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RESEARCH ARTICLE

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLET OF BACLOFEN BY DIRECT COMPRESSION METHOD USING TWO DIFFERENT SUPERDISINTIGRANTS

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ABSTRACT

Mouth dissolving tablets facilitates in resolving swallowing issues of oral dosage forms. Baclofen was selected as a model drug. Reverse concentration of croscarmellose sodium and cross povidone were used as superdisintigrants in concentration of 40% of total tablet weight with appropriate concentration of other excipients. Prepared batches of tablets were evaluated for hardness, friability, content uniformity, wetting time, Water absorption ratio, disintegration time, dissolution studies and stability studies. The optimization is based on immediate disintegration time (approximately 25-35 seconds) and in-vitro drug release pattern. Disintegration time and in-vitro drug release were tested in 0.01N Hcl solution occur relevant drug release pattern. The formulation F5 and F3 contained 40% w/w. Crospovidone emerged as an impending polymer (95% release and total DT is 1.31 minutes) based on drug release characteristic (in 0.01N Hcl solution) compared to controlled formulation.

INTRODUCTION

Center of drug evaluation and research (CDER, US FDA) defined Mouth dissolving Tablets (MDT) as a solid dosage form containing medical substances, which disintegrates rapidly, usually within a matter of seconds, when located ahead tongue. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain avoidance, versatility (to accommodate various types of drugs), and most importantly appropriate patient compliance. Mouth-dissolving tablet dissolves or disintegrates rapidly within few seconds (25-60 sec) in oral cavity without any need of water or chewing (1-4). Recent developments in this area have presented viable dosage alternatives for patients. Development is based on Formulation and Evaluation of mouth dissolving tablet of baclofen by using many ingredients such as diluents, super disintegrates polymer, Flavoring agent, sweetening agent, Permeation enhancers, Preservatives, Lubricant. Baclofen has broad spectrum therapeutic category such as Muscle relaxant, Cerebral Palsy, hiccups, alcohol withdrawal (4-8). Baclofen mouth dissolving Core tablet was prepared from direct compression method and evaluated. Optimization of croscarmellose sodium and cross povidone as superdisintigrant serves as important tool for fast disintegration in mouth within 25 sec to 60 seconds within saliva , without need of water and having pleasant mouth with attainment of appropriate bioavailability regulatory requirement on the grounds of IVIVC (in-vitro in-vivo correlation) (9-13).

MATERIALS AND METHODS

Baclofen was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad and Crospovidone, Croscarmellose sodium from (Lupin pharmaceuticals), Lactose, Magnesium stearate, Mannitol (Rankem, Mumbai), Ascorbic acid (vitamin c) Talc (merck chemicals, mumbai)(14-16).

PREFORMULATION STUDY

Physical appearance

Baclofen powder was examined for its organoleptic properties like colour and odour. Visually and optically both. It was observed that baclofen was white odourless crytalline powder with hygroscopic property (18).

Solubility study

Baclofen was tested qualitatively for its solubility in various solvents. Solubility can be affected by temperature, pressure, purity

of the compound, pH, composition of the buffer solution and other characteristics (polymorphs, aggregation, and super saturation) data presented in table no. 2 (19-20).

Melting point determination

Melting point was determined by capillary method using Digital Melting point apparatus. The temperature was noted at which the drug started melting, Observed melting point temperature was start 207˚C - 210˚C end (21).

Preparation of calibration curves

The spectrophotometric method of analysis of Baclofen was found to be reproducible and highly sensitive, λ_{max} was 221 nm. standard curve of Baclofen is prepared in Distilled water , 0.1 N Hcl solution in the concentration range of 2-20 µg/ml. in water The slope and intercept of the calibration curve were 0.013and 0.002 respectively. The correlation coefficient 'r^2' values were calculated as 0.997 as shown in table 3 and figure 1. In 0.1 N Hcl The slope and intercept of the calibration curve were 0.043and 0.012 respectively. The correlation coefficient 'r^2' values were calculated as 0.996 as shown in table 4 and figure2 (22-25).

Determination of partition coefficient

In order to determine a partition coefficient, for concentrations of the substances dissolved in the two phases (lipophilic, Hydrphilic) must be determined. The partition behavior of drug was examined in n-Octanol: Water systems. By using separating funnels and both phase was analysed spectrophotometrically at 221 nm (26).

$$\text{PartitionCoefficient}, K = \frac{\text{Amount of drug in organic layer}}{\text{Amount of drug in aqueous layer}}$$

Fourier-Transform Infra Red spectroscopy (FTIR)

The aim of compatibility study is to test interaction between the excipients and drug. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted. There is no drug polymer interaction was found (27).

PREPARATION OF MOUTH DISSOLVING TABLETS OF BACLOFEN

Direct compression method

The required amounts of ingredients were weighed accurately. 20.0 mg of baclofen was taken as model dose because of its high potency, total 6 formulations were made (F1, F2, F3, F4, F5 &F6) (table no. 1) for better optimization and analysis of variation in concentration of superdisintigrant's followed by preparation of granules, 1ml of methanol and 0.5 ml of ethanol were mixed by adding sufficient quantity of hot distilled water. This binder solution was added to baclofen, mixed well to get moist dough and passed through 22 mesh sieve two times to prepare granules, other ingredient were mixed with this. The uniform blend is then directly compressed in rotary punching machine (multistation tablet punching machine in size of 6 mm) (28-29), obtained tablets weight approximately 150 mg tablets and hardness 4-5 Kg/cm^2. The formula and Composition of Baclofen mouth dissolving tablets is shows in table no. 1.

EVALUATION OF TABLETS

Weight variation test

20 tablets were selected randomly and average weight was determined. Then individual tablets were weighed and compared with average weight.

Content uniformity

Two tablets were placed in a 100 ml of water and stirred until completely dispersed. A smooth dispersion produced and passed through a sieve screen 710 mm (20 meshes), sample was analyzed spectrophotometrically with respect to concentration and absorbance (36).

Drug estimation

10 tablets were taken and weighed accurately. Average weight is calculated and equivalent to 100 mg of drug was taken for estimating the drug content in the total tablet. Percentage of drug content is calculated by

$$Y/X \times 100$$

Where Y = Total Tablet weight (mg)

X = Actual amount of drug (mg)

Friability test

Friability was determined by Roche friabilator at 25 rpm with dropdown of 10 tablets at a height of 6 inches in each revolution subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed (36). The friability (f) is given by the formula:

$$F = (1-W_0/W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test.

Hardness test

Hardness or tablet crushing strength (Fc) (the force required to break a tablet in a diametric compression) was measured using Monsanto and Pfizer tablet hardness tester.

Disintegration test

Disintegration time is determined using the disintegration apparatus USP (E.I. Instrument, Hariyana, India) in 0.1N HCl maintaining the temperature at 37 ± 2°C (30).

Water Absorption Ratio and Wetting Time

Wetting time: The wetting time and capillarity of the mouth dissolving tablets were measured by a conventional method. Tablets were placed in a Petridish of 6.5 cm diameter containing 10 ml water at room temperature; time for complete wetting of tablets was recorded.

Water absorption ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of distilled water. A tablet was put on paper and the time required for complete wetting of the tablet was measured, wetted tablet was then weighed. Water absorption ratio "R" was determined using the equation as follows

$$\frac{\mathbf{Wa} - \mathbf{Wb}}{\mathbf{Wb}} \times 100 = \mathrm{R}$$

Where, Wa is Weight of tablet after water absorption and Wb is Weight of tablet before water absorption (30).

In-Vitro Dissolution rate study

USP Type II (paddle type) method was selected for dissolution profile of Baclofen. The dissolution was carried out for 5 hours (300 min) in 0.1N HCl (13), temperature was maintained at 37 ± 2°C at a constant paddle speed of 50 rpm. Sample (10 ml) was withdrawn every 30 min and filtered through membrane filter (pore size 0.22 μm). The absorbance was measured spectrophotometrically at 221 nm. Actual amount of released drug was determined from formula.

$$\mathbf{Dw/dt = KS\ (C_{sat} - C_{sol})}$$

Here dw/dt = drug release, K = Dissolution constant, S = Surface area, C_{sat} = conc. of saturated sol., C_{sol}= conc. at given time (31).

Stability Study

Stability studies were carried out in various temperature range and RH (Relative Humidity) of selected formulations for 1 month.

Temperature	Relative humidity (RH)
25°C ± 2°C	60% ± 5%
35°C ± 2°C	60% ± 5%
40°C ± 2°C	75% ± 5%

Twenty tablets of optimized formulation were placed in Petri dish, which were kept in desiccators containing calcium chloride (desiccant) at room temperature for one day. Then the tablets were weighted and placed in humidity chamber, which was maintained at 3^0c 25^0 c, 40c, 50^0c, with75% RH for one month (32).

DISCUSSION

Mouth/fast/oral dissolving tablets were prepared by direct compression method Crosscarmilose sodium and Crosspovidone were used as super disintegrating agents. In vitro dissolution studies of various formulations (CCS, CPD) were carried out in 0.1N Hcl solution. Formulation containing crosspovidone showed highest dissolution rate. In the presence of super disintegrants the matrix might be distorted resulting in higher surface area, hence rapid rate dissolution.

CONCLUSION

As a majority of the people polled indicated they would refer an MDT formulation over a traditional tablet, it is likely that patients will ask for more and more MDT products as the get more familiar with the technology and its convenience. The main factor that will differentiate the drug company fitting for market share in an increasingly crowded pharmacy will be test. For an MDT, the success or failure of a new drug (or an old drug in a few forms) will be determined by how much the customer enjoys the overall experience.

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RESULT OF EXPERIMENTAL DATA

Table 1: Composition of mouth dissolving tablets of Baclofen

Sno.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Baclofen Hydrochloride	20	20	20	20	20	20
2.	Crosscarmellose sodium	50	50	50			
3.	Crosspovidone				50	50	50
4.	Lactose	20	20	20	20	20	20
5.	Mannitol	20	20	20	20	20	20
6	Ascorbic acid (vitamin c)	20	20	20	20	20	20
7.	Magnesium stearte	10	10	10	10	10	10
8.	Talc	10	10	10	10	10	10

Table: 2 Solubility of Baclofen

S. No.	Solvent	Ratio	Solubility
1.	Water + Baclofen	10:1	Soluble
2.	Methanol + Baclofen	10:1	Slightly Soluble
3.	Ethanol + Baclofen	10:1	soluble
4.	0.1 N Hcl + Baclofen	10:1	Freely Soluble
5.	N- Octanol + Baclofen	10:1	Slightly Soluble
6.	Ethyl acetat + Baclofen	10:1	Slightly soluble

Table 3: Calibration Curve of Baclofen in Distilled Water

S.No.	Drug Conc. (µg/ml)	Absorbance	Statistical Parameters
1.	2	0.024	Correlation coefficient- $\mathbf{r^2}$ = 0.997 Slope **m** = 0.013 Intercept **c** = +0.002 Equation of Line- y = 0.013x+0.002
2.	4	0.061	
3.	6	0.078	
4.	8	0.102	
5.	10	0.137	
6.	12	0.161	
7.	14	0.186	
8.	16	0.215	Total Absorbance
9.	18	0.229	
10	20	0.261	1.454

Fig.1 Calibration curve of Baclofen in water

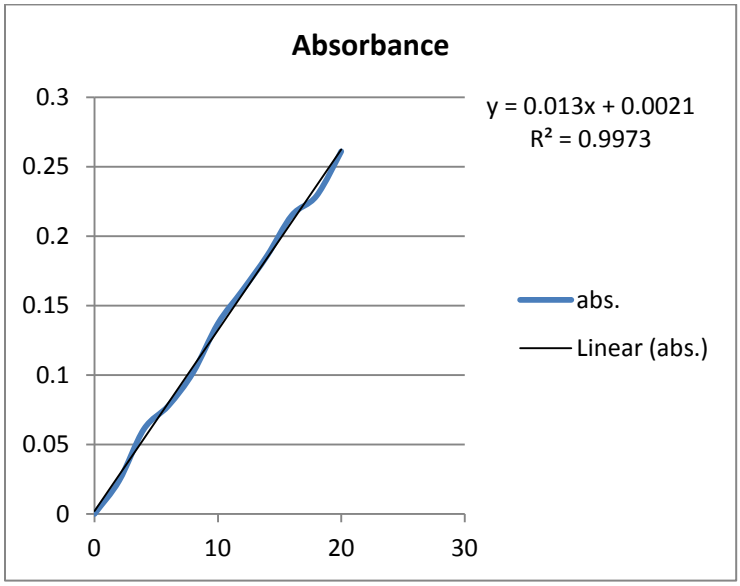

Table 4: Calibration Curve of Baclofen in 0.1 N Hcl

S.No.	Drug Conc. (µg/ml)	Absorbance	Statistical Parameters
1.	2	0.083	Correlation coefficient- $\mathbf{r^2} = 0.996$ Slope **m** = 0.043 Intercept **c** = -0.012 Equation of Line- y = 0.043x-0.012
2.	4	0.161	
3.	6	0.240	
4.	8	0.331	
5.	10	0.413	
6.	12	0.501	
7.	14	0.576	
8.	16	0.668	Total Absorbance
9.	18	0.752	
10	20	0.893	4.618

Fig.2 Calibration curve of Baclofen in *0.1 N Hcl*

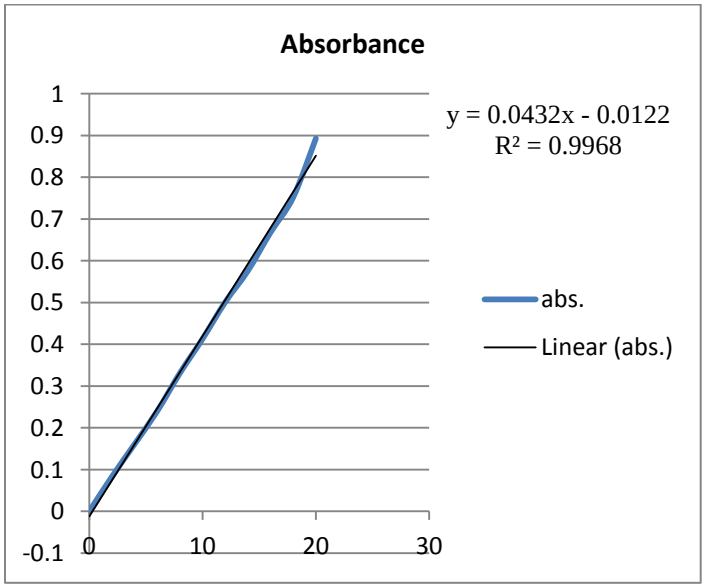

Table 5: Partition co-efficient of Baclofen

S.NO.	SOLVENT	w.length	ABSORBANCE
1.	N-Octanol	221.0	1.496
2.	Distill water	221.0	3.991

Partition coefficient of Baclofen was 0.37

Table: 6 Evaluation of Blends Micromeritics property of Blends

Micromeritics Property of blends	F1	F2	F3	F4	F5	F6
Angle of repose	29.32	25.21	27.23	26.34	25.42	26.12
Bulk density	0.48	0.83	0.47	1.09	0.59	0.57
Tapped density	0.62	0.84	0.65	1.21	0.73	0.54
Carr's index (%)	8.84	6.56	11.22	9.47	6.72	7.00

Table no. 7 Evaluation of baclofen tablets formulation

Code	D.T (sec)	Friability	Hardness	Wetting Time	Drug content	Average Weight (mg)	Palatability
F1	62	2.5 ±0.22	4.5	16	97.3	152.1	Good
F2	47	1.02 ± 0.14	5.7	14	998	151.4	Good
F3	51	0.58 ± 0.24	4.2	15	95.7	152.7	Good
F4	48	1.26 ± 0.14	5.5	18	97.8	150.9	Very Good
F5	49	1.2 ± 0.20	5.0	20	95.8	154.4	Poor
F6	50	1.03 ± 0.14	4.7	15	96.7	153.2	Fair