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Research Paper

Formulation and Evaluation of Baclofen Orally Disintegrating Tablets

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ABSTRACT: The purpose of this study was to evaluate the potential of polymers for masking the taste of bitter drugs when incorporated into orally disintegrating tablets. The tablets were produced by simple wet granulation technique with a model compound (baclofen) which is moderately bitter. The formulating procedure had two variables to obtain good taste masking with desirable characteristics. The optimal granulation process parameters were polymer selection and its concentration (w/w), suitable for pilot scale level. Dextrates, β- cyclodextrin, eudragit EPO and PVP K-30 were used in preparation of granules by using water and iso-propyl alcohol. Crospovidone was used intra and extra granularly as superdisintegrant. Sodium bicarbonate and citric acid were used as effervescent for fast disintegration of tablets, which also optionally act as desensitizer of taste buds. Results from evaluation of tablets indicated a disintegration time (avg) of 30-35 sec and 100% drug release was achieved within 5 min. But taste masking was achieved by only with eudragit EPO. Results from an evaluation by a panel of six human volunteers demonstrated that the orally disintegrating tablets which are prepared by using polymer Eudragit EPO (5% and 7.5% w/w of tablet) and PVP (7.5% w/w of tablet) improved taste, significantly. On studying physical parameters, F9 formulation demonstrated acceptable level of hardness and friability with good taste masking and it was thus considered as an optimized formulation.

KEYWORDS: Baclofen, Taste masking, orally disintegrating tablets, wet granulation, Eudragit EPO, PVP.

Introduction

Although tablets and capsules constitute a major portion of the drug delivery systems, some patient groups, such as pediatrics, geriatrics, and bedridden or disabled patients, may have difficulties in swallowing such dosage forms. Many pharmaceutical manufacturers are now switching to ODT technology and offering a wider choice of pharmaceutical actives covering many therapeutic categories to both physicians and patients. To meet these medical needs, formulators have devoted considerable efforts to develop a novel dosage form known as orally disintegrating tablet (ODT), which can disintegrate rapidly in the saliva without water (Abdelbary et al., 2004). However, taste masking for some pharmaceutical actives with bitter or unpleasant taste can be challenging for this dosage form to achieve patient acceptability.

The mechanisms of the taste masking methods may be either to mask the distasteful sensation by the addition of flavors, sweeteners and effervescent agents, or to avoid the bitter drugs coming into direct contact with patients' taste buds. Various techniques have been developed to improve taste like polymeric coating strategies, complexation with cyclodextrins, ion exchange resins, salt formation, using liposomes, microencapsulation technique and coating or granulation [Lieberman et al., 1989; Ishikawa et al., 1999; Hiroyuki et al., 2003; Gao et al., 2006; Kayumba et al., 2007]. Moreover, the coatings and the granulation of the active ingredient may often rupture during compressing and chewing of the tablet as well as contribute to a gritty feel. But in this study, evaluation of coating by simple wet granulation using polymer dispersions were used as granulating agents, which coat the active ingredient with acceptable taste masking. More considerations are involved in the polymer selection process like polymer solubility to make a perfect coat around drug particles, solvent selection which do not solubilize the drug particles, polymer physical characteristics, polymer viscosity to give a good process of granulation and granule strength which gives a good formulation. It has also been reported that in turn these granules remained intact without undergoing merging or rupturing during tabletting [Sveinsson et al., 1993; Vilivalam and Adeyeye, 1994; Soppimath et al., 2001; Raghavendra et al., 2008] and the potential of granules for taste masking when incorporated into orally disintegrating tablets was investigated.

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Wet granulation is a simple and economical process compared with spray drying. Even though spray drying is a single step process but amount of drug loss is more compared with wet granulation process.

In this investigation, dextrates, HP-β-cyclodextrin, PVP, polymethacrylates (Eudragit® EPO) were used. Dextrates is a processed polymer of starch having good viscosity and taste masking properties. HP-β-cyclodextrin is inclusion type polymer generally used to mask bitter taste of drugs but in this investigation simple kneading process was checked to test the efficienct masking property of CDs. PVP K-30 having low viscous properties which are suitable for simple granulation in small scale and large scale production for easy mixing and coating. It is also suitable to mask the bitter taste of drugs. Eudragit® EPO is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters. The cationic copolymer dissolved in pH <5. The copolymer dissolved fast in stomach (pH 1–3) without influencing the bioavailability and also it was kept intact in buccal cavity (pH 5.8–7.4) with good taste masking.

Baclofen was applied as a model compound. It belongs to a class of peripherally acting muscle relaxant and is used to treat spasticity and spinal cord injuries (kemstro™). Baclofen is very suitable for ODT; and it is a bitter tasting drug, requires masking. Currently, many baclofen immediate release tablets are commercially available in market. In this paper, a comparative study was performed between optimized formulation and marketed immediate release (IR) formulation.

Materials and Methods

Materials

Baclofen was obtained from Natco Pharma Limited, Hyderabad. Polymethacrylates (Eudragit® EPO) was gifted by Degussa. Dextrates was purchased from JRS Pharma, Mumbai. HP-β-cyclodextrin was donated by Signet chemicals, Mumbai. PVP K-30 was donated by Prachin chemicals, Mumbai. Micro crystalline cellulose (avicel pH 101) was procured from FMC Polymers. Spray dried mannitol (mannozem) from SPI Polyol. Crosspovidone from Prachin Chemicals, Mumbai. Citric acid and sodium hydrogen carbonate from Merck Labs, India, Aspartame from Nutrasweet, Vanilla flavor from Pan aroma, and magnesium stearate from Ferro Industrias Quimicas were obtained. Baclofen (IR) tablets were purchased from Watson Pharmaceuticals.

Preparation of Taste Masked Granules

Aqueous dispersion or alcoholic dispersion of polymers was first prepared by dispersing the required amount of polymer in solvent like water or IPA and a clear dispersion was made by simple agitation or heating method. To prevent evaporation or hydration of polymers that could lead to increase in viscosity, after preparation the granulating fluid was kept in a cool place. Required quantity of drug, MCC, lactose and a ratio of cross povidone were taken and blended to form a uniform blend. The granulating fluid was added to the above blend and mixed properly to prepare a wet mass which was coated uniformly leading to the coating of the drug particle. This wet mass was then passed through mesh no-14 and then kept for drying in tray dryer. Every 30 mins the moisture content was checked using halogen lamp moisture analyzer. The LOD value should be below 2% w/w. These dried granules were sifted through mesh # 20 or 30 to get uniform granules with fewer amounts of fines.

Preparation of Final Blend and Compression to make an ODT Tablet

Required amount of citric acid and sodium hydrogen carbonate sifted through mesh no-40 was taken. Then remaining excipients like aspartame, mint flavour were sifted and added to above blend. The colour was passed through mesh no- 180/150 and added to the above blend which was mixed uniformly. This blend was added to granules to make a uniform blend. Finally magnesium stearate which is sifted from mesh no-40 was added and the above blend was mixed uniformly for 2 mins. The tablets were then prepared by punching the final blend on single punching machine using 10mm flat and round punches with optimum hardness.

Technological parameters

The eight formulations thus prepared were assessed for a variety of technological parameters. Granules were tested for residual humidity, flowing time and Carr's index. After being checked for weight and hardness, the tablets were also tested for crushing strength, friability, disintegration time and dissolution rate.

Carr's Index

Carr's "percent compressibility" was calculated using the equation $([p_{tap} - p_{bul}]/p_{tap}) \times 100$. The bulk and tap densities were determined as follows. A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density. For tap density, the cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder.

Crushing Test

The crushing strength of six tablets at each compression force level was determined using an Erweka hardness tester (Type TBH 30, Erweka, Heusenstamm, Germany). Hardness and friability tests were carried out according to EP IV Ed. for OD tablets.

Wetting and de-aggregation Time

(Adamo Fini et al 2007)

A sample of the final tablet was placed in petri dish (10 cm in diameter) containing 10 ml water at room temperature. The wetting time is that necessary for the complete wetting of the tablet. The results of this test carried out in triplicates for the different samples was calculated. The de-aggregation test was performed according to the methods described in USP. The de-aggregation time carried out by using USP type disintegration apparatus 1. The de-aggregation time is the time required to transform a tablet into small fragments and passed through the mesh with out remains.

Mouth Disintegration Time

The final tablet sample was placed on the tongue and disintegration time was noted by taking 6 volunteers for the test. Average disintegration time was noted.

Dissolution Test

A dissolution test was performed at 37 °C using the USP type-1 basket apparatus at 25 rpm with 1000 ml 0.01N HCl as a dissolution medium. At predetermined intervals (5, 10, 15, 30 min), 5 ml of the medium was sampled and filtered and 5 ml of fresh dissolution medium was replaced. The filtrate was analyzed by HPLC analysis.

HPLC Analysis

Distribution uniformity of the drug inside the different size fraction of the granules or after preparation of the tablets was assessed by means of HPLC. A alliance system equipped with a variable-wavelength UV detector UV3 006 was used for this purpose. *Experimental conditions:* Column C18; mobile phase: 0.3N acetic acid: methanol: 0.36 N sodium 1-pentane sulfonate; flow rate 1.0 ml/min; detection UV-detector; wavelength 220 nm; injection volume 100 µl.

Results and Discussions

The composition of the formulations is shown in Table 1. The weight uniformity, content uniformity, hardness, disintegration time and wetting time of the prepared ODTs were satisfactory (Table 2). The results of mouth feel by taste masking test are listed in Table 3. The last four formulations (6, 7, 8 and 9) sufficiently alleviate the bitter taste of drug. The disintegration time in the oral cavity was 35±6 for taste masked formulations. Formulations F6, F7, F8 and F9 did not give any bitter to metallic taste after disintegration in mouth. Above formulations showed a good dissolution results in 5 mins were 99±0.6%. Formulations F6 and F7 showed friability problem compared to F8 and F9. The comparative dissolution studies between marketed product and optimized formulation (F9) is depicted in Table 5.

Table 1. Composition of the formulations.

Component (%)	Function	F1	F2	F3	F4	F5	F6	F7	F8
Granules									
Baclofen	Active agent	20	20	20	20	20	20	20	20
Avicel PH 101		101	101	101	101	101	101	101	101
Mannozem		172.4	162.4	172.4	162.4	177.4	172.4	162.4	172.4
Dextrates	Coating	20	30						
HP-β-cyclodextrin	Coating			20	30				
Eudragit EPO	Coating					15	20	30	
PVP k-30	Coating								20
Cross povidone	Super disintegrant	20	20	20	20	20	20	20	40
Tablets									
Cross povidone	Super disintegrant	20	20	20	20	20	20	20	
Anhydrous citric acid	Effervescent	10.2	10.2	10.2	10.2	10.2	10.2	10.2	10.2
Sodium hydrogen carbonate	Effervescent	12	12	12	12	12	12	12	12
Aspartame	Sweetener	15	15	15	15	15	15	15	15
Vanilla flavour	Flavouring agent	3	3	3	3	3	3	3	3
Quinoline yellow	Coloring agent	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Magnesium Stearate	Lubricant	6	6	6	6	6	6	6	6

Table 2. Quality control tests of the formulations.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Parameter of the granules									
Residual humidity (% ±0.2)	1.76	1.82	1.98	2.02	2.23	2.34	2.35	2.14	2.24
Apparent density (mg/ml ± 0.03)	0.37	0.32	0.34	0.36	0.41	0.42	0.42	0.42	0.41
Packed density (da/di ± 0.02)	0.57	0.56	0.56	0.56	0.62	0.63	0.61	0.59	0.62
Carr's index (% ± 0.05)	34.8	42.4	39	35.9	33.4	33.2	30.7	29.4	32.6
Tablets									
Mean mass (mg ± 0.4)	401	401.5	402	401.6	403.4	402.2	403.6	403	402.8
Hardness (kp ±0.1)	3.4	6.8	5.7	5.7	5.8	4.5	3.4	6.5	6.5
Friability (% ±0.03)	0.05	0.04	0.45	0.45	0.5	1.05	1.23	0.18	0.12
Wetting time (s ±3) sec	2 min	40	25	30	30	60	60	10	25
De-aggregation time (s ±6) sec	60	45	35	30	30	35	35	30	30
Mouth disintegration time(v =6) sec	50	55	40	45	40	40	45	35	35
Drug content uniformity(c±2)%	97.6	98.4	98.2	99.7	97.9	99.3	100.2	102.3	101.1

Table 3. Taste evaluation.

Taste evaluation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Number of volunteers	6	6	6	6	6	6	6	6	6
Number volunteers accepted (good taste)	0	0	1	1	2	6	6	4	6

Table 4. Dissolution Profile of Formulations.

Sampling time (mins)	Cumulative % drug release			
	F6	F7	F8	F9
5	96.95	97.37	100.68	99.06
10	97.43	97.91	101.18	99.55
15	97.66	98.45	101.68	100.04
30	98.20	99.00	102.18	100.54

Table 5. Dissolution Profile Marketed IR formulation and Optimized F9 OD Tablet.

Sampling time	% Of Drug Release (IR tablet)	% Of Drug Release (F9 OD tablet)
5	76.05	99.06
15	86.87	99.55
30	90.29	100.04
45	92.3	100.54

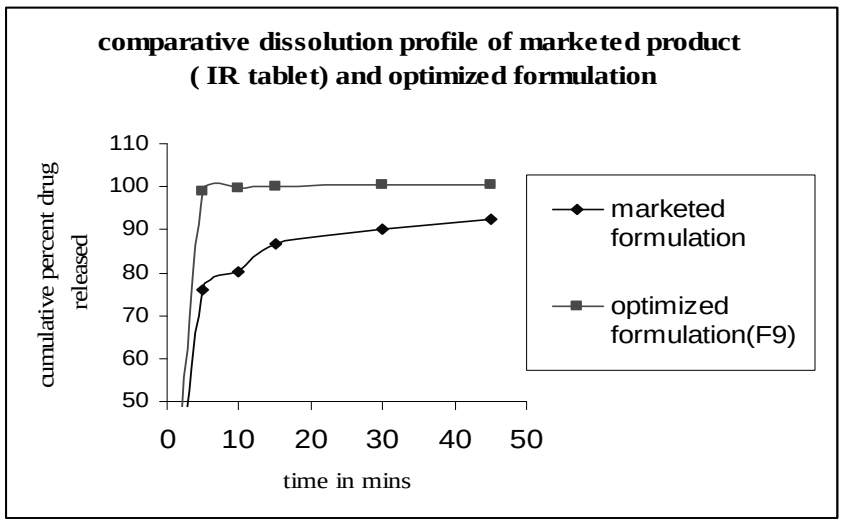

Fig. 1 Comparative dissolution with IR Tablet and Optimized OD Tablet.

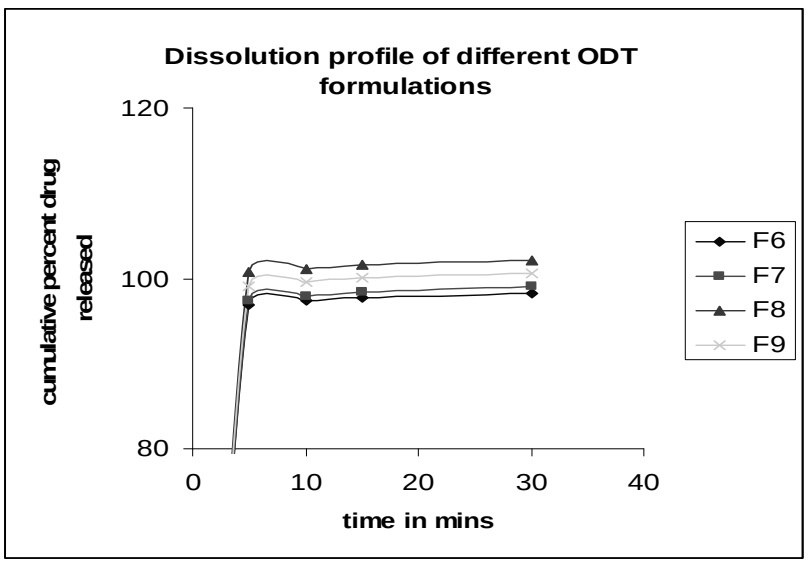

Fig. 2 Dissolution profile of the formulations.

Conclusion

Orally disintegrating tablets transform into easy-to-swallow suspension on contact with the saliva, after ingested in mouth. These are particularly useful for pediatric or geriatric patients, and can be taken without liquids and facilitate treatment of emergent pain, irrespective of the place and situation where it may arise. The developed formulations have suitable characteristics that distinguish them from common solid dosage forms, such as rapid de-aggregation, combining advantages of both liquid and conventional tablet formulations, ease of swallowing and possible taste-masking components for an acceptable taste in the mouth. The presence of a super disintegrant makes it possible to produce sufficiently hard tablets that still disaggregate within seconds and most of the developed tablets can be considered as "fast dispersible". Finally these tablets can be prepared by means of a conventional tabletting technique. On comparing results of physical properties of four taste masked formulations F6, F7, F8 and F9, gave better results except in friability studies. In case of friability consideration, F9 gives a better formulation with optimum hardness in scale up level.

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