FORMULATION AND EVALUATION OF BACLOFEN CONTROLLED POROSITY OSMOTIC PUMP TABLETS

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ABSTRACT

In the present study, attempts were made to develop and evaluate the controlled porosity osmotic pump (CPOP) based drug delivery system of sparingly water soluble drug Baclofen. Formulation variables, such as, levels of solubility enhancer, ratio of drug to osmogens, coat thickness of semi permeable membrane (SPM) and level of pore former were found to affect the drug release from the developed formulations. Cellulose acetate was used as the semi permeable membrane. Drug release was directly proportional to the level of the solubility enhancer, osmotic pressure generated by osmotic agent and level of pore former; however, was inversely proportional to the coat thickness of SPM. Drug release from developed formulations was independent of pH and agitation intensities of release media. Burst strength of the exhausted shells decreased with increase in the level of pore former. This system was found to deliver Baclofen at a zero-order rate. The optimized formulations were subjected to stability studies as per ICH guidelines, and formulations were found to be stable after 45days study.

Keywords: Baclofen, Controlled porosity osmotic pump, osmogen, pore former, cellulose acetate.

INTRODUCTION

Amongst various routes of drug delivery Oral route is the most preferred route as it is the safest and most convenient method of drug administration in achieving both systemic and local effect. In conventional oral drug delivery systems, there is little or no control over release of the drug and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern results are constantly changing, unpredictable and sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases. Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled rapid release of drug may also cause local gastro intestinal or systemic toxicity. Hence better dosage form design and delivery can minimize many of these problems. Various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled drug delivery system. Oral osmotically controlled release (CR) delivery system provide a uniform concentration of drug at the site of absorption and thus after absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system¹⁻⁵. The historical developments of osmotic systems include seminal contributions such as the rose nelson pump, higuchi leeper pumps, alzet osmotic pump, elementary osmotic pump and push pull osmotic pump. The osmotic drug delivery systems suitable for oral administration typically consist of compressed tablet core that is coated with a semi permeable membrane that has an orifice drilled on it

by means of a laser beam. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume which pushes the drug solution or suspension out of the tablet through one or more delivery ports. To obviate the need for complicated laser drilling, tablets coated with a membrane of controlled porosity have been described. These membranes consist of leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. Drug release from these systems is independent of pH and hydrodynamic conditions of gastro-intestinal tract to a large extent, and release characteristics of delivery system⁶⁻⁸.

Baclofen is a skeletal muscle relaxant with a half life of ~2.5 to 4 hours in plasma thereby requiring twice daily dosing in large number of patients, which often leads to non-compliance. Many reports stated that absorption of baclofen is through facilitated-intestinal transport. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug. As a result, variable oral bioavailability may be expected. Hence baclofen is suitable candidate for development of a controlled release dosage form for the long-term treatment of spasticity resulting from multiple sclerosis and spinal cord injuries in the form of controlled porosity osmotic pump tablets^{9,10}.

MATERIALS AND METHODS**Materials**

The model drug Baclofen was obtained as a gift sample from Strides Acro Labs, Bangalore. Cellulose acetate, Methanol, Acetone, NaCl and Hydrochloric acid were obtained from SD Fine Chem Ltd, Mumbai. Dibutyl Phthalate and Mannitol from Hetero Drugs Pharma Ltd. All other chemicals and ingredients used for study were of Analytical grade.

Development of Formulation

Formulation of Core Tablets

Core tablets were prepared by direct compression method. Required amounts of drug and avocet were weighed and passed through sieve # 60. Then the blend was lubricated with sieve # 60 passed magnesium stearate and talc. The powder blend was compressed on compression machine using 8.0 mm round standard concave punches.

Coating of CPOP Tablets

Release of the drug from the osmotic pump tablets is mainly dependent on its coating membrane which is responsible for creating osmotic pressure inside the device. Release can be controlled by optimizing cellulose acetate and pore former in the coating membrane and the pores are created on the membrane. The coating process of the formulations is most important because the composition of coating solution, coating thickness and concentration of pore former so that the pump can affect the release of the drug. So, efforts were made to control the drug release by optimizing composition of coating solution, thickness of semi permeable membrane and the pore former concentration.

Selection of Solvent and Plasticizer Concentration for Coating Solution

For the selection of the solvent and plasticizer for preparation of coating solution, 3% w/v cellulose acetate was prepared in different solvents viz. DCM: Methanol (80:20) and acetone: Methanol(80:20). These solutions were divided into five parts. To each part of these solution different concentrations of PEG 400 and DBP (0, 5, 10, 15, 20% w/w of cellulose acetate) were added and mixed well using mechanical stirrer. The resultant solutions were poured into petridishes and allowed to dry in a tray dryer at 45 °C overnight. Films were tested for appearance and integrity. Based on the appearance and integrity, a solution of Acetone, Methanol (80:20) mixture containing 10% w/w DBP was selected.

Preparation of Coating Solution

Required quantity of cellulose acetate was accurately weighed and dissolved in a beaker containing acetone and methanol using mechanical stirrer. The stirring was continued till a clear solution was formed and DBP was added slowly to the beaker with stirring. Sorbitol was separately dissolved in a beaker containing measured quantity of Methanol and was added slowly to the cellulose acetate mixture with stirring.

Coating Procedure

Core tablets were placed in a coating pan along with 200 mg of filler tablets. The coating pan was rotated at 12 rpm and heated air was passed through the tablet bed. Coating process was started when the outlet air temperature reaches to 33 °C. Coating solution was sprayed at the rate of 2-4 ml/min and atomizing air pressure was kept at 2.0 atm. The outlet temperature was maintained above 33 °C by keeping the inlet air temperature in the range of 45-50 °C. Coating was continued until desired weight gain was obtained on the core tablets. The coated tablets were dried at 50 °C overnight in a tray dryer.

Evaluation of Coated Tablets

Percentage Weight Gain

From the batch of tablets, 10 core tablets were randomly selected subjected to coating. The initial weight of 10 uncoated tablets was recorded. After period of coating,

spraying of coating solution was stopped and allowed to drying for 10–15 min, in the coating pan at 45 °C to remove the majority of solvent moisture. The weight of 10 coated tablets was recorded. The percent weight gain was calculated. Samples were collected for predetermined weight gain (approximately). Coated tablets were subjected for overnight drying in tray drier 45 oC to remove complete solvent. The dried tablets were weighed again and % weight gain was calculated accurately.

In-vitro Drug Release

In-vitro drug release of the samples was carried out using USP-type II dissolution apparatus (paddle type). The dissolution was done using pH change method in 900 ml 0.1 N hydrochloric acid for 2 h followed by 900 ml of 0.15 M sodium phosphate buffer affording a pH of 6.8. The temperature of the medium was maintained at 37±0.5 °C. The apparatus was allowed to run for 24 h at 100 rpm. Aliquots of 5 ml samples were withdrawn at various intervals (0.5, 1, 2, 4, 6, 8, 10, 12 h). The samples were filtered through wattman filter paper. The fresh dissolution medium (37 °C) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 220 nm using 0.1 N Hydrochloric acid as blank for the first 2hrs samples and at 220 nm using phosphate buffer pH 6.8 as a blank for rest of the samples. The percentage cumulative drug release (% CDR) was calculated.

Effect of Various Parameters on Drug Release

Effect of % Weight Gain

The % weight gain in the coating formulation was varied and its effect on the drug release was evaluated. The tablets were coated to achieve a weight gain of 6%, 8%, and 10% of total weight of tablet. All these tablets were subjected for dissolution studies using USP II (paddle type) apparatus as per procedure specified in the previous sections for in-vitro release studies.

Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted in various mediums of varying pH (0.1N HCl, water, phosphate buffer pH 6.8). Dissolution apparatus used was paddle type (USP-II) at 50 rpm for 12 h. The samples (5 ml) were withdrawn at predetermined intervals and analyzed.

Drug Release Kinetics

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: Zero Order as cumulative percentage of drug unreleased vs. time, First Order as log cumulative percentage of drug remaining vs. time, Hixson-Crowell Cube Root Law Model as the cube root of the percentage of drug remaining in the matrix vs. time, and Higuchi Model as the square root of time vs. % drug release.

Accelerated Stability Study

Baclofen tablets were packed in 0.04 mm thick aluminum foil strips laminated with PVC. The packed tablets were placed at 40±2°C, 30±2°C for 45 days. The samples were withdrawn for every 15 days and were observed for changes on the coating membrane (i.e. change in color, appearance of spot, any kind of microbial or fungal growth, any bad odour,

smoothness). Samples were evaluated for hardness and drug content^{11,12}.

Table 1: Flow Properties of the Pure Drug

Parameter	Result
Bulk density (gm/cc)	0.241 ± 0.050
Tapped density (gm/cc)	0.611 ± 0.025
Compressibility index (%)	60.55 ± 0.065
Hausners ratio	2.535

Table 2: Solubility Study of the Drug in Different Medias

Media	Solubility (mg/ml)
Purified water	2.09
0.1 N HCl, pH 1.2	25
Phosphate buffer, pH 6.8	5.1
Phosphate buffer, pH 7.4	4.2

Table 3: Formulation of Baclofen Tablets with Mannitol

Ingredients	Formulation trial codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
	Core Tablet Formulation (in mg)								
Drug	25	25	25	25	25	25	25	25	25
Mannitol	50	50	50	100	100	100	150	150	150
Avicel PH101	170	170	170	145	145	145	95	95	95
Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250	250	250	250	250
	Coating Formulation (w/v)								
Cellulose Acetate	3%	3%	3%	3%	3%	3%	3%	3%	3%
DBP*	10%	10%	10%	10%	10%	10%	10%	10%	10%
Sorbitol*	0%	10%	20%	0%	10%	20%	0%	10%	20%

Drug = Baclofen * w/ w of Cellulose Acetate

Table 4: Formulation of Baclofen Tablets with Nacl

Ingredients	Formulation trial codes					
	F10	F11	F12	F13	F14	F15
	Core Tablet Formulation (in mg)					
Drug	25	25	25	25	25	25
NaCl	50	50	50	100	100	100
Avicel PH101	170	170	170	145	145	145
Mg.Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250	250
	Coating Formulation (w/v)					
Cellulose Acetate	3%	3%	3%	3%	3%	3%
DBP*	10%	10%	10%	10%	10%	10%
Sorbitol*	0%	10%	20%	0%	10%	20%

Drug = Baclofen * w/ w of Cellulose Acetate

Table 5: Coating Composition for All the Formulations

Ingredients	Composition
Cellulose acetate	3 % w/v of solution
Di butyl phthalate	10 % w/w of CA
Acetone: Methanol	80 : 20
% coating	8 %

Table 6: Composition of Core for Formulations F1-F6

Ingredients	Quantity(mg/tab)					
	F1	F2	F3	F4	F5	F6
Drug	25	25	25	25	25	25
Mannitol	50	50	50	100	100	100
Avicel pH 101	145	145	145	95	95	95
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250
Sorbitol	0%	10%	20%	0%	10%	20%

Table 7: Pre compression Properties of the Blend of F1-F6

Parameter	F1	F2	F3	F4	F5	F6
Angle of Repose	25	23	20	23	22	20
Bulk density (gm/cc)	0.291	0.282	0.301	0.481	0.491	0.501
Tapped density (gm/cc)	0.332	0.325	0.556	0.541	0.552	0.581
Compressibility index (%)	12.34	13.23	22.125	14.240	11.05	13.76
Hausner ratio	1.141	1.152	1.391	1.124	1.124	1.159

Table 8: Physical Properties of Core Tablets for Formulations F1-F6

Parameter	F1	F2	F3	F4	F5	F6
Weight variation (mg) [#]	251.71±2.93	249.57±2.76	251.52±2.76	249.57±4.61	252.17±7.83	250.33±5.82
Hardness (Kg/cm ²) [*]	9.350 ±1.57	6.03 ± 0.68	7.38±0.79	9.13±0.53	6.57±0.75	7.42±1.25
Thickness (mm) [*]	3.37±0.04	3.38± 0.11	3.14±0.03	3.25±0.03	3.42±0.02	3.38±0.02
Friability (%) [#]	0.09	0.34	0.22	0.06	0.29	0.36

[#] Results of one batch ^{*}each value represents the mean ±SD (n=6)**Table 9: Physical Properties of Coated Tablets for Formulations F1-F6**

Parameter	F1	F2	F3	F4	F5	F6
Weight variation (mg) [#]	270.33±1.25	270.15±2.89	271.21±1.59	269.31±2.21	270.07±1.45	267.47±2.65
Thickness (mm) [*]	3.74 ± 0.044	3.84 ±0.117	3.48 ±0.038	3.45±0.039	3.56±0.254	3.49±0.027
Assay (%)	100.92	97.527	102.40	99.20	98.21	100.25

[#] Results of one batch ^{*}each value represents the mean ±SD (n=6)**Table 10: Composition of Core for the Formulations F7-F9**

Ingredients	Quantity (mg/tab)		
	F7	F8	F9
Drug	25	25	25
Mannitol	150	150	150
Avicel pH 101	45	45	45
Magnesium stearate	2.5	2.5	2.5
Talc	2.5	2.5	2.5
Total weight	250	250	250
Sorbitol	0 %	10 %	20 %

Table 11: Pre compression Physical Properties of the Blend F7-F9

Parameter	F7	F8	F9
Angle of Repose	27	30	31
Bulk density (gm/cc)	0.422	0.401	0.322
Tapped density (gm/cc)	0.483	0.471	0.402
Compressibility index (%)	12.62	14.86	19.90
Hausner ratio	1.144	1.174	1.248

Table 12: Physical Properties of Core Tablets for Formulations F7-F9

Parameter	F7	F8	F9
Weight variation (mg) [#]	251.17 ± 7.83	248.5 ± 5.82	252.52±3.87
Hardness (Kg/cm ²) [*]	7.85 ± 0.54	7.65 ± 0.39	7.82±0.056
Thickness (mm) [*]	3.36 ± 0.20	3.44 ± 0.16	3.43±0.05
Friability (%) [#]	0.12	0.06	0.21

[#] Results of one batch ^{*}EACH value represents the mean ±SD (n=6)**Table 13: Physical Properties of Coated Tablets for Batches F7-F9**

Parameter	F7	F8	F9
Weight variation (mg) [#]	271.66 ±5.62	269.74 ±4.98	274.57 ±7.25
Thickness (mm) [*]	3.72 ± 0.20	3.84 ± 0.16	3.93 ± 0.05
Assay (%)	100.92	97.527	102.40

[#] Results of one batch ^{*}each value represents the mean ±SD (n=6)**Table 14: Composition of Core for the Formulations F10- F15**

Sl. No	Ingredients	Quantity (mg/tab)					
		F10	F11	F12	F13	F14	F15
1	Drug	25	25	25	25	25	25
2	Sodium chloride	50	50	50	100	100	100
3	Avicel PH 101	170	170	170	120	120	120
8	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
9	Talc	2.5	2.5	2.5	2.5	2.5	2.5
	Total weight	250	250	250	250	250	250
Pore Forming Agent Percentage							
10	Sorbitol	0%	10%	20%	0%	10%	20%

Table 15: Pre compression Properties of the Blend of F7 – F10

Parameter	F10	F11	F12	F13	F14	F15
Angle of Repose	21	27	20	19	21	23
Bulk density (gm/cc)	0.558	0.309	0.463	0.509	0.486	0.463
Tapped density (gm/cc)	0.597	0.569	0.536	0.569	0.588	0.536
Compressibility index (%)	19.23	21.69	18.25	14.98	16.56	15.69
Hausner ratio	1.246	1.236	1.301	1.249	1.248	1.236

Table 16: Parameters of the Core Tablets for Formulations F10 –F15

Parameter	F10	F11	F12	F13	F14	F15
Weight variation (mg) [#]	249.67±4.3	251.33±5.32	250.83±4.46	251.82±3.3	249.48±2.4	252.16±3.56
Hardness (Kg/cm ²) [*]	7.85 ± 0.54	6.20 ± 0.61	6.02 ± 0.62	7.72 ±0.51	6.20 ± 0.61	6.02 ± 0.62
Thickness (mm) [*]	3.54 ± 0.02	3.184 ± 0.04	3.55 ± 0.11	3.42 ±0.12	3.28±0.12	3.33±0.19
Friability (%) [#]	0.12	0.20	0.16	0.18	0.20	0.16

[#] Results of one batch ^{*}each value represents the mean ±SD (n=6)

Table 17: Properties of Coated Tablets for Batches F10-F15

Parameter	F10	F11	F12	F13	F14	F15
Weight variation (mg) [#]	270.39±3.2	274.20±3.45	268.58±4.28	273.22±4.26	267.44±3.75	273.84±2.45
Thickness (mm)*	3.87±0.044	3.75 ± 0.03	3.70 ± 0.05	3.98±0.65	3.45±0.55	3.67±0.18
Assay (%)	99.201	98.27	101.25	98.54	101.94	98.60

[#] Results of one batch *each value represents the mean ±SD (n=6)

Table 18: Comparison of Orders of in Vitro Release of the Drug from the Formulation F5

Release kinetics / Release mechanism	R ² value	Regression equation
Zero-order kinetics	0.984	y = 8.874x + 8.552
First-order kinetics	0.964	y = -0.066x + 2.013
Higuchi model	0.941	y = 26.44x - 8.744
Korrs mayer peppas	0.983	y = 0.833x + 1.108
Hixon Crowell Cube root	0.987	y = 0.198x + 4.658

Table 19: Stability Studies of Optimized Formulation (F5) At Temperature 30±20°C

Parameters	Specifications	Test Condition			
		Temperature (30 ± 2°C)			
		Initial	15 Days	30 Days	45 Days
Description	White to off white round shaped tablets.	Comply	Comply	Comply	Comply
Assay	NLT 90% & NMT 110% of labeled amount of drug.	98.5	98.3	97.87	97.87

Table 20: Stability Studies of Optimized Formulation (F6) At Temperature 40±20°C

Parameters	Specifications	Test Condition (Accelerated)			
		Temperature (40 ± 2°C)			
		Initial	15 Days	30 Days	45 Days
Description	White to off white round shaped tablets.	Comply	Comply	Comply	Comply
Assay	NLT 90% & NMT 110% of labeled amount of drug.	98.63	97.54	97.41	97.39

Figure 1: Theeuwes Elementary Osmotic Pump

Figure 2: FTIR spectra of Baclofen

Figure 3: In-vitro drug release of drug from tablets of batches F1 – F6

Figure 4: In-vitro drug release of drug from tablets of batches F7 – F9

Figure 5: In-vitro drug release of drug from tablets of batches F10 – F15

Figure 6: Effect of % weight gain on drug release

Figure 7: Effect of pH of the dissolution media on drug release

Figure 8: Comparison drug profiles with Marketed product

Figure 9: FTIR Spectrum of Optimized formulation F5

Figure 10: In-vitro release profile of drug from F5 formulation fitted in Zero order release

Figure 11: In vitro release profile of drug from F5 formulation fitted in first order release

Figure 12: In-vitro release of drug from F5 formulation– Higuchi's model

Figure 13: In-vitro release of drug from F5 formulation– koresmeyer peppas model

Figure 14: In-vitro release of drug from F5 formulation–Hixson crowell model

RESULTS AND DISCUSSIONS

Pre formulation Study

Drug Excipient Compatibility Studies - FTIR Studies

The FTIR studies were carried out to confirm the compatibility of excipients with drug used in the formulation. It was found that there is no significant change in the peaks of drug excipient mixtures in comparison to pure drug, indicating that there is no incompatibility of excipients with the drug.

API Characterization

Melting Point

The melting point of the drug sample was found to be 208 °C with reference to the literature it was found to be 206°C - 208°C. The drug sample showed compliance with the data given in Merck index, which reflects its quality and purity.

Flow Properties

The flow properties of the pure drug were determined. It was observed that the drug showed poor flow properties and poor compressibility characteristics.

Solubility studies

The solubility of drug was determined in the water and in different buffer solutions of pH 1.2 to 7.4 and it was found that the drug is having a pH dependent solubility which decreases with increase in pH. The study indicates that the drug has better solubility in the acidic pH.

In vitro Drug Release Studies

For formulations F1-F6, the % cumulative drug release was found to be in the range of 24 – 94% in 12h and simultaneously the osmogens used were capable to create desired osmotic gradient with increasing pore former (sorbitol) concentration (0%-20%). However, the Mannitol was used as an osmogen for further studies with increased concentrations to verify osmotic drug release.

For formulations F7-F9, it is evident that there is a considerable decrease in the drug release in the formulations. This decreased drug release from the formulations could be accounted for higher levels of Mannitol, which retard sufficient osmotic pressure and might block formation of pores. Hence, an attempt must be made to decrease the concentration of osmogen in the core.

For formulations F10-F15, it was found to be the drug release was increased and ranges from 35 to 98%. The formulation F15 showed highest drug release (95%) in 12 h. This increased drug release from the formulations F10 to F15 could be accounted for higher levels of NaCl, which has high

osmotic pressure than mannitol creates sufficient osmotic pressure.

Effect of Various Parameters on Drug Release

Effect of % Weight Gain

It is clearly evident that drug release decreases with an increase in weight gain of the coating membrane. No bursting of tablet was observed during the dissolution in any formulation.

Effect of pH

There lease studies of optimized formulations were conducted in media of different pH. The release media are 0.1 N HCl, pH 6.8, and water. Release profile of the drug from these formulations is reported.

Kinetics of In vitro Drug Release

The optimized coated F5 formulation followed Zero order release kinetics. The in- vitro release data were processed as per Higuchi's model and Hixson–Crowell Cube root models. The equations were generated through statistical procedures R2 values are higher for Hixson-Crowell Cube root model from optimized formulation F5 hence followed osmotic mechanism.

Stability Studies

Stability studies for the optimized tablets were carried out at a temperature of 40±2oC and 30±2oC for a period of 45 days. Tablets are evaluated for physical appearance, assay. Tablets have not shown any significant change during storage. Hence it was concluded that the optimized tablets have good stability during their shelf life.

CONCLUSION

A porous osmotic pump-based drug delivery system can be designed for controlled release of slightly water-soluble drug Baclofen. It is evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, level of pore former, and membrane weight with release to be fairly independent of pH and hydrodynamic conditions of the body. Baclofen release from the developed formulations was directly proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release.

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