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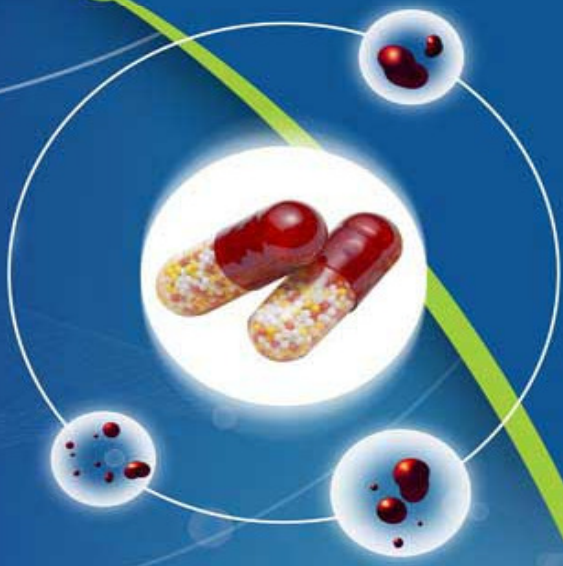

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Research Article

DESIGN AND DEVLOPMENT OF TASTE MASKED ORALLY DISINTEGRATING TABLET OF ACECLOFENAC

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ABSTRACT

Orally disintegrating tablets are gaining popularity over conventional tablets due to Their convince in administration and suitability for patients. The purpose of this research was to mask the intensely bitter taste of aceclofenac and to prepare orally disintegrating tablets for achievement of quick onset of action of the drug. Aceclofenac is an analgesic which has been proved to be efficient in managing relief from pain and including pain after surgery. In the present study an attempt has been made to prepare bitterless orally disintegrating tablet of Aceclofenac using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules and tablet was prepared with using superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate, were prepared blend and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from orally disintegrating tablets increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

Key words*: Aceclofenac, Superdisintegrants, Mass extrusion, orally disintegrating Tablets.*

INTRODUCTION

Recent advance in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration. [1]. Difficulty in swallowing is experienced by patient such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of non-compliance and ineffective therapy. [2].

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To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication.[3] . Orally disintegrating tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing.[4] . It is suited for tablets undergoing high first pass metabolism and is improving bioavailability with reducing dosing frequency to minimize side effect. Aclofenac is a synthetic opioid analgesic used for moderate to severe pain like labor pain, postoperative surgical pain, traumatic pain and cancer pain. Aceclofenac can be administered

orally, intravenously or rectally. Aceclofenac is rapidly absorbed orally is subjected to first pass metabolism and absolute bioavailability is only approximately 68%.[5] .It is bitter in taste. Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, Where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor.[6].Taste masked granules of bitter drugs can be prepared by using Eudragit E100 and ethanol. The extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymeric carrier while shaping the composite material to form a pharmaceutical product[7].In present study an attempt has been made to prepare taste masked granules of Aceclofenac. Taste masking of Aceclofenac was carried out by using Eudragit E100 (Mass extrusion method). These taste masked granules or complex was further formulated into the orally disintegrating tablets by direct compression method using sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of analgesic for postoperative pain.

MATERIALS AND METHODS

Characterization of DPC

Drug Content determination

DPC equivalent to 100 mg of drug was stirred by using magnetic stirrer with appropriate volume of 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) for 60 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper. Further, solution diluted with 0.1 N HCl and the drug content was determined spectrophotometrically at 271 nm.

Materials

Aceclofenac was obtained as a gift sample from Aldoc pharmaceutical Pvt. Ltd. Kota, India. Crospovidone was gift sample from Aldoc pharmaceutical Pvt. Ltd. Kota, India. Eudragit E-100 was gift sample from Evonik Degussa India Pvt.Ltd. Mumbai. Crosscarmellose sodium, Sodium starch glycolate and Avicel PH 102 were gift samples from Aldoc pharmaceutical Pvt. Ltd. Kota, India. All chemicals and reagents used were of analytical grade.

Methods

Preparation of drug-Eudragit E100 taste masked granules by mass extrusion Technique

The drug polymer complex (DPC) was prepared by using different ratios of drug and Aminoalkyl methacrylate copolymer (Eudragit E-100) and then 10% Isopropyl alcohol (IPA) was added to the mixture of each drug with Eudragit E-100 in a glass beaker. The consistency of the above solution is reduced to get gel type of preparation, and it is extruded through a 10 ml syringe on clean glass slab. After extrusion of the gel dried overnight till IPA is evaporated and solidified material (gel) crushed into granules using a mortar and pestle. The granules passed through a sieve sized 255 µm and collected.

Three batches were prepared containing drug-Eudragit E-100 in the ratio of 1:1, 1:1.5, 1:2, 1:2.5, 1:3 1:3.5, 1:4, 1:4.5, 1:5 in IPA by the above-mentioned method.

In Vitro Taste Evaluation

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.8) to predict release in the human saliva. DPC, equivalent to 100 mg of drug (i.e., its dose), was placed in appropriate volume of SSF and shaken for 60 seconds. Then the solution was filtered

through whatman filter paper. The amount of drug released was analyzed at 271 nm

In-Vivo Taste Evaluation: Taste evaluation was carried out in six healthy human volunteers, with DPC equivalent 10 mg of Aceclofenac sample held in the mouth for 5 to 10 s, then asked to spat out and the bitterness level was then recorded. A numerical scale was used with the following

Values: 0_tasteless, 0.5_very slight, 1.0_slight, 1.5_slight to moderate,

2.0_moderate, 2.5_moderate to strong, 3_strong, and 3__very strong

Formulation of [bitterless] fast dissolving tablet of drug: Eudragit E 100 granules by disintegrate addition method Fast dissolving tablets of Aceclofenac: Eudragit E100 granules were prepared using direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. Mannitol, Avicel PH 101 was used as directly compressible diluents. Nine formulations of Aceclofenac: Eudragit E100 granules were prepared and each formulation contained one of the three disintegrates in different concentration. Tablet weight was 250 mg; 8 mm punch was used for compression.

Table1. Drug Content and in-Vitro Taste Evaluation of Drug-polymer complex

S.No.	Drug-Polymer ratio	% Drug content *	% Drug Dissolved
1.	1:1	98.16	1.51
2.	1:1.5	98.55	1.44
3.	1:2	97.88	1.39
4.	1:2.5	98.61	1.22
5.	1:3	99.08	0.92
6.	1:3.5	98.20	0.89
7.	1:4	98.65	0.85
8.	1:4.5	99.17	0.74
9.	1:5	98.89	0.71

Table 2. Bitterness Evaluation of DPCs by Taste Panel

Volunteer	1	2	3	4	5	6
Pure drug	3	3	3	3	3	3
DPC (5 s)	0.5	0.0	0.0	0.5	0.0	0.5
DPC (10 s)	0.5	0.0	1.0	0.5	0.0	0.5

Evaluation of fast dissolving tablets of Aceclofenac

Pre compression parameters

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$\tan \theta = h/r$

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

Where, □ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed. [8]

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped

for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.[.

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

***Carr's Compressibility index*:** Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula.[8].

Carr's Index % = TBD – LBD/TBD X 100

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in Table

***Weight variation test*:** Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight.[9].

***Hardness test*:** The hardness of the tablet was determined using Monsanto Hardness Tester.[9].

***Friability test*:** Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.[9].

%Friability = (Loss in weight/Initial weight) x 100

***Water absorption ratio*:** A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and

Allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation.

R = 100 (Wa – Wb)/Wb

Where Wa and Wb are the weight before and after water absorption, respectively.[10]

***Wetting time*:** A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet

Completely. The time required for complete wetting of the tablet was then recorded.[10].

***Content uniformity test*:** Five tablets were weighed and powdered, 10 mg of equivalent of Aceclofenac was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 270 nm.[11]

***In vitro disintegration time*:** The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24±0.50C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.[10].

In vitro dissolution testing: Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 500 ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 370C±0.50C. Five milliliter's of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution

medium. The samples were analyzed spectrophotometrically at 270 nm.[10].

TABLE 3: COMPOSITION OF ACECLOFENAC – EUDRAGIT E100 FAST DISSOLVING TABLETS

Ingredients(mg)	Formulation code								
	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8	TM9
Aceclofenac:Eudragit	130	130	130	130	130	130	130	130	130
Avicel PH102	47.5	45	42.5	47.5	45	42.5	47.5	45	42.5
Crospovidone	2.5	5.0	7.5						
Crosscarmellose				2.5	5.0	7.5			
Sodium starch							2.5	5.0	7.5
Mannitol	50	50	50	50	50	50	50	50	50
Aspartame	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	250	250	250	250

*130 mg of drug-polymer complex Equivalent to 100 mg of drug

TABLE 4: PRE-COMPRESSIONAL PARAMETERS OF ALL FORMULATIONS

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
TM1	0.544	0.652	16.56442	1.198529	$28^{O}72'$
TM2	0.572	0.686	16.61808	1.199301	$26^{O}51'$
TM3	0.565	0.672	15.92262	1.189381	$28^{O}54'$
TM4	0.569	0.661	13.91831	1.161687	$25^{O}52'$
TM5	0.567	0.667	14.9925	1.176367	$28^{O}31'$
TM6	0.548	0.651	15.82181	1.187956	$27^{O}85'$
TM7	0.546	0.626	12.77955	1.14652	$27^{O}77'$
TM8	0.541	0.631	14.26307	1.166359	$28^{O}61'$
TM9	0.545	0.633	13.90205	1.161468	$26^{O}12'$

TABLE 5: POST-COMPRESSIONAL PARAMETERS OF ALL FORMULATIONS

Formulation code	Hardness test (kg/cm^2) ±SD, n=3	Friability (%) ± SD, n=10	Weight variation (%) n=10	Thickness (mm) ±SD, n=5	Drug content (%) ±SD, n=3
TM1	3.13 ± 0.21	0.8217± 0.01	Passes	2.56 ±0.03	99.53±0.42
TM2	3.70 ± 0.30	0.7262 ±0.05	Passes	2.59 ±0.05	99.41±0.51
TM3	3.51 ± 0.50	0.5314 ±0.03	Passes	2.55 ±0.03	98.77±0.71
TM4	3.73 ± 0.29	0.6425 ±0.11	Passes	2.56 ±0.06	99.12±0.49
TM5	3.81 ± 0.51	0.6346 ±0.05	Passes	2.55 ±0.03	99.33±0.66
TM6	3.50 ± 0.40	0.7114 ±0.16	Passes	2.52 ±0.05	98.51±0.75
TM7	3.66 ± 0.29	0.5612 ±0.07	Passes	2.56 ±0.04	99.65±0.42
TM8	2.77 ± 0.71	0.8554 ±0.11	Passes	2.54 ±0.05	98.80±0.62
TM9	3.12± 0.42	0.7377 ±0.15	Passes	2.56 ±0.04	99.27±0.48

TABLE 6: POST-COMPRESSIONAL PARAMETERS OF ALL FORMULATIONS

Formulation code	**Wetting Time (n=3)(sec.) Mean ± SD**	**Water Absorption Ratio (%)(n=3) Mean ± SD**	**In vitro Disintegration Time(sec.) (n=3) Mean ± SD**
TM1	35 ±0.05	81.71±0.66	39.11±0.56
TM2	29±0.08	85.65±0.58	31.45±0.71
TM3	21±0.05	91.12±0.69	27.66±0.41
TM4	45±0.04	78.33±1.12	51.12±0.22
TM5	38±0.03	82.51±1.41	43.25±1.23
TM6	29±0.05	86.56±0.20	36.31±1.53
TM7	46±0.05	77.41±1.06	68.23±0.96
TM8	39±0.04	82.66±1.81	54.22±0.69
TM9	30±0.05	85.25±0.91	41.15±1.15

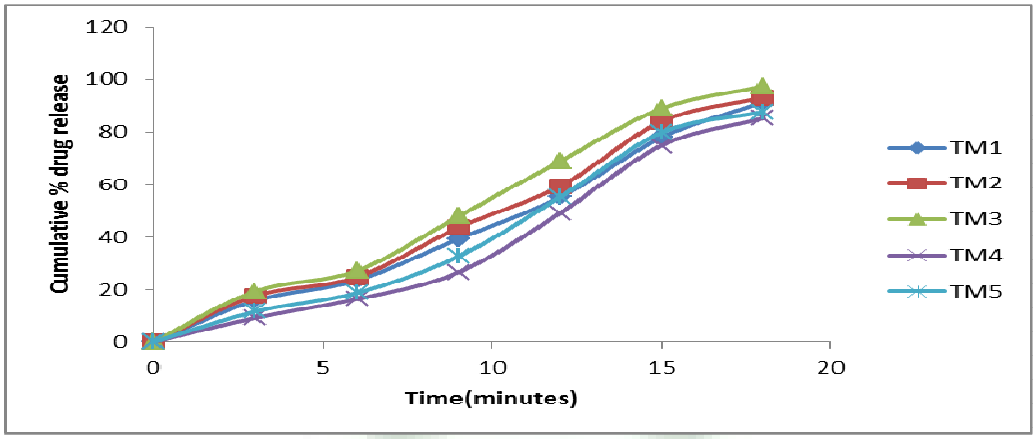

Fig.1: Zero order release kinetics

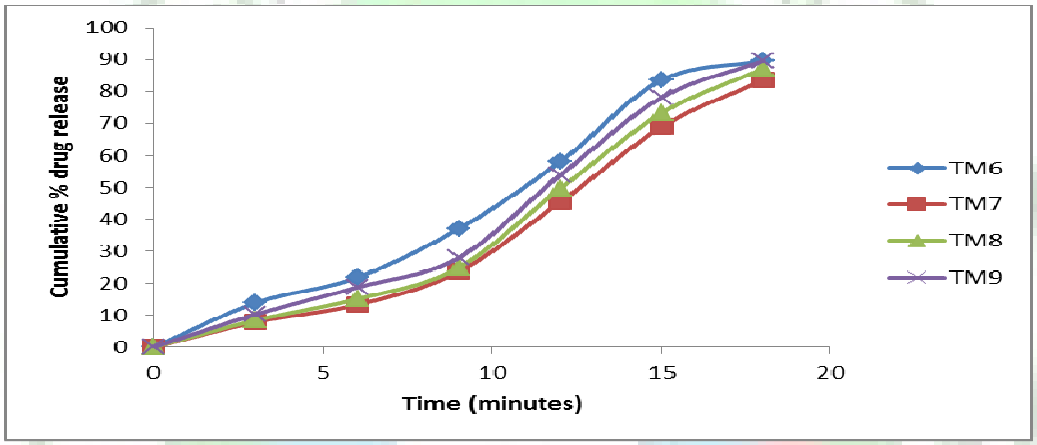

Fig. 2: Zero order release kinetics

RESULTS AND DISSCUSSION

Eudragit E100 was selected for the taste masking of Aceclofenac. The taste-masked granules of drug and Eudragit E100 were prepared by simple mass extrusion\ technique using syringe. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tableting. Loose density was found in the range of 0.54-0.572g/cm3 and the tapped density between 0.626-0.686g/cm3. The powder blends of all the formulations had Hausner's factor values which were in the range of 1.14652-1.199301 indicating good flowability. The compressibility index was found between 12.77955-16.61808. Hence the prepared blend spossessed good flow properties and these can be used for tablet manufacture. All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, wetting time, water absorption ratio, disintegration and dissolution which were reported in Table. All above properties and value were near to boundary of standard limit. All the tablets maintained hardness in the range 2.77 –3.81 kg/cm^2. The loss in total weight of the tablets due to friability was in the range of 0.5314 - 0.8554 %. The drug content in different formulation was highly uniform and in the range of 98.51-99.65%.

Wetting time is used as an indicator of the ease of tablet disintegration and found to be 21-46sec. Water absorption ratio ranged from 77.41-91.12. The result in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets, the value were with 27.66-68.23sec. In vitro dissolution studies are shown in Figure 1. The cumulative % of drug release increased in 18 min with increased in the concentration of superdisintegrant. At 5% superdisintegrant level the drug release at the end of 18s min. were found to be 97.40%, 89.54% and 89.54% with crospovidone, crosscarmellose sodium and sodium starch glycolate respectively.

CONCLUSION

In the present study it can be concluded from the characterization of orally disintegrating tablets of Aceclofenac that formulation containing crospovidone is most acceptable. It was observed that to further increase the drug release from orally disintegrating tablets, solubility enhancement of Aceclofenac required and is under investigation.

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