets by using direct compression technology [6], with the aim of reaching a high serum concentration in a short period of time, Crospovidone, Croscarmellose sodium and Sodium Starch Glycolate were used as superdisintegrants.

MATERIALS AND METHODS:

Diclofenac Potassium was obtained from Aurobindo Pharma Ltd., and all excipients were purchased from the S. D. Fine Chemicals, Mumbai. All excipients and solvents used were in analytical grade.

Preparation of ODTs:

Tablets containing 50mg of Diclofenac sodium are prepared by direct compression method and the various formulae used in the study are shown in Table I. The drug, diluents, Superdisintegrants and sweetener are passed through sieve # 60. All the above ingredients were properly mixed together (in a poly-bag). Magnesium Stearate was passed through sieve # 30, mixed and blended with initial mixture in a poly-bag. The powder blend was compressed in to tablets on ten station rotary (9.5 mm punches) punch-tabletting machine

Table 1: Formulation composition of Diclofenac Potassium oral disintegrating tablets

Ingredients	F1	F2	F3	F4	F5	F6
Diclofenac Potassium	50	50	50	50	50	50
Anhydrous lactose	100	125	100	125	100	125
Vanillin	5	5	5	5	5	5
Magnesium stearate	2	2	2	2	2	2
Croscarmellose sodium	10	15	10	15	10	15
Sodium starch glycolate	5	10	15	20	25	30
crosprovidone	2	-	5	-	10	-
Micro crystalline cellulose	10	10	10	-	-	-
Sodium saccharine	10	10	10	10	10	10

Pre- compressional parameters:

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below

$$D_b = M / V_b$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$D_t = M / V_t$$

Where, M is the mass of powder

V_t is the tapped volume of the powder.

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder.

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r, \quad \theta = \tan^{-1}(h / r)$$

Where,

θ is the angle of repose , h is the height in cms r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder partials slip and roll over each other through the sides of the funnel.

Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density of the powder and

D_b is the bulk density of the powder.

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, Dt is the tapped density.

D_b is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)

POST COMPRESSIONAL PARAMETERS:

1. Organoleptic properties of tablets

Organoleptic properties such as taste, color, odour, were evaluated. Ten tablets from each batch were randomly selected and tested for taste, color, odour and physical appearance**.**

2. Thickness

The thickness of individual tablets of 6 numbers were measured with vernier calipers, it permits accurate measurements and provides information of the variation between tablets. Tablet thickness should be controlled within ± 5% variation of standard value.

3. Weight Variation Test

Twenty tablets from each batch were weighed with electronic digital balance and average weight was determined. Then individual tablets were weighted and individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Standard deviation was calculated. Using this procedure weight variation range of all the batches were determined and recorded.

4. **Friability**

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Thirty three tablets (6.600gms.) were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

5. Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester for 6 tablets. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge on the barrel to indicate the force. The force of fracture is recorded and the zero force reading is deducted from it. Generally, a minimum hardness of 5 - 7 kg/cm^2 is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 2-4 kg/cm^2.

6. Wetting time

The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten millilitres of water containing a water soluble dye eosin is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time.

7. Drug Content Uniformity

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to one tablet was dissolved in 100 ml of 6.8 pH phosphate buffer, stirred for 15 min and filtered. 1 ml of the filtrate was diluted to 100 ml with 6.8 pH phosphate buffer. Absorbance of this solution was measured at 226nm using 6.8 pH phosphate buffer as blank and content of drug was estimated.

8. In vitro Disintegration time

Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 phosphate buffer maintained at 37±2C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±2c. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

9. *In vitro* Dissolution studies:

Dissolution of the tablet of each batch was carried out using USP type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900ml of 6.8 pH of phosphate buffer used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 ^{0}C. 5 ml of sample was withdrawn at predetermined time interval of 2min., 4min., 6min., 8min and 10min. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV-visible spectrophotometer at 310 nm using buffer solution as blank solution.

RESULTS AND DISCUSSION:

Before formulating, preformulation study has been performed, drug excipients (1:1) mixture of (drug: superdisintegrant) compatibility study by using IR spectrophotometer (Model-Spectrum Rx, Perkin Elmer) has been studied. There are not any changes in functional groups of the drug. The powder mixture shows good flow properties, Low Hausner ratio (1.34), compressibility index (25.33) and angle of repose (18.54), these values indicate that the powder is having fairly good flowability properties. All the formulations were prepared under similar conditions to avoid processing variables.

Generally, compressibility index values up to 15% result in good to excellent flow properties. In addition, Bulk density may influence compressibility, dissolution and other properties. The result of angle of repose was found to be 14.73-18.75. All the formulations showed angle of repose within 30° which indicates good flow of powder mixture. Angle of repose little higher above 30° is indicative of fair flow behavior of powder. The loose bulk density and tapped bulk density for all formulations varied from 0.32 to 0.48 gm/cm3 and 0.38 to 0.57 gm/cm3 respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. All formulations showed good compressibility hence these tablets can directly compressed.

Table 2: Precompression Evaluation of the tablet blend

Formulation Code	Bulk Density	Tapped Density	Powder Flow properties	Hausner ratio
F1	0.46	0.55	16.36	1.01
F2	0.45	0.54	16.66	1.2
F3	0.46	0.55	16.52	1.19
F4	0.32	0.38	14.73	1.18
F5	0.45	0.52	18.75	1.15
F6	0.48	0.57	15.32	1.18

The post compression parameter have also evaluated .the friability of all the formulation was found to be less than 1.0%.The results shown resistance to loss of weight indicates the tablets ability to withstand abrasion in handling, packaging and shipment. The disintegration time of tablets was varied 20 to 38 seconds.The average weight of the prepared tablet was found 195 to 210 mg. A tablet requires certain amount of hardness to withstand the mechanical shocks in handling packaging and at time of application. The hardness of the tablet varied from 3.5-3.8 kg/cm 2 which have satisfactory strength to withstand the mechanical shocks.

***In vitro* dissolution studies**

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus (M/s Lab India (Model – DS 8000) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 6.8) was taken in vessel and the temperature was maintained at 37 ± 0.5°C. The results were shown in Table 4. The cumulative% of drug release of formulations prepared by hole technology was found to be, F1 showed 86.2% drug released at 30 mins. F2 showed 82.40% drug released at 30 mins, F3 showed 75.50% drug released at 30 mins, F4 showed 60.80% drug released at 10 min, F5 showed 98.96% drug released at 15 mins, F6 showed 88.43% drug released at 30 mins.

From the results F5 was selected as best formulation since it showed total drug release in 15 minutes.

Table 3: Post-compression parameters of ODTs of Diclofenac potassium

Formulation code	Weight Variation	Hardness Kg/cm^2	Friability %	Disintegration Time (sec)	Wetting Time (sec)	%Assay
F1	passes	3.7	0.41	35	45	94.81
F2	passes	3.6	0.46	30	40	88.09
F3	passes	3.6	0.46	24	35	76.01
F4	passes	3.5	0.3	48	55	69.26
F5	passes	3.8	0.3	20	30	99.89
F6	passes	3.6	0.42	38	47	88.52

Table 4: In vitro dissolution studies of all formulations in pH 6.8 Phosphate buffer

S.No	Time(min)	F1	F2	F3	F4	F5	F6	MF
1	0	0	0	0	0	0	0	0
2	5	47.70	26.80	29.90	25.50	48.60	30.67	37.00
3	10	60.10	38.30	38.34	33.50	55.40	45.40	45.6
4	15	71.10	46.40	53.34	42.70	98.60	54.50	76.62
5	20	84.60	68.50	65.9	57.80	-	73.70	88.44
6	25	87.20	78.20	74.25	61.70	-	86.10	95.52
7	30	86.2	82.4	75.50	60.8	-	88.43	97.34

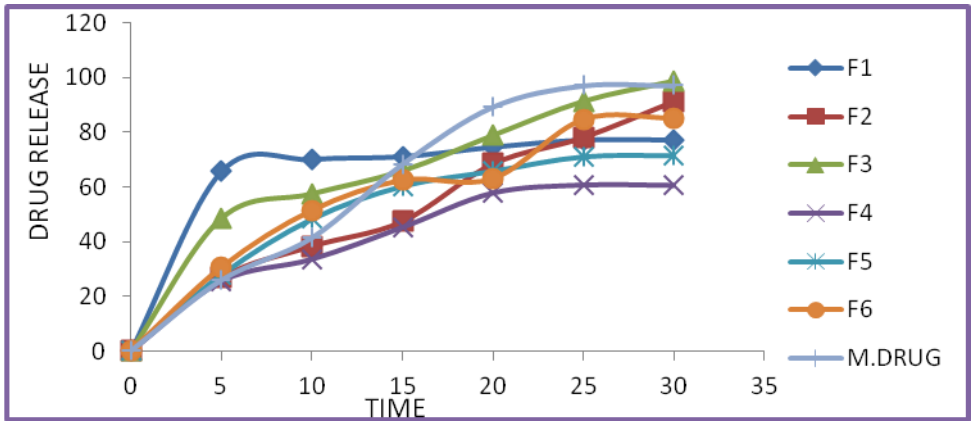

Fig 1: Comparative dissolution profile of all formulations F1-F6 with marketed drug

CONCLUSION:

Diclofenac potassium is a non steroidal anti-inflammatory drug (NSAID) used to treat pain or inflammation caused by arthritis or ankylosing spondylitis. Cataflam is available in generic. Conventional Diclefenac potassium tablets available in market are not suitable where quick onset of action is required. To overcome these problems, there is a need to develop a rapidly disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administrated without water anywhere at any time.

In the present work, mouth dissolving tablets were prepared by superdisintegrant addition, and evaluated for disintegration time, hardness and friability. From all these techniques, Superdisintegrant addition technique was selected based on less disintegration time.

The mouth dissolving tablets of Diclefenac potassium were prepared by superdisintegrants addition method using crospovidone, Croscarmellose sodium and Microcrystalline cellulose There are total six formulations were prepared and evaluated for Weight variation, thickness, friability, hardness, disintegration time, Wetting time, assay and in-vitro dissolution study.

The formulation F5 with 25 mg of SSG, Croscarmellose Sodium 10mg and Crospovidine 10mg showed disintegration in 20 sec and a wetting time of 30 sec and showed total drug release in 6 min. The formulation is effectively useful in treatment of acute pains.

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