Formulation and *In-Vitro* Evaluation of Controlled Release Tablet of Bupropion Hydrochloride by Direct Compression Technique and Stability Study

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ABSTRACT

Purpose: The aim of the study was to develop and evaluate matrix based controlled drug delivery system by direct compression technique of Bupropion hydrochloride tablet and stability studies. Methods: Controlled release tablets were prepared by employing Eudragit RS 100, HPMC K15M, HPMC K100M at different concentration. Result and conclusion: All 10 batches pass friability, hardness, weight variation, assay but only three batches (CRB3D, CRB4D and CRB7D) passed the dissolution as per USP 30 NF25 for extended release tablet of Bupropion hydrochloride. All batches follow Higuchi Model followed by Pappes model. HPMC (K15M & K100M) as a matrix polymer used in tablet formulation provide a good initial retardation in the release as well as helped to enhance the overall release rate of the drug than that of Eudagit RS 100. It was observed that increase in polymer concentration retards the release of drugs in case of HPMC K15 M and HPMC K100 M. Self life of CRB7D tablet was found to be 2.37year.

Keywords: Controlled release, Bupropion Hydrochloride, Polymers, Dissolution study, Mathematical modeling and Stability

INTRODUCTION

Oral route of drug is the most common, convenient and preferred route for administration. Conventional oral drug does not offer targeting and controlled release properties. The most important objective of controlled release drug delivery system is the prolonging of gastric residence time. The prolonged residence time of the drug in the body believed to prolong action of drug (1, 2). Bupropion hydrochloride (±)-2-(tert-butylamino)-3-chloropropiophenone hydrochloride (Figure 1) is drug belonging to BCS class I having higher solubility and higher permeability. It is an antidepressant belonging to aminoketone having molecular weight 276.20gm/mol. Bupropion primarily act via a noradrenergic mechanism but also exhibits some dopaminergic activity (3). Increase in dopamine level at neuronal sites may reduce the nicotine cravings and urge to smoke. A Controlled release tablet formulation of Bupropion was developed for quieting of cigarette smoking by using Eudragit RS 100 (4), HPMC K 15 M (5) and HPMC K 100M (6) polymers.

EXPERIMENTAL

Materials and methods

Bupropion hydrochloride & Microcrystalline cellulose PH 101, were obtained as gift sample from OHM Pharmaceutical Laboratories Pvt. Ltd, Bhaktapur, Nepal. Eudragit RS100, HPMC K15M, HPMC K100M, Ethyl cellulose, Magnesium stearate were obtained as a gift sample from Elder Universal Pharmaceuticals Pvt. Ltd, Bhairahawa, Nepal. Marketed formulation of 150mg Bupropion HCl Sustain release tablet was bought from local market of Kathmandu, Nepal. All other chemicals and reagents used were of pharmaceutical and analytical grade.

Preparation of calibration curve

50 mg accurately weighed drug was dissolved in 20 ml of distilled water in volumetric flask and final volume was make up 50ml. From this stock solution different dilution were made and absorbance were measured at 298 nm in UV spectrophotometer. The calibration curve was prepared by plotting the concentration on X-axis and absorbance on Y-axis. The equation obtained was used to estimate the drug release in the dissolution study.

Preparation of Controlled release tablet

Controlled release tablet of Bupropion hydrochloride were prepared by direct compression technique. Polymers HPMC (K15M, K100M), and Eudragit RS100 were used to develop the tablet. Accurately weighed quantity of the ingredients Bupropion HCL, MCCP PH 101, different polymers and stearic acid previously sieved through #20 was mixed geometrically for 10 minutes. There after magnesium stearate and aerosol-200 (previously

sieved from # 60) were added and further blending was done in double cone blender for 10 minutes. Total 10 different formulations were prepared from the mixed powder using a 12- station rotatory tablet compression machine having punch diameter 12.50mm with flat and round shaped punches.

Evaluation of granules (4-7)

Angle of repose

Angle of repose of granules was determined by funnel method. Accurately weighed granules were allowed to flow through the funnel freely on to the surface, the height and diameter of the powder cone were measured. Angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone respectively.

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD)/ TBD]*100$$

Where,

TBD: weight of the powder/tapped volume of the powder

LBD: weight of the powder/volume of the powder

Evaluation of tablets (4-7)

Hardness

Hardness variations of 6 tablets were measured using Monsanto hardness tester. The average hardness was calculated and the result is expressed with mean ±S.D.

Friability (F)

Tablet strength was tested by Roche friabilator. Initial weight of 11 tablets was taken and allowed for 100 revolutions. Then final weight of tablets was taken after de-dusting. The % friability was then calculated by;

$F= (W_{initial} - W_{final}) / W_{initial} *100\%$

Weight variation: Randomly selected 20 tablets from each batch were weighed and average weight was calculated. The tablets passed the test, if not more than two tablets falls outside the percentage limit as per the IP (± 5.0%, for more than 280mg tablet).

Assay

Drug content of the manufactured tablets of each batch was determined by weighing and finely crushed 10 tablets from each batch. The powder sample equivalent to 25mg Bupropion HCl was weighed and dissolved in 25ml distilled water. Again 10ml of this solution was diluted to 100ml with distilled water and analyzed by UV spectrophotometer at 298nm.

Dissolution

The dissolution studies were carried out by using the tablet dissolution test apparatus USP type II. The study was carried out at 50 r/min for 12 hours at temperature 37± 0.5°C using 900 ml distilled water (pH 6.8-7.4) as the dissolution medium. 10 ml of sample was withdrawn at 1, 2, 4 8 and 12 hr and sink condition was maintained. The withdrawal samples were filtered and analyzed UV spectrophotometer at 298nm (8). The release amount of drug was calculated by using standard calibration curve. Cumulative (%) drug release versus time, curve was plotted.

Mathematical Modeling of drug release profile (9-10)

From the different data obtained from the dissolution study, zero order kinetics, 1st order kinetics, Higuchi model, Korsmayeer Peppas models were studied to characterize kinetics of drug release.

Stability Studies According to ICH Q1A (R2) and Determination of Shelf life

Stability study of the Controlled release Bupropion hydrochloride tablet was carried out as per the guidelines given in the ICH Q1A (R2) (ICH topic Q1 (R2), 2009). Tablets were stored under $25^0C \pm 2^0C$/ 65% ± 5% RH and $40^0C \pm 2^0C$/ 75% ± 5% RH for the period of 3 months in Thermo lab TH 90S. Samples at the predetermined time intervals (0, 30, 60 and 90 days) were analyzed for appearance, friability, dissolution studies and drug content (11). The amount of drug content remained after each interval was determined as above described procedure. A graph was plotted between log% drug remaining vs. time (days). The degradation rate constant (k) was determined from the following equation where the slope of the curve was determined from the graph.

Slope= - K/2.303

Where, K is the degradation rate constant.

The shelf life of the tablet at 25^0C was calculated by determining the time required to degrade 10% of the drug in Controlled release tablet from the following equation.

$t_{10\%}$= 2.303/ K x log (100/90)

Where, $t_{10\%}$ is the time required to degrade 10% of the drug from the tablet.

RESULT AND DISCUSSION

Calibration curve of Bupropion HCl

The standard calibration curve was prepared by plotting concentration versus absorbance. The absorbance of the different concentration of Bupropion HCL was measured by using distilled water as a blank (λ_{max} = 298nm) and the correlation co-efficient (R^2) was found to be 0.994 which is shown in Figure 2.

Evaluation of granules

The prepared granules of each 10 batches were evaluated on the basis of angle of repose and Carr's index.

Angle of repose

Angle of repose of all granules of 10 formulations was determined by funnel method. Among all formulation CRB6D has good flow properties (21.47°) and CRB8D has greatest angle of repose (32.0°). All the values are given in the Table 1.

Compressibility index

Compressibility index of granules of all 10 batches was determined. CRB4D has least C.I (18.31%) and the CRB10D has greatest compressibility index (30.58%). All the values are given in the Table 1.

Formulation of Controlled release tablet

Ten different formulations of controlled released tablet of Bupropion HCl were developed by employing different polymers with different concentrations as shown in Table 2. All the formulated batches were evaluated for the thickness, hardness, friability, weight variation and dissolution study.

Friability

All the10 batches passed the friability parameter as per the IP standard. 11 tablets from each batch were weighed and were subjected to friability test apparatus for 100 revolutions. The friability results are shown in Table 3.

Weight variation

20 individual tablets from each batch were taken and weighed, average weight, maximum and minimum weight variation were obtained, which is shown in Table 3. As per IP standard, all 10 batches passed the weight variation test.

Assay

Drug content of the manufactured tablets of each batch was determined by weighing and grinding finally 10 tablets from each batch. The powder sample equivalent to 25mg of Bupropion HCL was weighed accurately and dissolved in 25ml of distilled water. Appropriate dilutions were made and analyze by UV spectrophotometer at 298nm. All the 10 formulation passed the assay limit as per the USP30- NF25 with the assay range of 92.44% ± 1.03 to 103.4% ± 0.98 which is shown in Table 3. Due to low assay of CRB2D, the further study of this batch was not done.

Dissolution studies

The dissolution studies of nine formulations were carried out using the tablet dissolution apparatus USP type II (paddle). The study was carried out at 50 r/min for 12 hours at temperature 37 ± 0.5°C using 900 ml of distilled water as the dissolution medium. Each 10 ml of sample was withdrawn at 1, 2, 4, 8 and 12 hour interval with replacement of same volume of the dissolution medium maintained at temperature 37 ± 0.5°C. The withdrawal samples were filtered and analyzed by using UV spectrophotometer at the wave length 298nm. Cumulative drug release was calculated by using the equation from the standard calibration curve. Cumulative drug release versus time curve was plotted. Among 9 batches only CRB3D, CRB4D, CRB7D, meets the USP30-NF25 parameter. The entire cumulative % drug release is given in Table 4**.** The comparative dissolution studies are shown in Figure 3.

Drug release kinetics

The release mechanism of drug release from the matrix tablets, the release data were fitted into the kinetics equation of Zero order, First order Higuchi model and Peppas power law. The cumulative percentage drug release verse time, the logarithm cumulative percentage drug release verse time, cumulative percentage drug release verse square root of time and logarithm of cumulative % drug release vs. logarithm of time were used to evaluate for Zero order kinetic , First order kinetics, Higuchi model and power law respectively.

Considering correlation coefficient obtained using different kinetics equations, the formulation which passed the dissolution parameter as per UPS 30-NF 25 are Higuchi model, followed by Peppas model. All three batches follow Ficikan Diffusion. The result is shown in Table 5.

Stability Studies According to ICH Q1A (R2) and Determination of Shelf life

Among three batches only CRB7D was stored in air tight glass container under $25^0C \pm 2^0C$/ 65% ± 5% RH and $40^0C \pm 2^0C$/ 75% ± 5% RH for the period of 3 months in Thermo lab TH 90S. Samples at the predetermined time intervals (0, 30, 60 and 90 days) were analyzed for appearance, friability, dissolution studies and drug content as the data are shown in Table 6 & Table 7.The shelf life of CRB7D tablet was found to be 2.37 year which was obtained by the data of log% drug remaining vs. time as shown in Figure 4.

CONCLUSION

Matrix based Controlled release tablet of Bupropion hydrochloride tablet were prepared by using Eudragit RS 100, HPMC K15M and HPMC K100M. The different ratios of Drug to polymer were taken for the formulation of different batches. All the ten batches passed weight variation, friability, hardness, drug content. CRB2D has low assay content (92.44±1.03) so no further study was carried out for this batch. The dissolution study was done by using USP type II apparatus at 50 r/min with 900 ml distilled water (pH 6.8 – 7.4). Only CRB3D, CRB4D and CRB7D passed the dissolution study for the controlled release tablet and showed better result than the marketed product. On the basis of correlation coefficient value all three batch follow Higuchi model & followed by Peppas mode. Stability study of the CRB7D batch was studied for 3 month and self life of the drug was found to be 2.37 year.

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Table 1: Table showing angle of repose and carr's index

Formulation	Angle of repose(θ)	Carr's index (%)
CRB1D	28.21	24.14
CRB2D	29.8	26.73
CRB3D	25.73	24.9
CRB4D	29.03	18.31
CRB5D	29.11	18.35
CRB6D	21.47	26.72
CRB7D	30.5	28.57
CRB8D	32.0	23.72
CRB9D	26.8	28.3
CRB10D	30.5	30.58

Table 2: Composition of controlled release tablet of BHCl

Ingredients	CRB 1D	CRB 2D	CRB 3D	CRB 4D	CRB5 D	CRB6 D	CRB7 D	CRB8 D	CRB9 D	CRB 10D
Bupropion HCL	150	150	150	150	150	150	150	150	150	150
MCCP PH 101	327	302	277	364.5	352	302	352	327	302	227
EC	30	30	30	30	30	30	30	30	30	30
Eudragit RS	50	75	100	-	-	-	-	-	-	-
HPMC K-100M	-	-	-	12.5	25	75	-	-	-	-
HPMC K 15M	-	-	-		-	-	25	50	75	150
Stearic acid	30	30	30	30	30	30	30	30	30	30
Aerosil-200	3	3	3	3	3	3	3	3	3	3
Mg.stearaete	10	10	10	10	10	10	10	10	10	10
Total (mg)	600	600	600	600	600	600	600	600	600	600

Table 3: Hardness, friability, average weight, weight variation and assay.

Formulation	Hardness (kg/cm^2) ± S.D (n=6)	Friability (%)	Average wt(mg) ± S.D (n=20)	Maximum wt variation (%)	Minimum wt variation (%)	Assay ± S.D (%) (n=3)
CRB1D	9.6±0.41	0.4	595±4.56	2.05	1.36	98.2±0.78
CRB2D	10.2±0.27	0.47	591±6.01	2.81	2.57	92.44±1.03
CRB3D	8.6±0.65	0.5	596±3.85	3.00	1.59	94.38±1.37
CRB4D	9±0.79	0.41	598±2.17	1.37	1.09	103.4±0.98
CRB5D	10.7±0.27	0.28	598±3.94	1.74	1.18	98.48±0.34
CRB6D	10.5±0.5	0.43	604±2.45	1.30	1.70	96.21±0.73
CRB7D	8.9±0.65	0.34	589±4.56	3.18	2.17	99.44±0.91
CRB8D	9.9±0.74	0.3	595±2.94	1.89	2.16	96.14±1.13
CRB9D	10±0.93	0.28	595±4.46	1.04	2.21	101.13±0.39
CRB10D	10.5±0.61	0.24	605±2.04	0.87	2.81	101.2±0.93

Table 4: Cumulative (%) drug release at 1, 2, 4, 8, 12 h with S (n=3).

For ulation	C. drug release at 1h	C. drug release at 2h	C. drug release at 4h	C. drug release at 8h	C. drug release at 12 h
CRB1D	30.54±1.02	36.24±1.33	73.75±1.43	74.15±1.19	74.41±1.39
CRB3D	33.45±1.89	42.77±2.05	79.94±1.82	80.67±1.28	81.39±1.67
CRB4D	29.18±2.11	48.5.5±1.29	80.1±1.29	82.8±2,03	83.61±1.96
CRB5D	27.78±1.69	39.04±1.72	73.11±2.36	75.5±2.10	76.7±1.39
CRB6D	22.49±2.18	37.4±2.45	64.39±1.49	66.49±2.26	68.33±2.17
CRB7D	29.49±2.38	35.67±1.79	58.12±3.07	81.06±2.26	81.63±1.76
CRB8D	27.08±1.19	32.97±2.21	41.66±2.37	66.86±2.54	80.56±2.37
CRB9D	25.01±2.37	30.14±2.57	40.56±1.49	71.7±2.71	71.81±1.76
CRB10D	23.99±1.24	30.76±2.34	35.21±1.76	62.45±2.37	68.54±1.98
Marketed formulation	25.07±2.37	36.69±2.70	65.46±2.91	79.36±3.01	80.23±2.31

Table 5: R^2 value of different kinetic equations

B.NO	Zero order Model R^2	First order Model R^2	Higuchi Model R^2	Peppas model R^2	n value
CRB3D	0.672	0.759	0.883	0.871	0.39
CRB4D	0.667	0.761	0.894	0.856	0.425
CRB7D	0.825	0.919	0.968	0.963	0.454

Table 6: Stability studies of the CRB7D batch at $25^0C \pm 2^0C$/ 65% ± 5% RH and $40^0C \pm 2^0C$/ 75% ± 5%RH

Time (days)	Conditions		
	Appearance	Dissolution	Friability
0	Not changed	Passed	Passed
30	Not changed	Passed	Passed
60	Not changed	Passed	Passed
90	Not changed	Passed	Passed

Table 7: Stability data for the shelf life determination of CRB7D tablet

Temp	Days	% Drug remaining	Log DR	Slope	K	Self life
25^0C	0	99.44	1.99756			
	30	99.09	1.99602			
	60	98.62	1.99396	0.00006	0.0001218	2.37yr
	90	98.30	1.99255			
40^0C	0	99.44	1.99756			
	30	99.01	1.99567			
	60	98.50	1.99343			
	90	98.18	1.99202			

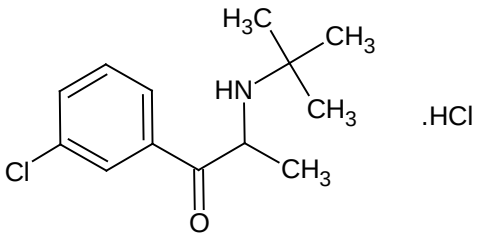

Figure 1: Structure of Bupropion hydrochloride

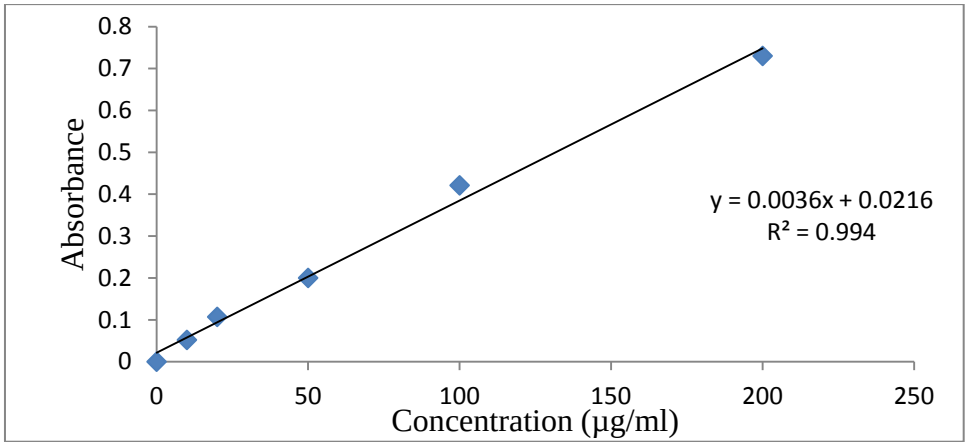

Figure 2: Standard calibration curve of Bupropion HCl

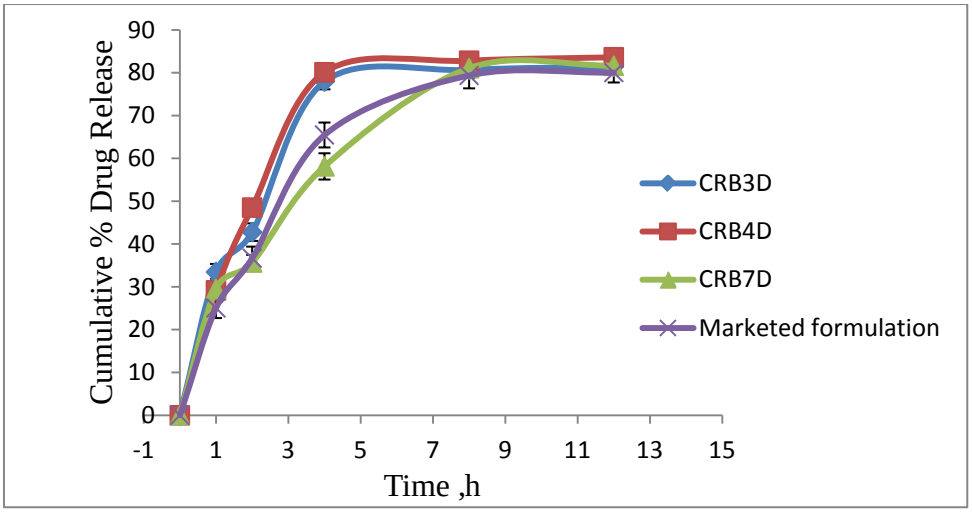

Figure 3: Comparative dissolution studies with Marketed Tablet

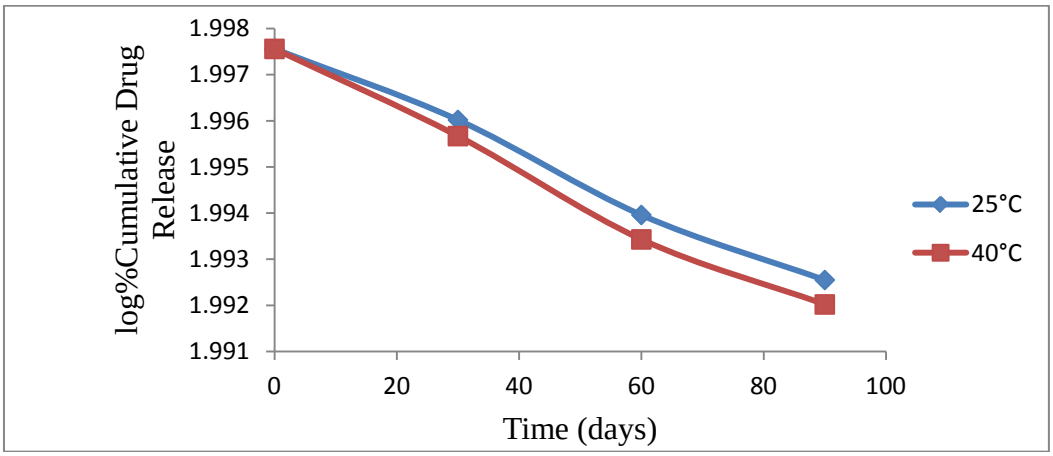

Figure 4: Stability study of CRB7D