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Formulation and Development of Orodispersible Tablet of Baclofen by Effervescent Method

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Abstract: The aim of the present study was to develop orodispersible tablets of Baclofen for improving patient compliance, by overcoming the difficulties in swallowing, with the prime objective of arriving at cost effective product by effervescent method. In the effervescent method, mixture of sodium bicarbonate and tartaric acid (each of 12% w/w concentration) were used along with super disintegrants, i.e., treated agar, sodium starch glycolate (SSG), Cross Carmellose Sodium (CCS) and Microcrystalline Cellulose (MCC). The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, *in vitro* dispersion time. The hardness and friability test reports revealed that the tablets had a good mechanical strength and resistance. The formulation containing high concentration of MCC, SSC and CCS and mixture of effervescent emerged as the best formulation based on *in vitro* drug release characteristics. The results of this work suggest that orodispersible tablets of Baclofen with rapid disintegration time, fast drug release and good hardness can be efficiently and successfully formulated by effervescent method.

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INTRODUCTION

For the past two decades, there has been an enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are now focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects (Kuchekar B. S., Aruagam V., 2001). Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups (Lindgreen S., Janzon L, 1993; Bhushan S. Y 2000). Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.

Baclofen is structural analog of gamma aminobutyric acid is a centrally acting skeletal muscle relaxant, which is widely used in the treatment of spasticity resulting from multiple sclerosis, muscle spasms, muscular rigidity and spinal cord injuries, (Kaushik D 2003) where pain persist predominantly, in such cases the quick onset of action is of prime importance. Baclofen is available in oral and intravenous formulation. Though the conventional oral tablets are widely used, they suffer from a few practical drawbacks such as its non-suitability when quick onset of action is required. Often time people experience inconvenience using conventional oral dosage forms in mentally ill and uncooperative patients. Some times it may be difficult to swallow conventional products due to unavailability of water (Kaushik D et al., 2003; Kuchekar B et al., 2004). Hence the present work was aimed to formulate the orodispersible tablets of Baclofen were designed using co-processed directly compressible excipient with the prime objective of arriving at a cost effective product.

MATERIALS AND METHODS

Materials

Baclofen was received as a gift sample from Sun Pharma, Baroda India. Sodium bicarbonate, Tartaric acid, Microcrystalline cellulose, Sodium starch glycolate, Croscarmellose sodium, Aspartame, Directly compressible mannitol (Pearlitol SD 200), Magnesium stearate and Purified talc were procured from Sd Fine Chem Limited, Mumbai, India. Sodium hydroxide and potassium dihydrogen ortho phosphate were procured from Qualigens Fine Chemicals, Mumbai, India.

Preparation of orodispersible tablets by effervescent method

Orodispersible tablets of Baclofen were prepared by effervescent method[7] according to the formulae. Sodium bicarbonate and Tartaric acid were preheated at a temperature of 80° to remove fascinated/enduring moisture and were thoroughly mixed in a mortar to get a uniform powder and then added to other ingredients. The ingredients after shifting through sieve No. 44 were thoroughly mixed. The blend obtained were evaluated for derived and flow properties of powder whose results were within the limits and was directly compressed using 8 mm round concave punches to get tablets of 120 mg weight on 9-station rotary tablet punching machine (Cadmach). A batch of 100 tablets was prepared for all the designed formulations are illustrated in Table 1.

Evaluation of Tablet

Weight variation

Twenty tablets were selected at random and weighted individually. The individual weights were compared with the average weight for determination of weight variation I(Banker GS 1987).

Hardness

The tablet hardness is the force required to break a tablet in a diametric compression force. Monsanto hardness tester was used in this study. This tester applies force to the tablet diametrically. The test was performed on six tablets and the average was calculated (Indian Pharmacopoiea., 1996).

Friability

The friability (F) of a sample of 20 tablets were measured using Roche friabilator ((ERWEKA, Germany). Twenty tablets were weighed, rotated at 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable (Bi YX et al., 1999).

Content uniformity

For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 5 mg of Baclofen was extracted into methanol and liquid was filtered. The drug content was determined by measuring the absorbance at 403 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations (Indian Pharmacopoiea., 1996).

Wetting time

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 6.5 cm) containing 6 mL of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in minutes (Sugimoto H 2002).

Disintegration time

In vitro disintegration time of the prepared tablets were carried out at (37 ± 2) ºC in 900 mL of distilled water. Using a disintegration test apparatus. Disintegration time of 6 individual tablets were recorded and carried out at (37± 2) ºC in 900 mL of distilled water(Bi YX et al., 1999).

***In vitro* dissolution study**

In vitro dissolution of Baclofen orodispersible tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5°C as dissolution medium (Banker GS et al., 1987). The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdraw and placed in a 10 ml volumetric flask, to it 1 ml of 5 % ninhydrin solution and 1 ml of 0.1 N NaOH solution was added. The solution was then boiled for 3 min at water bath, cooled it at room temperature and the volume was made up with distilled water. The absorbance of diluted sample was measured spectrophotometrically at 403 nm using UV-visible spectrophotometer(Shimadzu 1601, Shimadzu Corporation, Kyoto, Japan) (Meyya Nathan S.N 1998).

Table 1: Composition of different batches of Orodispersible tablets of Baclofen

Ingredient	Formulation Code (in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baclofen	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Tartaric acid	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30
Sodium starch glycolate	4	8	12	--	--	--	2	4	6
Croscarmellose sodium	--	--	--	4	8	12	2	4	6
Aspartame	3	3	3	3	3	3	3	3	3
Pearlitol SD 200	33	29	25	33	29	25	33	29	25
Magnesium stearate	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %
Purified talc	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %

Table 2: Evaluation of orodispersible tablets of Baclofen

Formulation code	Weight Variation (mg) ± SD	Hardness (kg/cm) ± SD	Friability (%)	Thickness (mm)	Percentage Drug content ± SD	In vitro Dispersion time (s) ± SD
F1	117±0.002	2.86±0.02	0.58	2.55±0.02	99.44±1.20	38.67±2.51
F2	118±0.002	2.79±0.01	0.59	2.67±0.02	97.52±0.63	41.67±2.88
F3	112±0.001	2.87±0.04	0.70	2.59±0.06	100.04±1.94	34.67±0.58
F4	120±0.001	2.79±0.03	0.68	2.73±0.77	98.44±0.57	53.00±4.58
F5	118±0.002	2.78±0.04	0.75	2.71±0.05	98.29±0.68	50.93±2.00
F6	117±0.002	3.00±0.04	0.52	2.83±0.02	99.85±1.99	34.67±0.58
F7	121±0.002	2.58±0.04	0.59	2.85±0.05	98.18±0.16	18.91±1.14
F8	112±0.001	2.57±0.02	0.65	2.59±0.06	99.92±1.12	15.21±1.31
F9	120±0.002	2.83±0.02	0.52	2.48±0.09	100.18±0.01	10.01±1.32

RESULTS AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limit and indicated good free flowing property, tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications. Drug content was found to be in the range of 97.52 to 101.56 %, which is within acceptable limits.

One of the primary requirements of immediate release preparation is faster disintegration. It is well known to formulation scientists that the tablets with higher crushing strength show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of fast disintegrating tablets. Hardness of the tablets was found to be 2.5 to 3 kg/cm. But friability was observed between 0.58 to 0.75%, which was not within the acceptable limit, however it is acceptable due to its low hardness value which in turn supports for quick disintegration. The results obtained after various evaluation were mentioned in table 2.

The wetting time for all the formulations were found to be (10±0.6) to (22±0.9) seconds. *In vitro* disintegration time for formulations F9 was 10 secs which is shown in figure 1. Based on the *in vitro* drug release study, F9 was identified as the best formulation among all the other formulations and in vitro release profiles was more than 99 % within 15 minutes which is shown in Figure 2. The formulation F9 contains Microcrystalline cellulose with high concentration of both Sodium starch glycolate, Croscarmellose sodium and effervescent substance which causes the rapid disintegration. It causes the maximum *in vitro* dispersion within 10 sec, hence the formulation F9 was optimized after conducting the reproducibility study.

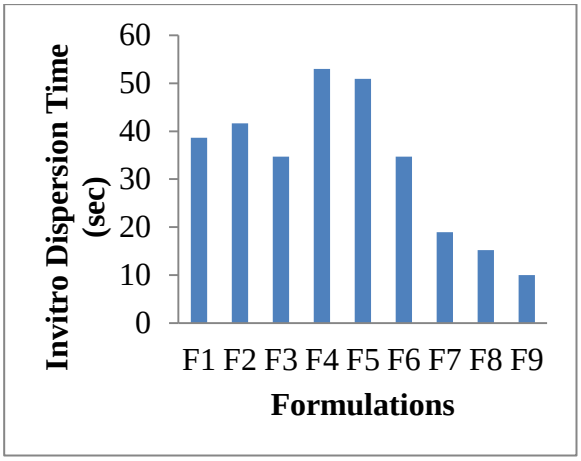

Figure 1: *In-Vitro* Dispersion time of all formulations

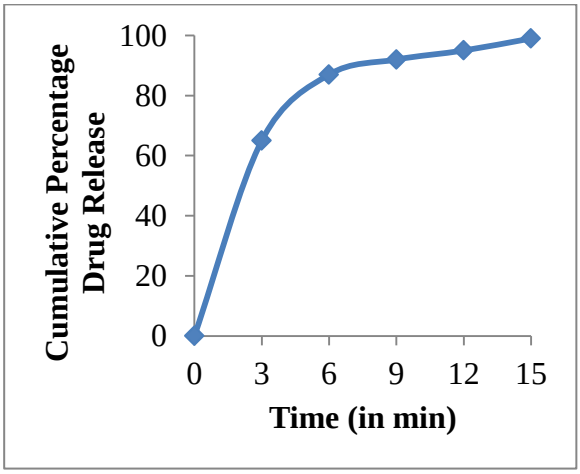

Figure 2: *In-Vitro* Dissolution profile of formulation F9

CONCLUSION

Orodispersible tablets of Baclofen were successfully prepared by direct compression method in a cost effective manner. The use of effervescent mixture further assists in taste masking. Effervescent method would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast dissolving tablets.

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