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Formulation and Evaluation of Fast Dissolving Tablets of Aceclofenac by Direct Compression Using Novel Co-Processed Granulating Technique

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Abstract
Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology. Aceclofenac is a nonsteroidal agent with marked anti-inflammatory and analgesic properties having poor water solubility leading to variable dissolution rate. Fast dissolving tablet is an approach to increase the dissolution rate faster and gives quick onset of action of poorly soluble drug. The purpose of this study was to formulate and evaluate fast dissolving tablets of famotidine using sodium carboxy methyl cellulose, pregelatinized starch and sodium starch glycolate as superdisintegrants. Tablets were prepared by direct compression technique. The granules were evaluated for 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, In-vitro disintegration time. % drug release from the In-vitro dissolution profile for the prepared formulations was 98.89% and for the marketed conventional formulation was 75.45% at the end of 20 minutes. The present study demonstrated potentials for faster dissolution, rapid absorption, improved bioavailability, effective therapy and patient compliance

Keywords: *Aceclofenac, Superdisintegrants, Fast dissolving tablets.*

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I. INTRODUCTION

The fast dissolving drug delivery system is rapidly gaining acceptance as an important novel drug delivery system. This delivery system offers better patient compliance than conventional tablet dosage form [1]. Difficulties with and resistance to tablet-taking are common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric, and psychiatric patients. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties [2].

Fast dissolving tablets (FDTs) are prepared by various techniques, mainly direct compression, lyophilization, spray drying, freeze drying and moulding. FDTs disintegrate and/or dissolve rapidly in the saliva without the need for water, releasing the drug immediately. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosageform [3,4]. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies [5]. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants [6].

Aceclofenac is a nonsteroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of Aceclofenac is largely based on the inhibition of prostaglandin synthesis, a decrease in the expression of several cytokines including interleukin and tumor necrosis factor [7]. It is specially used for osteoarthritis, rheumatoid arthritis, spondylitis, dental pain, postoperative pain, post-traumatic pain, low back pain, and gynecological pain [8]. As a result, it could be concluded that aceclofenac may be a better option for the management of pain. Therefore, it was chosen as a model drug for preparation of the fast dissolving tablets dosage form.

II. MATERIALS AND METHODS

2.1 MATERIALS

Aceclofenac was obtained as gift sample from Wockhardt Ltd., Microcrystalline cellulose (MCC), Sodium carboxy methyl cellulose, Pregelatinized starch, Mannitol and Aspartame were gift sample from Signet Chemical Corporation. All chemicals and reagents used were of analytical grade.

2.2 PREPARATION OF TABLETS

Accurately weighed quantities of Aceclofenac, mannitol, aspartame and microcrystalline cellulose, were mixed and passed through sieve no. 60. The blend was suspended in 100% of iso-propyl alcohol (IPA) for the period of 10 minutes, homogenously mixed using normal mortar and pestle and the process was further carried out for the period of 20 minutes and passed through sieve no 40. The granules were dried at 40ºC for 30 minutes in a controlled humidity chamber. The obtained dry granules were re-granulated by passing through sieve no. 40. The granules obtained were blended with microcrystalline cellulose and a super disintegrant sodium carboxy methyl cellulose/pregelatinized starch/sodium starch glycolate and a mixture of magnesium stearate and colloidal silicon dioxide. The lubricated granules were subjected for direct compression to produce 300 mg tablets in a Rimek 10 station tablet press. The tablets obtained were containing 100 mg of Aceclofenac, respectively and compositions of the ingredients are shown in Table.1.

Table 1: Composition of Aceclofenac Fast Dissolving Tablets

Ingredients in (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Aceclofenac	100	100	100	100	100	100
MCC	90	85	90	85	90	85
Mannitol	50	50	50	50	50	50
Aspartame	3	3	3	3	3	3
Sodium carboxy methyl cellulose	5	10	-	-	-	-
Sodium starch glycolate	-	-	5	10	-	-
Pregelatinized starch	-	-	-	-	5	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Total	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

2.3 EVALUATION OF GRANULES

Granules were evaluated for the flow parameters such as angle of repose Tap density, Hausner ratio and Carr's index as given Table 2.

2.3.1 Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [9,10].

$$\tan\theta = h/r$$

$$\text{Therefore } \theta = \tan h/r$$

Where θ = angle of repose, h = height of the pile, r = radius of the pile base

2.3.2 Bulk Density

Apparent bulk density (Pb) was determined by pouring blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula [11].

$$Pb = M / Vb$$

2.3.3 Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend as measured. The tapped density (Pt) was calculated using the formula [11].

$$Pt = M / Vt$$

2.3.4 Carr's compressibility index

The simplex way of measurement of the free flow of blend is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (I) which is calculated by using the following formula [11].

$$I = \{(Vb – Vt)/ Vb\} X 100$$

2.4 EVALUATION OF TABLETS

2.4.1 Uniformity of weight

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight [12].

2.4.2 Thickness

The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness were measured [12].

2.4.3 Hardness

Hardness was determined by taking six tablets from each formulation, using a Monsanto Hardness Tester [12].

2.4.4 Friability

The friability of sample of six tablets ware measured using a Roche Fribilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screen and the percentage of weight loss was calculated [12].

$$\% \text{ Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

2.4.5 Drug content uniformity

Two tablets were weighed and powdered. An amount of the powder equivalent to 100 mg of Propranolol was dissolved in 100 ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 276 nm using UV-Visible spectrophotometer (UV 1601- Shimadzu, Japan) [12].

2.4.6 *In vitro* disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24±0.5^{o}C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported [13].

2.4.7 *In vitro* dissolution testing

In vitro drug release studies for the prepared fast dissolving tablets were conducted for a period of 30 min using USP type-II apparatus. The dissolution test was performed using 900 ml of phosphate buffer (PH 7.4) was taken as the dissolution medium at 50 rpm and 37±0.5^{o}C. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 276 nm by a UV-Visible spectrophotometer.

2.4.8 Wetting time

The tablet was placed in a Petri dish having a 6.5 cm in diameter, containing 10 ml of water and the time for complete wetting was recorded. The experiment was carried out in triplicate at room temperature [14,15].

III. RESULT AND DISCUSSION

The co-processed granules ready for compression containing drug and various excipients were evaluated pre-compression parameters to study the flow properties of granules, to achieve uniformity of tablet weight Table 2.

The data obtained for angle of repose for all the formulations were tabulated in Table No. 2 and the values were found to be in the range of 24.35º to 30.04º. All the formulations showed the angle of repose less than 30º, which reveals good flow property of the granules. Bulk density was found in the range of 0.47-0.56g/cm^3 and the tapped density between 0.53-0.66g/cm^3. The results of Carr's compressibility index for the entire formulation blend ranged from 12.70 to 15.87%. Granules had shown excellent compressibility index values up to 15% resulting in good to excellent flow properties. The results for all the formulations were recorded in Table No. 2.

Table 2: Evaluation of prepared Aceclofenac granules

Formulations	Angle of Repose (θ)	Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	% Compressibility
F1	26.22^o	0.47	0.54	12.96
F2	30.02^o	0.56	0.66	15.15
F3	25.49^o	0.55	0.63	12.70
F4	30.04^o	0.53	0.61	13.11
F5	24.35^o	0.48	0.56	14.29
F6	26.58^o	0.53	0.63	15.87

The tablets prepared by direct compression by using novel co–processed granulating technique were subjected for evaluation according to various official specifications and other parameters. Shape, thickness, hardness, friability, weight variation, drug content, *In-vitro* disintegration time, wetting time, *In-vitro* dissolution studies were performed.

Shape and colour of tablets from each batch were examined under lens for shape and in presence of light for colour. Tablets of all the batches were flat, circular in shape and white in colour. Thickness of the tablets was measured by dial caliper by picking tablets randomly from all the batches. The results of thickness for tablets were shown in Table No.3. The mean thickness was almost uniform in all the formulations and values ranged from 3.10±0.03 to 3.16±0.06 mm, respectively. The standard deviation values indicated that all the formulations were within the range. Hardness of the tablets was in the range of 3.12±0.39 to 3.69±0.13 kg/cm2, respectively. The mean hardness test results are tabulated in Table No. 3. Friability of all the formulation was in the range of 0.33±0.06 to 0.36±0.04 %, respectively. The obtained results were found to be well within the approved range (<1%) in all designed formulations. The results are shown in Table 3. Weight variation for all the formulations is shown in Table No.3. All the formulations passed weight variation test, average percentage weight variation was found within the pharmacopoeial limits of ±10%. The obtained results were found to be 98.33±1.87 to 100.13±1.34% RSD. Drug content uniformity was performed for all the formulations and results are tabulated in Table No.3. The drug content was found to be 99.13±0.15to 99.89±0.11%. The results were within the range and that indicated uniformity of mixing of the drug with excipients in the developed formulations. *In-vitro* disintegration time of all the formulations recorded was in the range of 12.45±0.4 to 18.81±0.2 seconds, respectively. All the formulations are disintegrated in less than 20 seconds. The results are shown in Table.3 Wetting time of all the formulations recorded was in the range of 17.45±1.23to 20.04±1.21 seconds, respectively. The results of wetting time are shown in Table No 3. Wetting time is closely related to the inner structure of the tablet. The obtained results mimic the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of the tablet. The wetting process was very rapid in all the formulations. This phenomenon may be due to ability of swelling and also capacity of water absorption and cause swelling.

The results of *In vitro* dissolution studies are shown in Table 3. At 10% superdisintegrant level the drug release at the end of 20 minutes were found to be 91.85, 94.45 and 98.89 % with Sodium carboxy methyl cellulose, pregelatinized starch, Sodium starch glycolate respectively (Figure 1). It was observed that as the concentration of superdisintergrant increased the drug release also increased. With reference to the type of superdisintergrant, the release rate was found to follow the order: Sodium starch glycolate > pregelatinized starch > Sodium carboxy methyl cellulose. It was found that drug Release from the prepared formulation was 98.89% and for the marketed conventional formulation was 75.45% at the end of 20 minutes (Figure 1).

Table 3: Evaluation data of the prepared Aceclofenac fast dissolving tablets

Evaluation Parameters	F1	F2	F3	F4	F5	F6
Thickness (mm) ±SD	3.11±0.02	3.13±0.05	3.15±0.08	3.10±0.03	3.14±0.04	3.16±0.06
Hardness (kg/cm^2)	3.69±0.13	3.53±0.15	3.52±0.36	3.55±0.18	3.12±0.39	3.23±0.46
Friability (%)	0.36±0.04	0.34±0.02	0.34±0.07	0.36±0.02	0.34±0.03	0.33±0.06
Weight variation (% RSD)	98.56±1.54	100.04±1.04	100.13±1.34	98.33±1.87	99.66±1.11	98.45±1.59
Drug content (%)	99.85±0.15	99.89±0.11	99.13±0.15	99.79±0.11	99.78±0.17	99.63±0.13
Disintegration time (sec.)	18.81±0.21	13.12±0.34	14.66±0.12	13.12±0.51	12.45±0.42	17.53±0.45

Wetting Time (sec.)	19.13±1.42	18.23±1.63	20.04±1.21	18.56±1.61	18.91±1.64	17.45±1.23
Cumulative % drug release	86.67	91.85	89.16	94.45	92.16	98.89

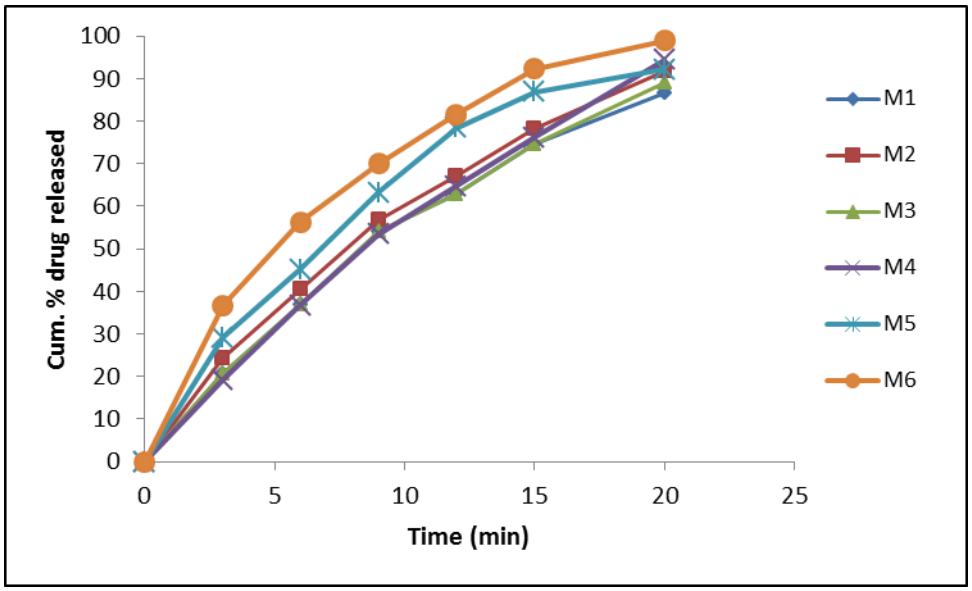

Figure 1: *In-Vitro* release profile of Aceclofenac fast dissolving tablets

IV. CONCLUSION

Results of fast dissolving tablets of Aceclofenac prepared direct compression by using novel co–processed granulating technique revealed that it is possible to mask the bitter taste of Aceclofenac using aspartame and mannitol. Moreover, % drug release from the developed tablet formulations were comparatively higher than the obtained marketed conventional tablet. All the developed fast dissolving tablets formulations disintegrated rapidly in the oral cavity and from the characterization it was found that tablet containing sodium starch glycolate was the best super disintegrating agent with acceptable limits. Hence it can be concluded that the superdisintegrant based fast dissolving tablets of Aceclofenac would provide quick onset of action without need of water for swallowing or administration. Further investigations are needed to correlate in vitro and in vivo release studies data.

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