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Formulation and evaluation of sustained release tablets of bupropion hydrochloride

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ABSTRACT

The objective of the present investigation is to design and evaluate sustained release dosage form of bupropion hydrochloride and compare with innovator product (Wellbutrin sustained release tablets). Sustained release tablets were prepared by wet granulation method using HPMC and Microcrystalline Cellulose as matrixing agents. The granules prepared were shown satisfactory flow properties and compressability. Prepared Granules were evaluated for Angle of repose, bulk density, tapped density, compressibility index, Hausner ratio. The granules shown satisfactory flow properties and compressability. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. . Formulation of sustained release tablet of bupropion hydrochloride as formulation batches F-1 and F-2 with a variation in the quantities of HPMC and Microcrystalline indicated that the formulation F-II be taken as an ideal or optimized formulation resembling the marketed product of Wellbutrin sustained release tablets for 10 hour release as it full fills all the requirements for sustained release tablet.

Keywords: Sustained release Tablets, bupropion hydrochloride, Hydroxy propyl methyl cellulose, Microcrystalline Cellulose, dissolution.

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INTRODUCTION

Drugs can be administered through different routes; however, of all the routes of administration, oral route of administration [1] is most convenient for administering drugs for systemic effect because of ease of administration by manufacturing and dosage adjustments. Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of products. Solid dosage forms of tablets and capsules are more commonly employed, the tablets have advantages than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed.

MODIFIED RELEASE DRUG SYSTEM: The term modified release [2] drug product is used to describe products that alter the timing and/or the rate of release of the drug substance.

TYPES OF MODIFIED RELEASE DRUG SYSTEM

Extended release dosage forms: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release form. Ex: Controlled release, Sustained release.

Sustained release: It includes any drug delivery system [3] that achieves slow release of drugs over an extended period of time not particularly at a pre-determined rate. Sustained release dosage forms to complement the pharmaceutical activity of thr medicament inorder to achieve better selectivity and longer duration of action [4]. Sustained release products are helpful to reduce the dose frequency and side effects of drugs and improve patient convenience [5].

Controlled release: It includes any drug delivery system from which the drug is delivered at a predetermined rate over a long period.

Delayed release dosage forms: A dosage form releases a discrete portion of drug at a time or times other than promptly after administration [6] although one portion may be released promptly after administration. Ex: Enteric coated dosage forms.

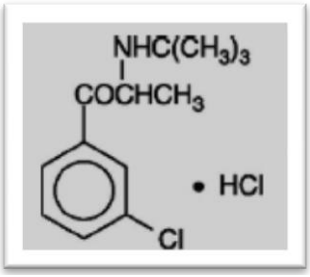
Targeted release dosage forms: A dosage forms that release drug at /near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics.

Repeat action dosage forms: It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a latter time.

Prolonged action dosage forms: It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period [7]. Extended release dosage forms are

formulated in such manner as to make the contained drug available over an extended period of time following administration. Expressions such as controlled-release, prolonged-action, repeat action and sustained-release have also been used to describe such dosage forms. A typical controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced fluctuations via slow release over an extended period of time.

Bupropion HCl is Chemically (±)-1-(3chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride tricyclic, tetracyclic, selective serotonin re-uptake inhibitor.



MATERIALS AND METHODS

Bupropion hydrochloride was obtained as a gift sample from SUN Pharma, Mumbai, India, and HPMC was purchased from Sigma Aldrich, Bangalore. Microcrystalline cellulose was obtained from Dow Chemical's Asia Pvt. Ltd., Mumbai. All other chemicals and reagents used were of pharmaceutical or analytical grade and were used as received.

PREPARATION OF SUSTAINED RELEASE TABLETS

Accurately weighed quantity of the ingredients bupropion Hcl, microcrystalline cellulose, hydroxypropylmethylcellulose are sifted through sieve # 20and blended in a polybag for 10 min. 50% binder solution is prepared by dissolving 20gms of L-cystine Hcl as Solution A and Solution B is remaining water. The above blended ingredients were set up for granulation by using automatic fluid bed granulator. Initially the solution of L-cystine Hcl in water is sprayed on to the bed by maintaining conditions indicated in (Table No.) and solution B was sprayed on the bed at a pump rate of 20 rpm. The above wet granules are dried at 50-55^0 c in fluidized bed dryer until loss on drying (LOD) reaches 2.5-3.0 % and passed through mesh # 30 and Magnesium stearate was added. Finally the material is to be compressed at desired or suitable compression force as to achieve perfect sustained release tablet. Two formulations were formulated as F-1 and F-2. (Table No.)

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EVALUATION OF GRANULES [8]

Angle of repose

The angle of repose of granules was determined by funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted just touches the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface the diameter of the powder cone was measured& angle of repose was calculated using the following equation. **(Table No. 4)**

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

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

Bulk density

Both loose bulk density & tapped bulk density were determined. A quantity of 2 gram of Powder from each formula, previously lightly shaken for the break of any agglomerates formed, was introduced into a 10 ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to falldownits own weight from the hard surface from a height of 2.5cm at 2 second intervals. the tapping was continued until no further change in the volume was noted.

LBD & TBD were calculated using the following formulas: **(Table No. 4)**

LBD: Weight of the powder/Volume of the packing

TBB: Weight of the powder/Tapped volume of the packing

Compressability index

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

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

Where

LBD: Weight of the powder/Volume of the packing
TBB: Weight of the powder/Tapped volume of the packing **(Table No. 4)**

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EVALUATION OF TABLETS [9,10]

Thickness

The thickness of the tablet was measured by using thickness guage (Mitutoyo). Six tablets from each batch were used and average values were calculated. **(Table No. 5)**

Weight variation

20 tablets from each batch were weighed using an electronic balance and the test was performed according to official method. The USP limit for weight variation in case of tablet weight between 161.72 and 167.25 mg that is 6.5%. **(Table No. 5)**

Hardness & friability

For each formulation that hardness of 6 tablets was determined using tablet hardness testers. The friability of 20 tablets was determined using Roche fibrilator. The limit for Friability is NMT 1% **(Table No. 5)**

In-vitro release studies [11]

Dissolution studies were performed using USP standard dissolution apparatus (TYPE II) at 37 ± 0.5ºC.Using one tablet at a time in a vessel. The basket was immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was initially 0.1N Hcl up to 2hrs.

During the test 10ml of the sample was withdrawn at specific time intervals 1, 2, 3, 4, 6, 8, 10, hrs after each withdrawal, same volume of fresh dissolution medium was added to maintained sink conditions. Different aliquots were suitably diluted. The absorbance was measured in the UV spectrophotometer at λ max 298nm. **(Table No. 5)**

RESULTS AND DISCUSSIONS

The objective of the study is to formulate and evaluate Bupropion Hcl sustained release tablets and to compare with marketed product. Two formulations of sustained release tablets were developed employing different proportions of HPMC and Microcrystalline Cellulose as F-I and F-II. All the finished products were evaluated for thickness, hardness, friability, weight variation and dissolution rate. Dissolution rate study was performed in 900ml of 0.01N Hcl using USP-II (paddle) apparatus. In the preformulation studies the Micromeritic flow properties of the Blend were assessed by determining angle of repose, compressibility index, and Hausner ratio**.** The release of Bupropion Hcl sustained release tablet of various formulations varied according to the ratio and degree of the polymer. The granules of different formulations are characterized

by Angle of repose LBD, TBD and compressability index. The granules indicate fair to good flowability with the angle of repose values ranging between 25.9^0 and 28.3^0 respectively for F-I and F-II respectively. The bulk density, tapped density and compressability index values for formulations F-I and F-II were 0.352±0.04, 0.490±0.03, 11.85±0.04, and 0.353±0.03, 0.448±0.02, 12.86±0.03(Table No. 3) respectively. All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values. The tablet mean thickness and mean diameter values were ranging from 4.59 ±0.032, 4.35±0.030 and 11.10±0.0019mm, 11.21±0.0007 respectively. The hardness of the tablets were10.4 kg/cm² and 10.8 kg/cm² respectively and the friability was 0.40 and 0.32 respectively. The invitro dissolution profile for the marketed product Wellbutrin sustained release tablets was 0, 33.7, 50.0, 61.3, 71.7, 87.0, 97.7 and 103 % respectively for 0, 1, 2, 3, 4, 6, 8 and 10 hrs .The dissolution profile for batch F-I was 0, 68.2, 74.6, 98.7, 99.6, 102.2, 106.8 and 107.8 % respectively. The dissolution profile for batch F-II was 0, 39.7, 56.7, 68.7, 77.4, 90.6, 99.8 and 100.9 respectively for 0, 1, 2, 3, 4, 6, 8 and 10 hrs Table No.4). The batch F-II has shown the similar result with the marketed tablet when compared with formulation F-I because in the formulation F-II the release was retarded due to the increase in the viscosity of the polymer, and given the accurate release that of innovator product.

STANDARD CURVE OF BUPROPION HYDROCHLORIDE (Table No. 1)

S. NO	CONCENTRATION (μg/ml)	ABSORBANCE(nm)
1	0	0
2.	2	0.087
3.	4	0.168
4.	6	0.251
5.	8	0.328
6.	10	0.435

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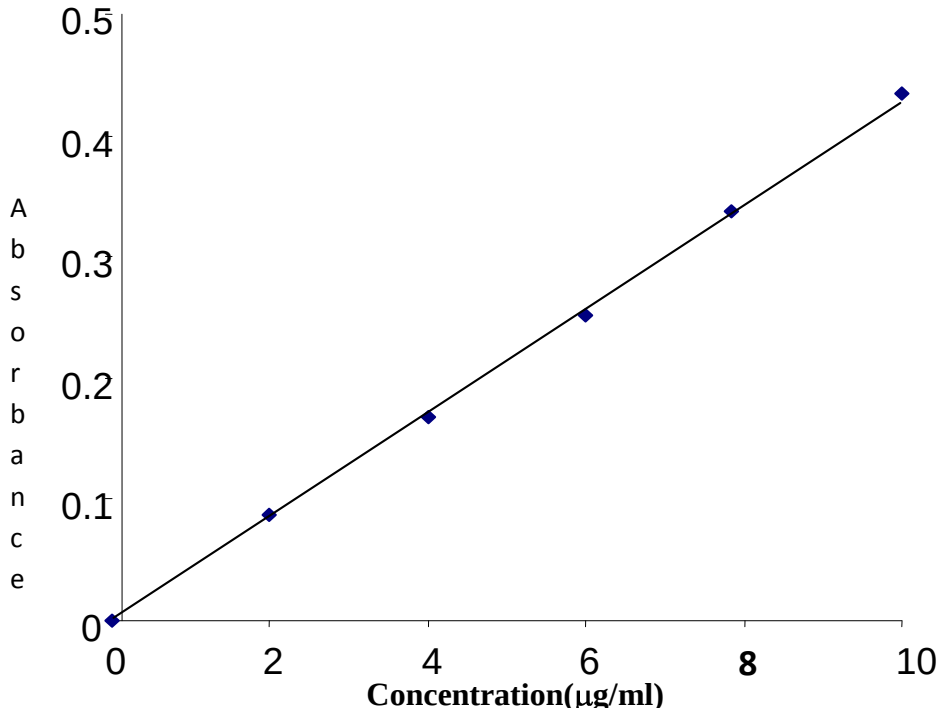
Standard Curve of BUPROPION HYDROCHLORIDE



FORMULATION OF BUPROPION HCL SR TABLETS (Table No.2)

S.NO	INGRDIENTS (mg/tablet)	F-I(mg)	F-II(mg)
1	DRUG	150	150
2	HPMC	218.5	198.5
3	HYDROXYPROPYLMETHYLCELLULOSE	20.0	40.0
4	L-CYSTINE Hcl	7.5	7.5
5	MAGNESIUM STEARATE	4.0	4.0

PHYSICAL CHARACTERSTICS OF GRANULES (Table No.3)

PHYSICAL CHARATERSTICS	FORMULATION-I	FORMULATION-II
Angle of Repose	25°.9"	28°.3"
Bulk density	0.352±0.04	0.353±0.03
Tapped density	0.490±0.03	0.448±0.02
Compressability index	11.85±0.04	12.86±0.03
Hausner ratio	1.391	1.402

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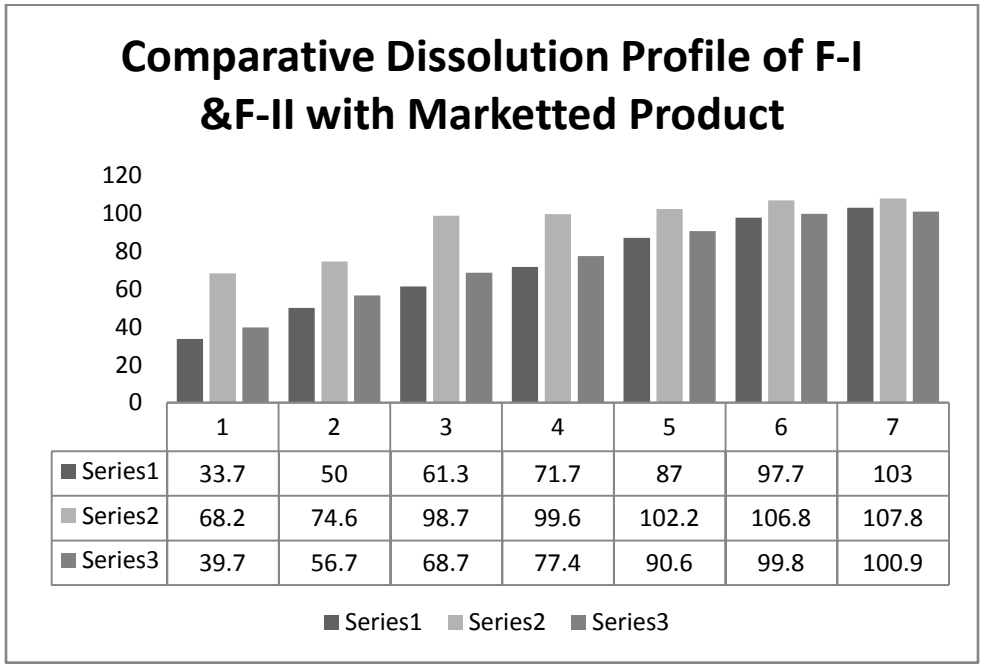
EVALUATION OF BUPROPION HYDROCHLORIDE SUSTAINED RELEASE TABLETS (Table No.4)

Evaluation Parameter	FORMULATION-I	FORMULATION-II
Weight variation(%) ±5	400.7	400.2
Diameter**(mm)**	11.10	11.21
Thickness**(mm)**	4.59	4.35
Hardness**(kg/cm²)**	10.4	10.8
Friability**(%)**	0.40	0.32
Assay**(%)**	97.6	98.6

COMPARATIVE DISSOLUTION STUDY OF FORMULATIONS F-I and F-II WITH MARKETTED PRODUCT. (Table No.5)

S.NO	Time in Hrs	% Cumulative Drug release		
		MARKETTED PRODUCT	F-I	F-II
1	0	0	0	0
2	1	33.7	68.2	39.7
3	2	50.0	74.6	56.7
4	3	61.3	98.7	68.7
5	4	71.7	99.6	77.4
6	6	87.0	102.2	90.6
7	8	97.7	106.8	99.8
8	10	103.0	107.8	100.9

Fig:1 COMPARATIVE DISSOLUTION PROFILE OF F-I &F-II WITH MARKETTED PRODUCT



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