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Research Article

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Formulation and evaluation of bupropion hydrochloride sustained release tablets using combination of hydrophilic polymers

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Abstract The objective of the present study was to develop the oral sustained release tablets of Bupropion hydrochloride using combination of hydrophilic polymers. Bupropion Hydrochloride is a Anti-Depressant agent used in symptomatic treatment of depression, maniac, and smoking withdrawal conditions. FT-IR studies were carried to know the interaction, showed that absence of any interactions between the drug and polymers. Optimization of the formulation was done by studying effect of drug to polymer ratio on drug release. The physicochemical properties of tablets were found within the limits. The drug release from optimized formulation BST-5 was extended for a period of about 12 h. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport. Release of the drug was retarded with increase in polymer concentrations. The optimized formulations were subjected to stability studies for two months at 40±2 ºC temperature with RH 75±5 %, and showed stability with respect to physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic polymers in the preparation of sustained release formulation of Bupropion hydrochloride.

Keywords Bupropion hydrochloride, Anti-Depressive agent, Sustain release tablet, Rate controlling polymer, *In-vitro* drug release.

Introduction

Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are follows: "tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed" [1]. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs [2].

Aim of the present study is to investigate the possibility of obtaining a prolonged, relatively constant level of Bupropion hydrochloride. Bupropion hydrochloride which is an Anti-Depressive agent (Dopamine uptake inhibitor) for the treatment of major depressive disorders and smoking cessation aid [3-4] to improve patient compliance and to decrease the incidence of adverse effects or side effects, and facilitating a reduction in dosage frequency of drug administration. Keeping these factors in view it was aimed to formulate and evaluate Bupropion hydrochloride SR 100 mg tablets by using combination of any two hydrophilic polymers (HPMC K4M, PMC K100, PVP) to provide a controlled and predictable release [5] of drug for twice daily administration.

Materials and methods

Materials: Bupropion Hydrochloride was gifted by (Hetero labs, Jeedimetla, Hyderabad, India), HPMC K4M produced by The Dow Chemical Company, PVP- K90 was obtained from ISP Technologies, HPMC K100 procured from Colorcon, MCC PH102 gifted by FMC Bio polymer, Magnesium Stearate was obtained from Peter grevens.

Methods:

Preparation of tablets:

Sustain release tablets of Bupropion hydrochloride were prepared by wet granulation method using purified water [6]. Sifting of active material, polymers and excipients through 40#, Dry mixing of all ingredients for 15 minutes, to this powder blend water was added for producing wet mass. Wet screening of this mass was passed through 10# for the preparation of granules, Drying of wet granules in a rapid dryer or hot air oven (75-80^{o}c) for 90 minutes, Dry screening of granules in 20#, to this dried granules magnesium stearate is added as a lubricant which is passed by 60# then compression of lubricated granules by Cadmach Tablet compression machine [7].

Table1: Development of various tablet formulations containing Bupropion HCl

Ingredients (mg) / Code	Bupropion HCl	HPMC K4M	HPMC K100	PVP K90	MCC $P^{H}102$	Mg. stearate	Total weight
BST-1	100	50	100	-	22.25	2.75	275
BST-2	100	100	50	-	22.25	2.75	275
BST-3	100	50	-	100	22.25	2.75	275
BST-4	100	100	-	50	22.25	2.75	275
BST-5	100	-	100	50	22.25	2.75	275
BST-6	100	-	50	100	22.25	2.75	275

Parameters for Evaluation of Designed Formulation

1) Thickness: Twenty tablets were randomly selected from formulations and thickness was measured individually with the help of vernier calipers. It was expressed in millimeter and average was calculated [8].

2) Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using pfizer hardness tester. It was expressed in kg/cm^2. Ten tablets were randomly selected from each formulation and hardness of the same was determined. The average value was also calculated [8].

3) Friability: The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). 20 tablets ($W_{initial}$) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were dedusted and weighed again (W_{final}). The percentage friability was calculated by,

$$F= W_{initial} - W_{final} / W_{final} \times 100$$

% Friability of tablets less than 1 % are considered acceptable [8].

4) Weight variation: Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation. The following percentage deviation in weight variation according to USP was allowed [9].

Table2: USP specification for tablet weight variation:

Average weight of tablet	Percentage weight variation
130 mg or less	10 %
More than 130 mg and less than 324 mg	7.5 %
324 mg or more	5 %

5) *In vitro* Dissolution studies: Six tablets of each formulation were randomly chosen and weighed. One tablet was transferred into each dissolution vessel containing 900 ml of water. Aliquot samples were withdrawn at specified time intervals up to 12 h. The sample volume was immediately replaced with fresh medium. The drug content present in the sample were estimated spectrophotometrically at 298 nm using water as blank [10].

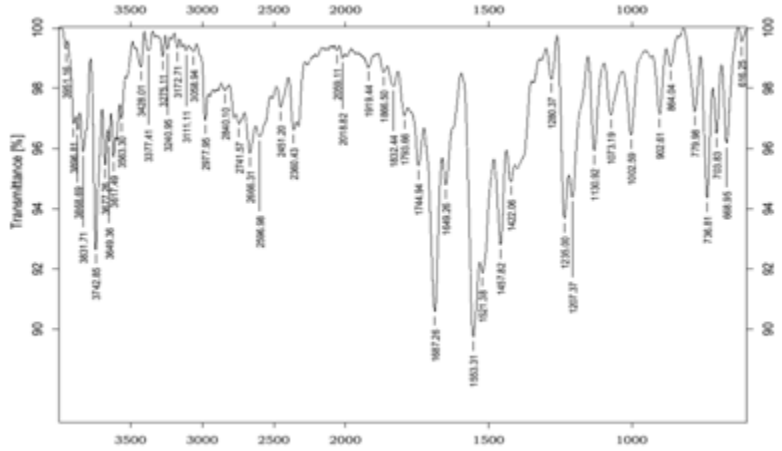
Table3: Dissolution parameters

Apparatus used	USP Type-Il, Paddle
Speed	50 rpm
Sampling volume	5ml
Sampling time interval	1 h interval up to 12 h

Results and Discussion

Preformulation Studies: Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development.

The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality [11].



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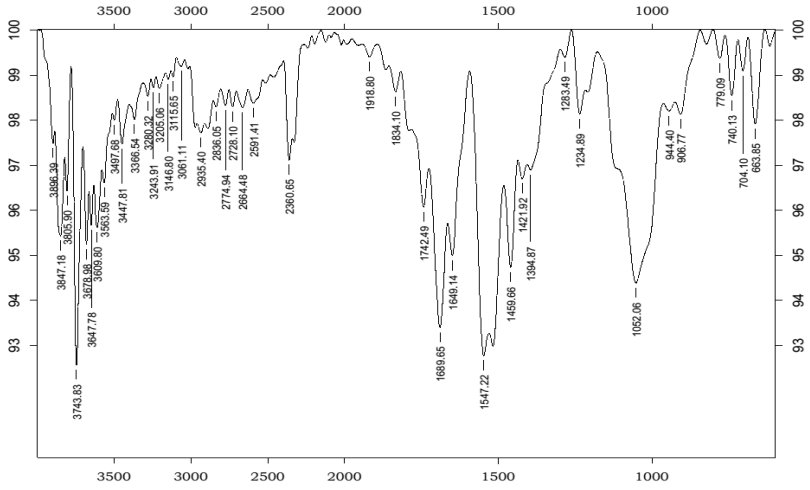

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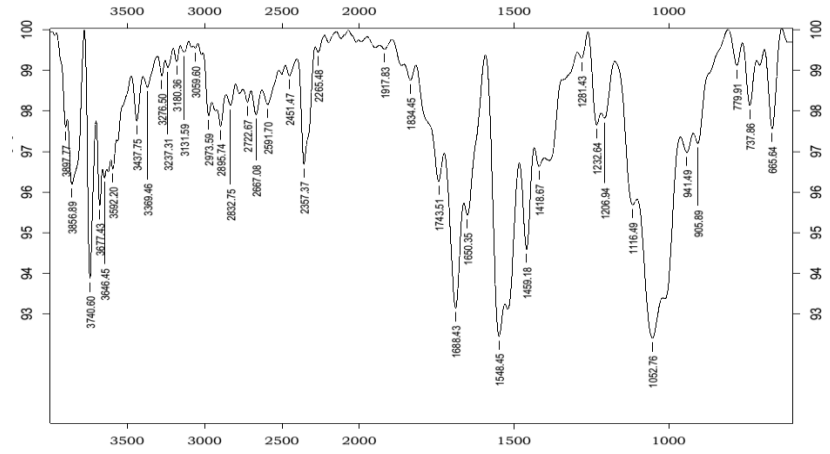

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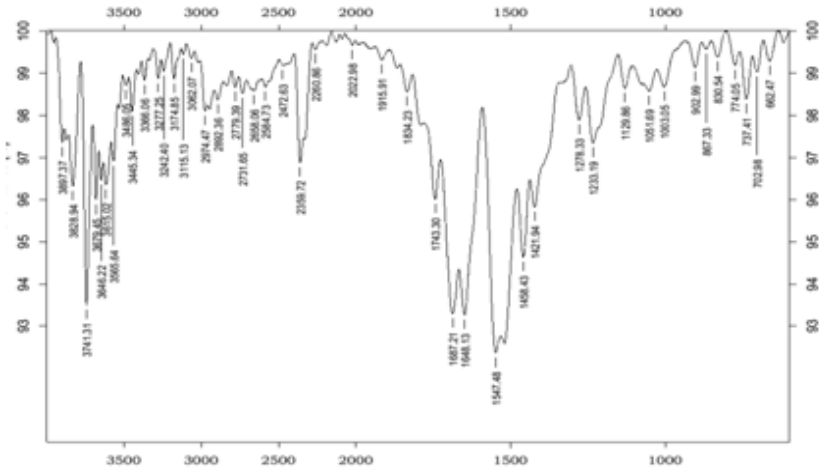

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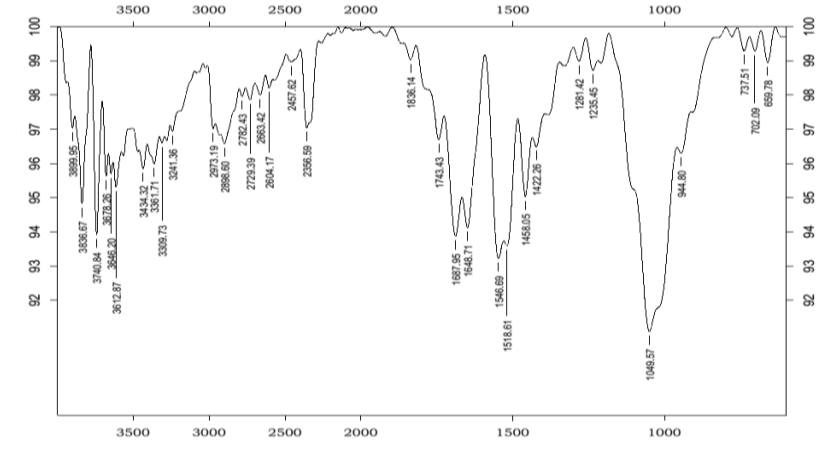

(e)

Figure 1: FTIR of **a)** Pure Bupropion HCl **b)** Bupropion HCl with hydroxy propyl methylcellulose K4M **c)** Bupropion HCl with hydroxy propyl methylcellulose K100 **d)** Bupropion HCl with PVP K90 **e)** Bupropion Hydrochloride + HPMC K4M+HPMC K100+PVP K90+MCC

Compatibility Studies of Bupropion HCl with Formulation Excipients: IR Specra of Bupropion HCl alone and its combination with polymers shown in figure 1. An IR Spectrum of pure Bupropion HCl showed the peaks 1553 cm^{-1} Amide (N-H Out of plane), 1687 cm^{-1} Ketone (C=O stretch), 902 cm^{-1} Dialkyl amine (R_2NH), 1235 cm^{-1} Alkyl halides (C-Cl), 1457 cm^{-1} Aromatic (C-C stretch). These peaks can be considered as characteristic peaks of Bupropion HCl and were not affected and prominently observed in IR spectra of Bupropion HCl along with polymers as shown in the figure1, indicated no interaction between Bupropion HCl and polymers.

Pre-compression parameters

Tapped density, Bulk density, Angle of Repose, Compressibility index, Hausner's ratio, and loss on drying (L.O.D) [12] were carried out for the blend of Bupropion HCl results were shown in Table 4.

Table 4: Pre-compression parameters of Bupropion HCl

Powder blend	Angle of Repose (°)*	Loose bulk density (g/ml)*	Tapped density (g/ml)*	Compressibility index (%)*	Hausner's ratio*	L.O.D	Powder blend
BUP	68.3±1.06	0.38±0.02	0.543±0.02	30.01±0.02	1.42±0.02	1.2	**BUP**
BST-1	26.6±0.82	0.518±0.02	0.611±0.11	15.21±0.05	1.17±0.04	0.97	**BST-1**
BST-2	29.1±1.11	0.595±0.04	0.677±0.03	12±0.02	1.13±0.01	0.98	**BST-2**
BST-3	28±0.76	0.498±0.03	0.601±0.05	17.13±0.05	1.20±0.03	0.98	**BST-3**
BST-4	27±0.92	0.485±0.02	0.628±0.04	22.72±0.07	1.294±0.02	1.2	**BST-4**
BST-5	27.2±0.86	0.636±0.03	0.777±0.06	18.14±0.04	1.22±0.05	0.89	**BST-5**

***Each value represents the mean ± standard deviation (n = 10)**

Post-compression parameters

The tablets of different formulations were physically characterized by parameters like Thickness, Average Weight, hardness and friability, uniformity of weight results were shown in Table 5.

1. Average Weight:

The average weights of tablets were tested for uniformity of weight. The tablets were found to be uniform. The average weight of the tablets was found to be in the range of 270 to 280 mg

2. Friability: In the present study, the percentage friability for all the formulations was found bellow 1% indicating that friability (%) is within the limits.

3. Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 97.5 to 99 %.

4. Hardness: The hardness of the tablets of all batches was ranged from 9.2 to 10.2 kg/cm^2 which was sufficient to maintain the mechanical strength.

5. Thickness: The thickness of the formulations was found in the range of 4.59 to 4.62 mm. The tablets exhibit uniform thickness among the different formulations.

Table 5: Post-compression parameters of Bupropion HCl

Formulation code	Average Weight (mg)*	Friability (%)*	Drug content (%)*	Hardness (Kg/cm^2)*	Thickness (mm)*
BST-1	275±0.85	0.26±0.02	99.5±1.2	9.8±0.32	4.62±0.21
BST-2	274±0.73	0.17±0.06	99.9±0.98	9.3±0.31	4.61±0.15
BST-3	272±0.87	0.21±0.02	98.9±1.1	10±0.21	4.59±0.08
BST-4	280±0.98	0.32±0.04	98.9±1.28	9.6±0.33	4.64±0.16
BST-5	276±0.76	0.20±0.01	99.9±0.86	9.8±0.10	4.62±0.01
BST-6	278±1.3	0.24±0.03	98.8±1.04	10.2±0.32	4.63±0.09

***Each value represents the mean ± standard deviation (n = 10)**

6. *In vitro* drug release: The drug and polymer ratio was further increased to 1:1.5, various blends of hydrophilic polymers were added to the formulations. The overall drug release rate increased further about 12 h. Formulation BST-5 fulfilled our objective of retarding the drug release effectively for a period of 12 h. Polymer blend of HPMC K 100- 100 mg and PVP K 90-50 mg was able to produce controlled release following zero order and drug release of 90.13% at the end of the 12 h.

Table 6: *In vitro* percentage drug release of different formulation

Time(hrs)	BST-1	BST-2	BST-3	BST-4	BST-5	BST-6
1	15.17	13.67	22.98	22.48	26.97	25.14
2	24.49	22.33	34.14	33.48	35.81	34.98
3	30.50	32.16	41.33	40.83	44.99	43.66
4	38.68	39.34	47.02	45.36	50.03	47.36
5	43.21	44.21	47.08	52.06	50.91	49.74
6	49.06	49.06	49.26	54.42	51.94	51.76
7	55.41	53.58	53.60	64.92	53.95	55.61
8	65.57	64.91	57.44	66.94	61.94	60.44
9	69.71	68.21	71.74	76.09	68.61	72.09
10	70.79	83.08	81.46	82.16	77.33	80.82
11	82.17	84.01	85.21	90.90	85.89	85.73
12	**95.06**	**97.23**	**99.93**	**98.15**	**90.13**	**99.95**

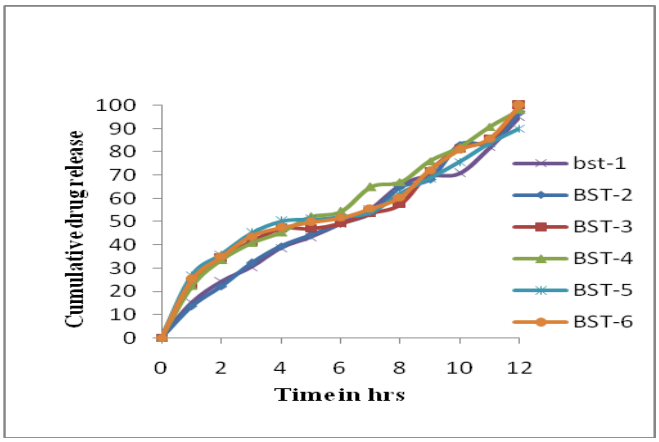

Figure2: *In-vitro* dissolution profile of different formulations

7. Stability studies:

The batch BST-5 was selected as an optimum batch and the stability study was carried out at room temperature and at accelerated condition of 40°C/75 % RH condition for a period of two months. The test values before the start of stability study and after the completion, were compared and found to have no significant change formulation which is found to be acceptable [13] and the results were shown in Table 7.

Table 7: Dissolution and Assay Profile of Optimized Formulation (BST-5)

S. No.	Test	Specifications	Initial	After 1 month	After 2 months
1.	Dissolution (In Water)	NLT 80% release after 12 h	97.9%	97.8%	97.5%
2.	Assay (By UV)	NLT 95.0 percent and NMT 105.0 %	99.86%	98.77%	98.69%

8. Drug Release Kinetics:

The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined The drug release data obtained were extrapolated by Zero order, First order, Higuchi model and Korsmeyer-Peppas plot for Best Formulation BST-5. The in-vitro kinetic data is subjected to log time-log drug release transformation plot (Korsmeyer-Peppas plot), the slope values is 2.017 (n > 1) revealed the fact that the drug release follows super case II transport diffusion possibly owing to chain distanglement and swelling of hydrophilic polymer. The kinetics of drug release from this formulations showed best fitting with Korsmeyer-Peppas model [14-15] and the results were shown in table 8.

Table 8: Drug release kinetics data for optimized formulation (BST-5)

Formulation Code	**Zero order**		**First order**		**Higuchi's plot**		**Peppa's model**	
BST-5	**Slope**	**r^2**	**Slope**	**r^2**	**Slope**	**r^2**	n	**r^2**
	0.1508	0.9575	10.867	0.8937	0.0398	0.9761	2.0708	0.9697

Summary and Conclusion

Physical properties such as bulk density and tapped density were more in case of granules ready for compression than that of raw powder. The above study demonstrated that concentrations of various viscosities of hydrophilic polymers ratios could be successfully employed for formulating sustained release tablets of Bupropion Hydrochloride. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Bupropion Hydrochloride tablets.

It was observed that Formulation BST-5 retards the drug release (90.13%) up to 12 h. The objective of the present work was fulfilled by formulating sustained release tablets of Bupropion Hydrochloride using combination of hydrophilic polymers. Hence it can be concluded that sustained release tablet of Bupropion Hydrochloride having satisfactory controlled release profile which may provide an increased therapeutic efficacy.

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References

1. Lachman L. and Lieberman H.A., Pharmaceutical Dosage Forms, In; Tablets, Vol. 2, Marcel Dekker, Inc., New York: 293
2. H. Popli and S. N. Sharma, Trends in oral Sustained Release Formulations, the East Pharmacist, Aug 1989: 9-100.
3. www.Drug bank.ca/drugs/.com
4. Properties of Bupropion Hydrochloride in US FDA
5. Vyas SP, Khar RK, Controlled Drug Delivery : Concepts and Advances, 1st edition, Vallabh Prakashan, New Delhi, 2002: 156.
6. Tiwari And Mahaparale, et.al., Effect of Hydrophilic and Hydrophobic Polymer on Sustained Release Matrix Tablet of Bupropion Hydrochloride, IJPSR, 2013; Vol. 4(7): 2835-2842.
7. Leon Lachman et.al; The Theory and Practice of Industrial Pharmacy, 3rd edition: 293- 345.
8. Remington: The science and practice of pharmacy, 20th edition volume1: 858-863.
9. Bentley's Text Book of Pharmaceutics, 8th edition:60-61.
10. United State Pharmacopoeia-30 National Formulary 25, Vol.1, Asian edition, United State Pharmacopoeial Convention, Inc, 2009, USPC, Inc. Official, USP Monographs, Bupropion Hydrochloride Tablets.
11. Thomsons, Physician's Desk Reference, 60th edition, 2006:2333-2334.

12. The Indian Pharmacopoeia, The Controller of Publication, Govt. of India, Delhi, Edition IV, Vol. 2, 1996, A82-A85. 34. The United States Pharmacopoeia XXVI, United States Pharmacopoeia convention, Inc., Rockville, MD, 2003: 279-282.
13. Stability Studies in Overview of ICH Guidelines for Drug products, Natalie M.C. Clure, Matric Pharmaceutical Inc. 1997.
14. Dr. Jaiswal SB, Dr. Brahmankar DM, biopharmaceutics and Pharmacokinetics – A Treatise, 1st edition, Vallabh Prakashna, New Delhi, 1995.
15. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Fifth Edition, 2004: 515.