Formulation Design and Evaluation of Baclofen Mouth Dissolving Tablets

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Abstract: The aim of this study was to prepare mouth dissolving tablets of Baclofen using various superdisintegrants like Kollidon CL-SF, crospovidone, sodium starch glycolate and Ludiflash by direct compression method. A total of four formulations were developed and the tablets prepared were evaluated for drug content, weight variation, friability, hardness and wetting time. *In vitro* disintegration and dissolution studies were also performed. Among the formulations tablets containing Kollidon CL-SF, sodium starch glycolate and Ludiflash showed superior organoleptic properties along with excellent *in vitro* disintegration and drug release pattern as compared to that containing croscarmellose. Our results suggest that addition of superdisintegrants is a useful technique for preparing mouth dissolving tablets by direct compression method and that proper selection of such agent ensures better drug release profile.

Key words: Baclofen · Crospovidone · Kollidon CL-SF · Ludiflash · Mouth Dissolving Tablet · Sodium Starch Glycolate

INTRODUCTION

Baclofen is chemically β-(amino methyl)-4-chlorobenzene propanoic acid. The molecular formula of Baclofen is $C_{10}H_{12}ClNO_2$ with the molecular mass 213.67g/mol. It is freely soluble in water, 0.1N HCl and 0.1N NaOH, slightly soluble in methanol and very slightly soluble in ethanol. It may act as an agonist for the $GABA_B$ receptors. Baclofen is rapidly and extensively absorbed and eliminated. The half-life of the drug is 2.5 to 4 hrs in plasma [1, 2].

Baclofen is a centrally acting synthetic skeletal muscle relaxant, which reduces spasticity in many neurological disorders like multiple sclerosis, amyotrophic lateral sclerosis, spinal injuries and flexor spasms, where pain persists predominantly [3-5]. In such cases the quick onset of action is of prime importance [5]. This drug is relatively ineffective in stroke, cerebral palsy, rheumatic and traumatic muscle spasms and Parkinsonism. The common adverse effects of Baclofen include drowsiness, lethargy and hypotension. Baclofen is available in oral and intravenous formulation. Though the conventional oral tablets are widely used, they possess a few practical drawbacks such as their nonsuitability when quick onset of action is required. Currently intrathecal Baclofen is the method of treatment for severe spasticity, however, chronic administration of Baclofen in the intrathecal space by implanted pumps is very expensive, uncomfortable and sometimes leads to several side effects [6].

Among many, oral route of drug administration has greater acceptance [7]. About 50-60% of all dosage forms is solid dosage form. This is popular because of ease of administration. Solid dosage forms offer certain benefits like accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are tablets and capsules; one important drawback of this dosage form for some patients, is the difficulty to swallow. In the past one decade, there has been an increased demand for more patient- friendly and compliant dosage forms. As a result, the attempts for developing new technologies have also been increasing. Since the development cost of a new drug molecule is very high, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and cost-effectiveness [8, 9].

Tablets that can rapidly dissolve or disintegrate in the oral cavity known as 'mouth dissolving tablets' have attracted a great deal of attention in recent time [10]. These tablets offer several benefits such as administration requires no water, quick disintegration facilitates rapid

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absorption, allow high drug loading and provide advantages of liquid medication in the form of solid preparation [11]. Mouth dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people [12-14]. The vivid advantages of mouth dissolving dosage forms are increasingly being recognized by manufacturers and researchers. The importance of such dosage form has recently been underlined when European Pharmacopoeia adopted the term "Orodispersible tablet (ODT)" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach in development of fast-dissolving tablets (FDT) is the use of superdisintegrant like cross linked carboxymethylcellulose (croscarmellose), sodium starch glycolate, crospovidone etc, which cause instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug quickly in the saliva [12, 15]. The common technologies used for manufacturing ODTs include freeze drying, moulding, spray drying, sublimation, disintegrant addition and direct compression [8, 16, 17]. Here direct compression has been applied in combination with superdisintegrants such as croscarmellose, sodium starch glycolate, Ludiflash, kollidon CL-SF to formulate Baclofen mouth dissolving tablets to have quick onset of action.

MATERIALS AND METHODS

Baclofen was received as a gift from Beximco Pharmaceuticals Limited. Kollidon CL-SF and Ludiflash were generously provided by BASF Bangladesh. Crospovidone, sodium starch glycolate and all other materials like aspartame, mannitol, microcrystalline cellulose and calcium stearate, used were of analytical grade and procured from commercial sources.

Preparation of Baclofen Mouth Dissolving Tablets: Baclofen mouth dissolving tablets were prepared by direct compression method according to formula given in the Table 1. Four different formulations were prepared. All the ingredients were sieved separately through sieve no. 40 except magnesium stearate which was sieved through sieve no. 60 and collected. The weighed amount of drug and other ingredients were mixed first and magnesium stearate was finally added and mixed thoroughly. The tablets were compressed in Clit Compression Machine (Pilot Press, Germany) using 8 mm standard concave punch.

Table 1: Composition of different formulations of Baclofen 5 mg mouth dissolving tablet

Formulation Ingredients	F1	F2	F3	F4
Baclofen	5	5	5	5
Croscarmellose sodium	-	-	8.75	-
Ludiflash	-	-	-	89.625
Kollidon CL-SF	7.5	-	-	-
Sodium Starch Glycolate	-	8.75	-	-
Microcrystalline Cellulose 102	5.625	5.625	5.625	-
Mannitol	77.5	75.25	76.25	-
Calcium stearate	1.25	1.25	1.25	1.25
Aspartame	1.25	1.25	1.25	1.25
Aerosil	1	1	1	1
Sodium Lauryl sulfate	1.875	1.875	1.875	1.875
Total	101	101	101	101

Micromeritics of Powder Blend: Before final compression of tablets, powdered mixture was subjected to pre-compression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density: Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described [18, 19].

Bulk Density $(D_b) = (M) / (V_o)$

where,

M = Mass or weight of the powder blend
V_o = Apparent volume of the powder blend into the cylinder

Tapped Density: Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance by either of the two methods as described below [18, 20].

Tapped density $(D_t) = (M) / (V_f)$

where,

M = Mass or weight of the powder blend
V_f = Final volume of the powder blend into the cylinder.

Powder Compressibility: Powder compressibility was determined by calculating the compressibility index (Carr's Index) and the Hausner Ratio [18, 20].

Carr's Index or Compressibility Index (I): This was calculated by the formula and expressed as percentage (%).

$$I = D_t - D_b / D_t \times 100\%$$

where,

D_b = Bulk density,

D_t = Tapped density.

Hausner Ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-
Hausner Ratio = D_t/D_b

where,

D_b = Bulk density,

D_t = Tapped density

Angle of Repose: The determination of angle of repose of Baclofen powder blend was carried out by employing fixed funnel method [21,22].

Angle of Repose $\theta = \tan^{-1}$ (H/R), H = height of the pile, R = radius of the pile.

Evaluation of Formulated Tablets: The prepared tablets were evaluated for various official and nonofficial specifications.

Weight Variation: Twenty tablets were selected at random and average weight was calculated. Then individual tablet was weighed and this weight was compared with an average weight [19].

Tablet Hardness and Friability: Tablets were evaluated for hardness and friability using Pharma Test Hardness Tester and Pharma Test Friabilator respectively [19].

Content Uniformity: Twenty tablets were taken and the amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100 mg of drug was transferred to 100 ml

volumetric flask. The powder was dissolved in 5 ml of 70% methanol and the volume was adjusted with phosphate buffer (pH 6.8). The sample was mixed thoroughly and filtered through a Whatman filter paper. The filtered solution was diluted suitably and analyzed for the drug content by UV spectrophotometer (Shimadzu 1700, Shimadzu Corporation, Kyoto, Japan) at 276 nm. The same phosphate buffer without drug served as blank [23].

Wetting Time: Ten petridishes (10 cm) containing tissue paper at the bottom were taken and ten ml of water containing eosin dye was added to each petridish. A tablet was then carefully placed on the surface of the tissue paper. The time required for the water to reach the upper surface of the tablet was noted as the wetting time in seconds [24, 25].

Modified Disintegration Time: The modified disintegration time was observed by placing the tablet into a petridish prefilled with water and allowing it to stand without shaking. The time required for complete disintegration was measured in seconds [26].

In vitro Disintegration Time: The *in vitro* disintegration time was determined using disintegration test apparatus (Eureka Alpha/Numeric Disintegration tester). A tablet was placed in each of the six tubes of the apparatus and a disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no discernible mass remaining in the apparatus was measured [26, 27].

Disintegration in Oral Cavity: The time required for complete disintegration of tablet in oral cavity was obtained from six healthy volunteers, who were given tablets from all the formulations [28, 29].

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was recorded. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation [28].

$$R = 100 \times (W_a - W_b)/W_b$$

where,

W_b = Weight of tablet before water absorption
W_a = Weight of tablet after water absorption

***In vitro* Drug Release Study:** *In vitro* drug release study was carried out using tablet dissolution test apparatus, USP Apparatus 2 (Paddle type) at 50 rpm (Eureka DT 700 Germany). 900 ml of phosphate buffer (pH 6.8) was placed in dissolution vessels and a temperature of 37±0.5°C was maintained. 10 ml sample was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated to the above temperature was added. The absorbance values of diluted sample were determined spectrophotometrically at 276 nm using UV spectrophotometer (Shimadzu 1700, Shimadzu Corporation, Kyoto, Japan) [30].

RESULTS AND DISCUSSION

Study of Flow Properties: In the present study, Baclofen mouth dissolving tablets were prepared by using Kollidon CL-SF, croscarmellose sodium, sodium starch glycolate and Ludiflash as superdisintegrants (Table 1). A total number of four formulations were prepared and tablets were made by direct compression technique.

As the flow property of the powder mixture is important for the uniformity of the mass of the tablets, both angle of repose and compressibility of the powder were analyzed before compression of the tablets. The angle of repose and compressibility index (%) ranged from 23.72±0.58° to 22.70±1.54° and 16.89±4.44 to 7.45±0.76%, respectively. The results of bulk density and tapped

density also ranged from 0.54±0.02 gm/ml to 0.51±0.03 gm/ml and 0.62±0.01 gm/ml to 0.58±0.02 gm/ml respectively. All these data indicate that the flow property of powder blends was satisfactory (Table 2).

Tablet Characteristics: The data obtained from post-compression parameters such as hardness, friability, weight variation, thickness are shown in Table 3. The hardness was found to be in the range of 2.85±0.11 to 4.79±0.03kg/cm^2 for all the tablets from all the formulations indicating that these formulations confer adequate mechanical strength to withstand physical and mechanical stress during handling of the tablets. In all the formulations, the friability values were less than 1% which met the pharmacopoeial limits. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values (100.45±0.11 to100.94±0.50) indicating that mixing of drug, disintegrants and excipients was efficient and homogenous.

***In vitro* Wetting and Disintegration Studies and Assay:** The *In vitro* disintegration time, modified disintegration time, wetting time, amount of drug content, disintegration in oral cavity and water absorption ratio were also determined and results are shown in Table 4. The percent drug content of Baclofen in all the tablets was found to be

Table 2: Micromeritics of powder blends*

Formulation batch code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility (%)	Hausner ratio	Angle of repose (θ)
01.	0.53±0.02	0.61±0.01	11.14±0.03	1.15±0.03	23.72°±0.58
02.	0.51±0.03	0.61±0.01	16.89±4.44	1.20±0.06	23.34°±0.62
03.	0.53±0.01	0.58±0.02	7.45±0.76	1.07±0.01	22.70°±1.54
04.	0.54±0.02	0.62±0.01	12.91±1.81	1.14±0.02	23.04°±0.98

*Data Expressed as: Mean± SD [Mean=3, SD=Standard Deviation]

Table 3: Physical parameters*

Formulation batch code.	Appearance	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)
01.	Passes	100.94±0.50	0.134±0.004	4.79±0.03	3.37±0.03
02.	Passes	100.46±0.11	0.356±0.01	2.85±0.11	3.34±0.01
03.	Passes	100.45±0.11	0.385±0.01	3.92±0.07	3.38±0.04
04.	Passes	100.47±0.13	0.231±0.007	3.35±0.09	3.34±0.01

*Data Expressed as: Mean± SD [Mean=3, SD=Standard Deviation]

Table 4: Analytical parameters*

Formulation batch code	*In-vitro* disintegration time (sec)	Modified disintegration (sec)	Wetting time (sec)	Disintegration in oral cavity (sec)	Water absorption ratio	Drug content (%)
01.	29.31±0.49	27.66±2.51	19.00±4.00	16.53±0.58	19.00±0.18	95.10±0.07
02.	32.50±1.16	34.33±3.98	12.3±2.510	19.92±4.21	19.93±1.78	105.07±0.56
03.	44.20±2.65	34.33±3.51	19.33±5.13	23.81±2.21	21.60±2.21	99.62±0.56
04.	31.10±1.24	34.33±5.85	19.33±5.10	24.73±3.02	18.58±0.50	103.20±0.02

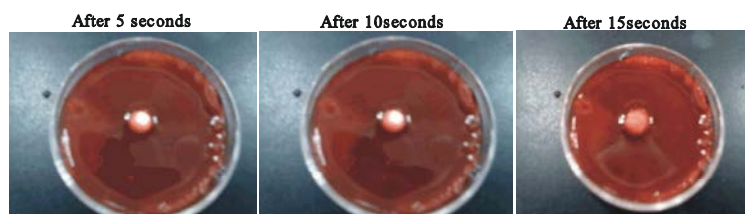*Data Expressed as: Mean± SD [Mean=3, SD=Standard Deviation]

After 5 seconds | After 10seconds | After 15seconds

Fig. 1: Observation of the wetting time for tablets at different time intervals

After 5 seconds | After 10 seconds | After 15 seconds

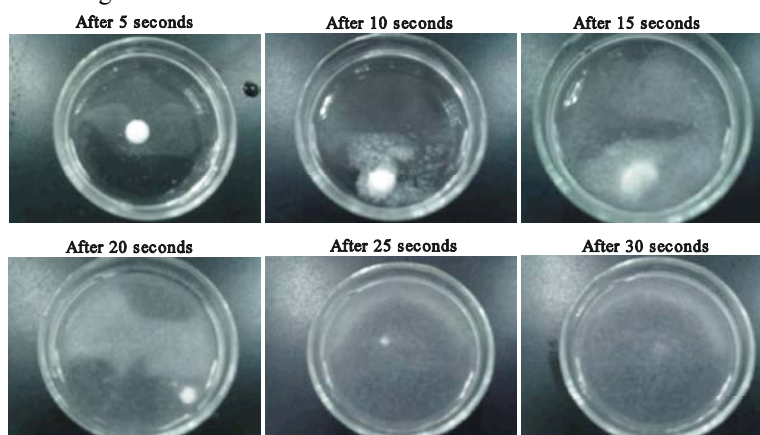After 20 seconds | After 25 seconds | After 30 seconds

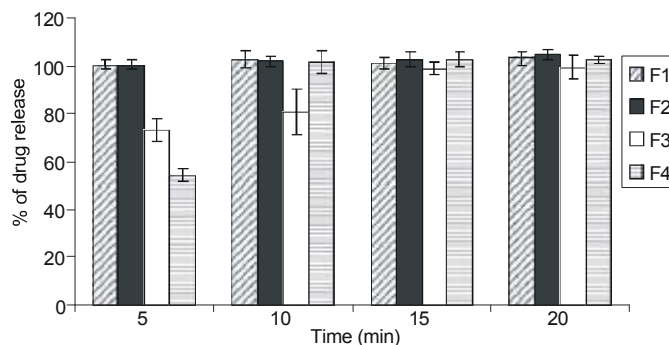Fig. 2: Observation of the modified disintegration time for tablets at different time intervals

Fig. 3: Drug release profile of different formulations at different time intervals

between 95.10±0.07% to103.20±0.08%, which was within the acceptable limit. The results obtained from *in vitro* wetting and *in vitro* disintegration tests for all the tablets were found to be within the acceptable limits and satisfied the criteria for mouth dissolving tablets (Table 4). The *in vitro* wetting time (Fig. 1) was in the range of 12.30±2.15 to 19.00±4.10 s while the *in vitro* disintegration time was 29.31±0.49 to 44.20±2.65 s (Table 4). Similarly modified disintegration time calculated was also compelling as found in the range of 27.66±2.51to 34.33±5.85 s (Table 4, Fig. 2).

It was observed that when Kollidon CL-SF, sodium starch glycolate and Ludiflash were used as disintegrants, the tablets disintegrated rapidly compared to other tablets prepared using croscarmellose sodium presumably by its

low water uptake and gelling tendency. Among the formulations, F1 and F2 containing Kollidon CL-SF and sodium starch glycolate were found to be the best as tablets from these formulations showed good hardness, low friability and least wetting and disintegration time.

Drug Release Studies: The cumulative percent of the drug release from all the formulations are shown in Fig. 3. F1 was found to release 102.89% drug while F2 released 101.99% drug at the end of 10 min of dissolution. Although F4 released lesser amount of drug at 5 min compared to others, however, this level was increased at 10 min (Fig. 3). On the other hand, F3 was found to be slow in drug release throughout. Since mouth dissolving tablets are expected to dissolve in least possible time [27],

we conclude both F1 and F2 can be considered for the preparation of Baclofen mouth dissolving tablet. These results suggest that a good bioavailability of drug is possible from mouth dissolving tablets containing superdisintegrants. Our results are consistent with previous studies demonstrating the effect of superdisintegrants in fast dissolving tablets [10, 11, 15].

CONCLUSION

From the above discussion, we understand that the formulation F3 shows superior organoleptic properties but at the same time exhibited decreased dissolution profile as evidenced from our study. The formulation F4 although showed good drug release profile but did not show other parameters as perfect as formulations F1 and F2. However, F1 and F2 have shown better results in all the tests, indicating that these two formulations may be transferred to scale up for large scale production. Based on our experimental data it can be concluded that mouth dissolving tablets of Baclofen can be prepared successfully using F1 and F2 formula as they satisfy the criteria of a mouth dissolving tablet and would be the alternative to the currently available conventional tablets.

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