CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION OF BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLET DOSAGE FORM

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Article Received: November 2021 **Accepted:** November 2021 **Published:** December 2021

Abstract:

The objective of the present investigation is to design and evaluate extended-release dosage form of bupropion hydrochloride and compare with innovator product (Wellbutrin extended-release tablets). Extended-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 compressibility. Prepared Granules were evaluated for Angle of repose, bulk density, tapped density, compressibility index, Hausner ratio. The granules shown satisfactory flow properties and compressibility. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. . Formulation of Extended-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: *Extended-release Tablets, bupropion hydrochloride, Hydroxy propyl methyl cellulose, Microcrystalline Cellulose, dissolution.*

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Please cite this article in press T. Divya et al, ***Formulation Of Bupropion Hydrochloride Extended-Release Tablet Dosage Form.,*** *Indo Am. J. P. Sci, 2021; 08(12).*

INTRODUCTION:

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high drugs [1].

Extended-release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. The advantages of extended-release dosage forms over conventional forms include the less fluctuation in drug blood levels, frequency reduction in dosing, enhanced convenience and compliance, reduction in adverse side effects and reduction levels, reduce dose and side effects, and increase the safety margin for high-potency in overall health care costs [2]. The rate of drug release from solid dosage form may be modified by the technologies, which in general are based on modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings and controlling drug diffusion rates from dosage forms. Generally, the different techniques employed to fabricate the modified release dosage forms are coated beads, granules and microspheres, multi tablet system, micro encapsulated drug, complex formation, ion exchange resins, and embedding drug in slowly eroding or hydrophilic matrix system [3].

The use of polymeric matrix devices to control the release of a variety of therapeutic agents as become increasingly important in the development of modified release dosage forms. This device may be a swellable, hydrophilic monolithic systems, erosion controlled monolithic systems or non erodible systems. The hydrophilic gel forming matrix tablets are extensively used for oral extended-release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping [4].

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.

FORMULATION DEVELOPMENT:

DEVELOPMENTAL DESIGN OF BUPROPION HYDROCHLORIDE 150 MG TABLETS

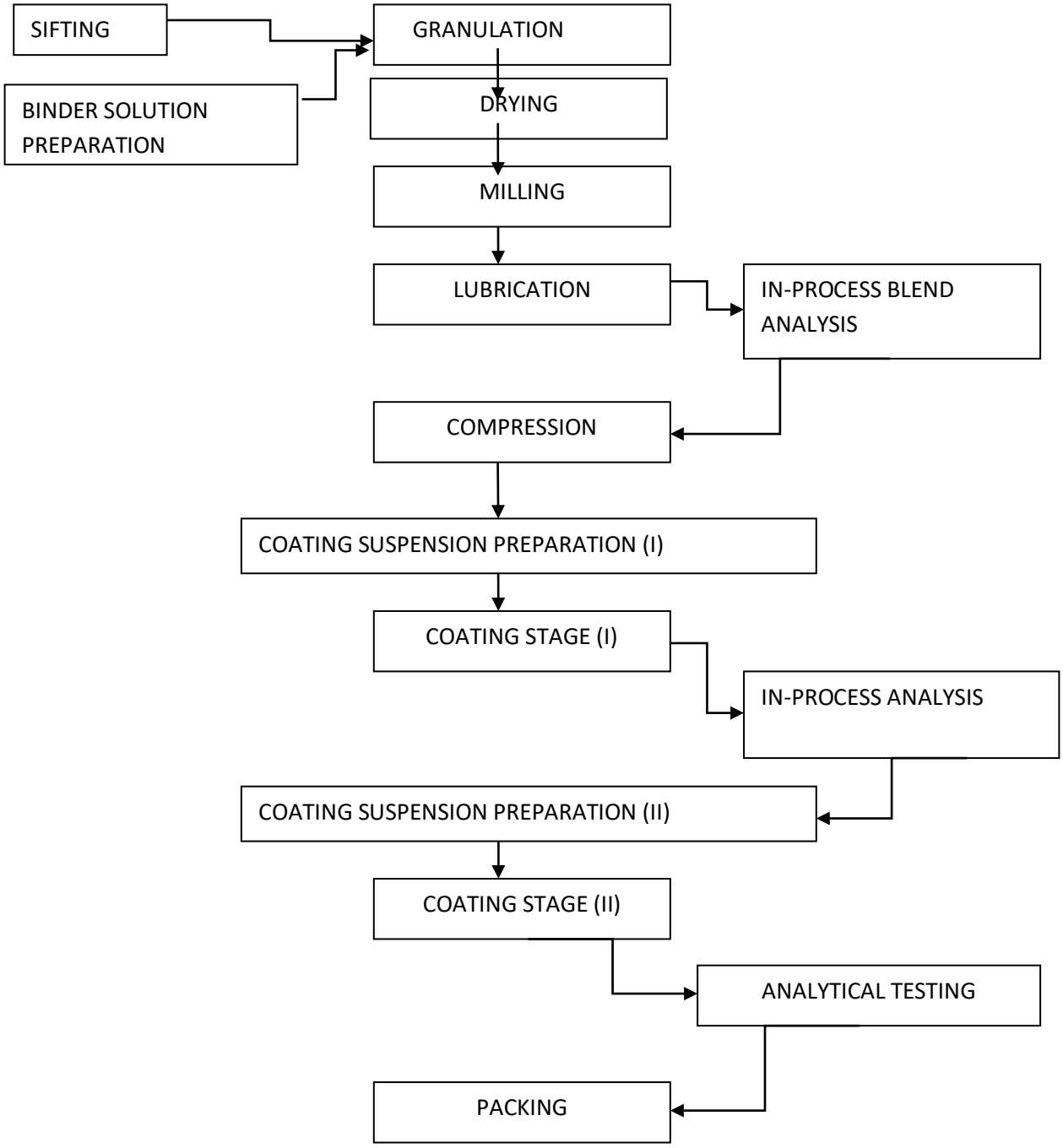


Table 1: TRIAL 1 - Composition of Core Tablet

INGREDIENTS	QUANTITIES (mg)
Bupropion Hydrochloride	150
Povidone 90F	7
Hydrochloric acid	0.4
Hydrogenated vegetable oil	5
Ethanol (96% v/v)	Q.S

Table 2: TRIAL 2 - Composition of Core Tablet

INGREDIENTS	QUANTITIES (mg)
Bupropion Hydrochloride	150
Povidone 90F	7
Hydrochloric acid	0.4
Sodium Stearyl Fumarate	5
Ethanol (96% v/v)	Q.S

EVALUATION OF GRANULES:

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. [4]

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 [5].

Compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index. Carr's index (%) = [(TBD-LBD) * 100] / TBD

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.

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% [6,7].

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%

In-vitro release studies:
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 [8,9].

Stability Study:
For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH guidelines [10].

RESULT AND DISCUSSION:

Table 3: Drug – Excipient Compatibility Stability Profile

S.No	ITEM	1 month / control	1 month / 60ºC
1.	API	No Change	No Change
2.	API + Hydrochloric acid	No Change	No Change
3.	API + Povidone	No Change	No Change
4.	API + Sodium stearyl fumarate	No Change	No Change
5.	API + Ethyl cellulose	No Change	No Change
6.	API + Hydroxy propyl cellulose	No Change	No Change
7.	API + Methacrylic acid copolymer	No Change	No Change
8.	API + Triethyl citrate	No Change	No Change
9.	API + Polyethylene glycol	No Change	No Change
10.	API + Silicon dioxide	No Change	No Change

There is no physical change observed in the admixture after one month at 60 ºC

Drug-Excipient Compatibility Studies:
The drug excipient compatibility studies were done by FT-IR method and the results are as follows:

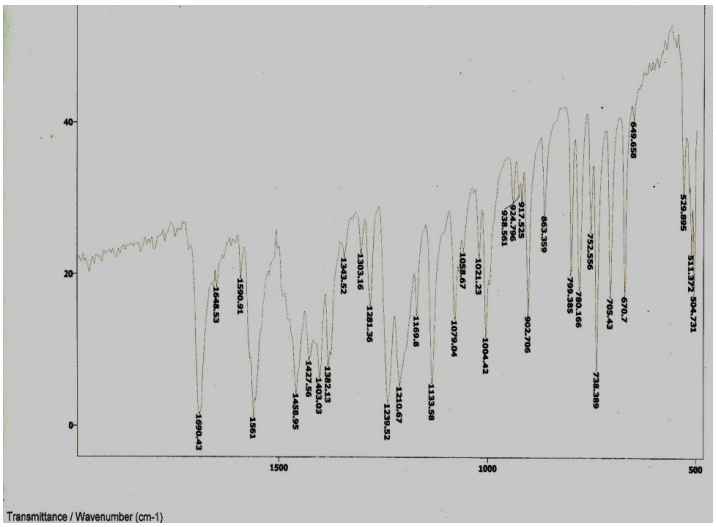


Fig 1: Bupropion Hydrochloride

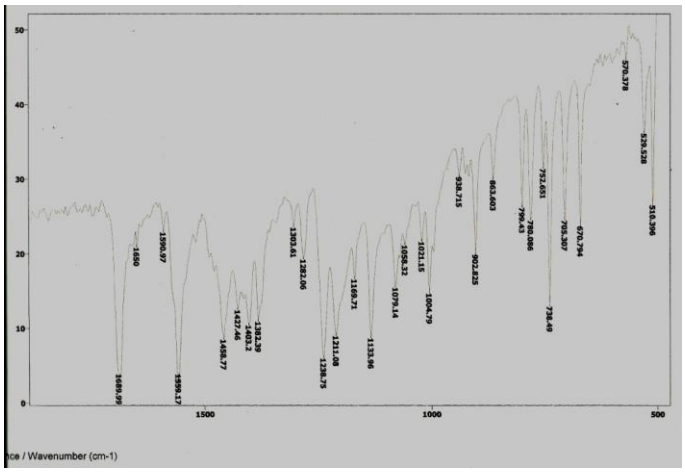


Fig 2: Bupropion Hydrochloride and Ethyl cellulose

CHARACTERIZATION OF BUPROPION HYDROCHLORIDE BLENDS:

Table 4: Pre-Compression Parameters:

Pre-Compression Parameters	Lubricant	
	Hydrogenated vegetable oil	Sodium stearyl fumarate
Bulk Density (g/cc)	0.475	0.492
Tapped Density (g/cc)	0.633	0.612
Compressibility Index (%)	25	19.60
Hausner's Ratio	1.33	1.24

NOTE: Picking of tablets was observed during compression of blend when hydrogenated vegetable oil was used. Thus, lubricant was replaced with Sodium stearyl fumarate.

Table 5: Post Compression Parameters:

Physical Parameters	Tablet no.									
	1	2	3	4	5	6	7	8	9	10
Weight Variation (mg)	158	162	162	172	160	158	165	158	160	160
Hardness (Kp)	7.5	7.8	8.2	7.5	7.5	7.9	8.1	8.4	8.2	8.1
Thickness (mm)	4.2	3.9	4.2	4.4	4.4	4.0	4.5	4.2	3.9	4.2
Friability (% w/w)	0.23	0.18	0.12	0.12	0.11	0.35	0.21	0.2	0.15	0.19

Table 6: Post coating parameters (FIRST STAGE OF COATING)

Test parameters	First stage coating formulations		
	F1 (5%)	F2 (5.5%)	F3 (6%)
Weight variation (mg)	168	172	176
Thickness (mm)	4.38	4.4	4.45
Hardness (Kp)	10.5	10.82	9.92

Table 7: Percentage drug release profile after 1st stage of coating:

Time (hrs)	% Drug release		
	F1 (5%)	F2 (5.5%)	F3 (6%)
1	40	26	20
2	74	56	45
3	94	78	66
4	99	92	80
5	100	98	87
6	101	100	89

Fig 3: Drug release profile after 1st stage of coating:

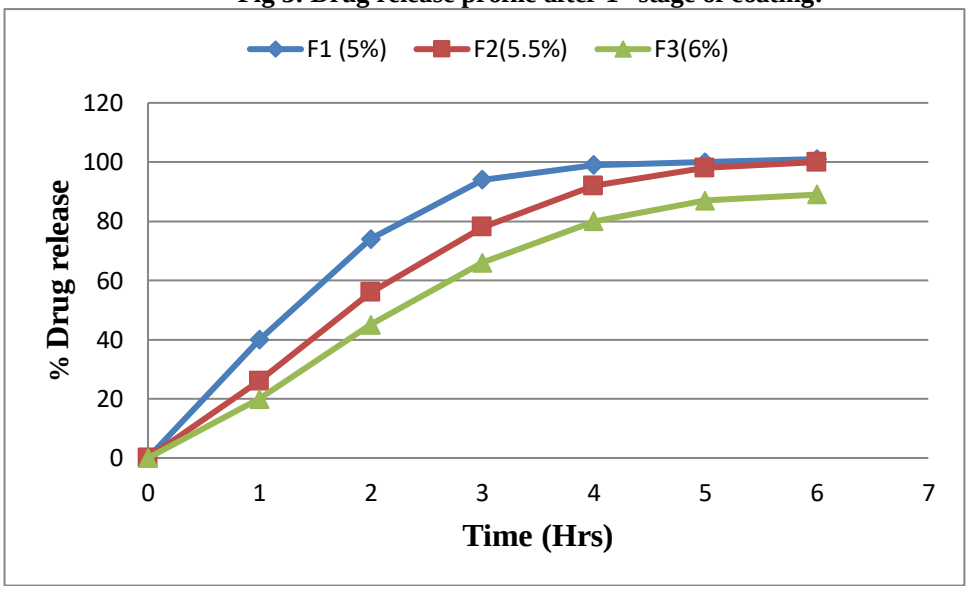


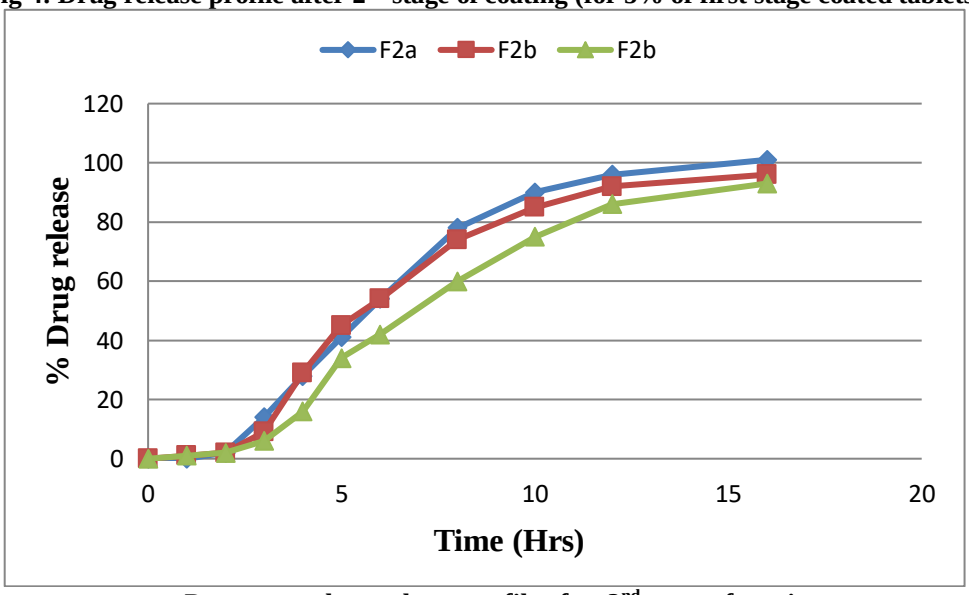
Table 8: Post coating parameters (SECOND STAGE OF COATING)

Second stage coating formulation	Weight variation (mg)	Thickness (mm)	Hardness (Kp)
F1a	178	4.7	12.8
F1b	176	4.8	11.6
F1c	180	4.6	11.3
F2a	179	4.72	12.3
F2b	182	4.63	12.8
F2c	180	4.73	12.6
F3a	187	4.69	12.8
F3b	179	4.82	13
F3c	184	4.8	12.9

Table 9: for 5% of first stage coated tablets:

Time (hrs)	% DRUG RELEASE		
	F1a (5% EC+ 6% Eudragit)	F1b (5% EC+ 7% Eudragit)	F1c (5% EC+ 8% Eudragit)
1	2	1	1
2	10	10	4
3	28	26	10
4	43	40	27
5	56	55	41
6	69	67	57
8	84	86	72
10	94	97	84
12	100	102	90
16	101	103	95

Fig 4: Drug release profile after 2nd stage of coating (for 5% of first stage coated tablets)

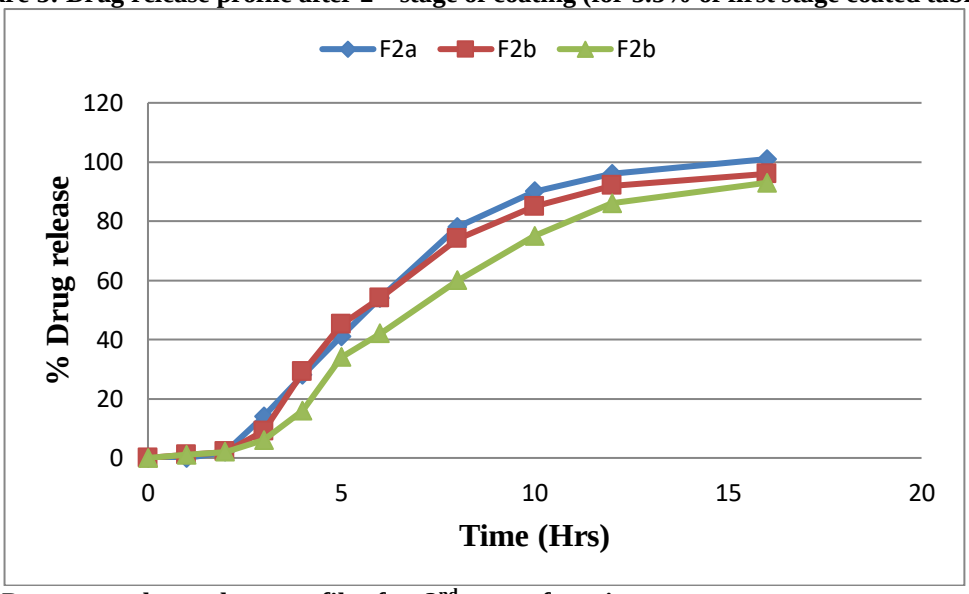


Percentage drug release profile after 2nd stage of coating:

Table 10: for 5.5 % of first stage coated tablets:

Time (hrs)	% DRUG RELEASE		
	F2a (5.5% EC+ 6% Eudragit)	F2b (5.5% EC+ 7% Eudragit)	F2c (5.5% EC+ 8% Eudragit)
1	0	1	1
2	2	2	2
3	14	9	6
4	28	29	16
5	41	45	34
6	54	54	42
8	78	74	60
10	90	85	75
12	96	92	86
16	101	96	93

Figure 5: Drug release profile after 2nd stage of coating (for 5.5% of first stage coated tablets)



Percentage drug release profile after 2nd stage of coating:

Table 11: for 6 % of first stage coated tablets:

Time (hrs)	% DRUG RELEASE		
	F3a (6% EC+ 6% Eudragit)	F3b (6% EC+ 7% Eudragit)	F3c (6% EC+ 8% Eudragit)
1	0	0	0
2	1	1	1
3	8	4	2
4	24	18	12
5	39	32	29
6	53	47	43
8	77	66	67
10	89	88	85
12	96	100	95
16	101	108	103

Fig 6: Drug release profile after 2nd stage of coating (for 6% of first stage coated tablets)

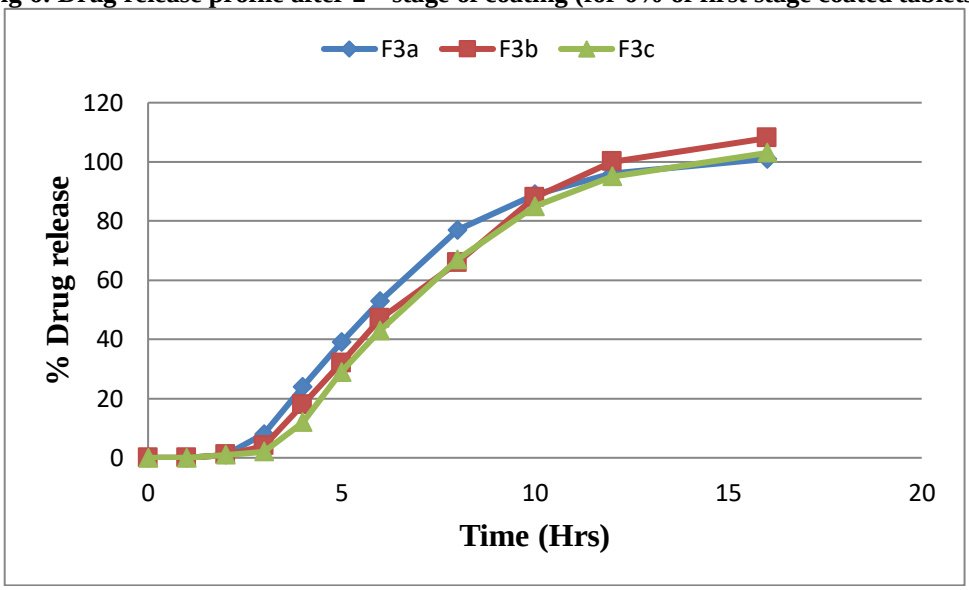


Table 12: Percent drug release of Innovator (WELLBUTRIN XL):

Time (hrs)	Wellbutrin 150mg (innovator)
1	0
2	3
3	15
4	32
5	45
6	60
8	82
10	92
12	94
16	98

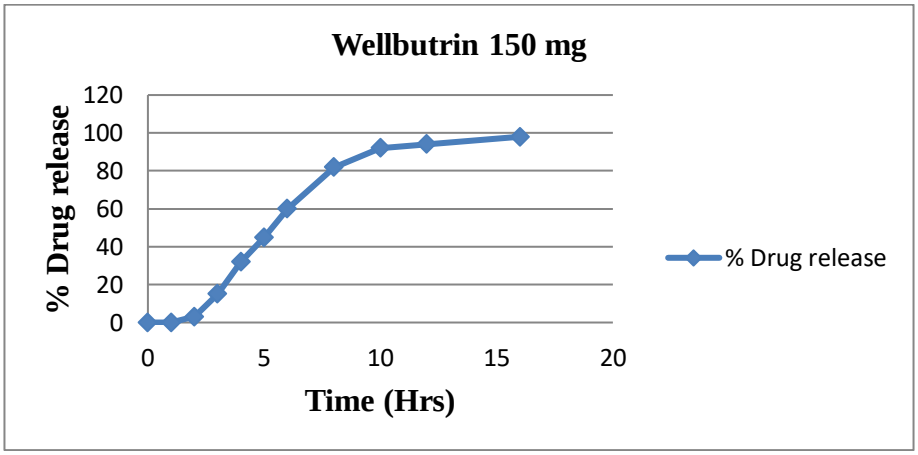


Fig 7: Innovator's drug release profile

Table 13: COMPARISON OF DISSOLUTION PROFILE OF INNOVATOR WITH FINALISED PROTOTYPE FORMULATION (F2b):

Time (hrs)	Wellbutrin (innovator)	F2b (5.5% EC and 7% Eudragit)
1	0	1
2	3	2
3	15	9
4	32	29
5	45	45
6	60	54
8	82	74
10	92	85
12	94	92
16	98	96

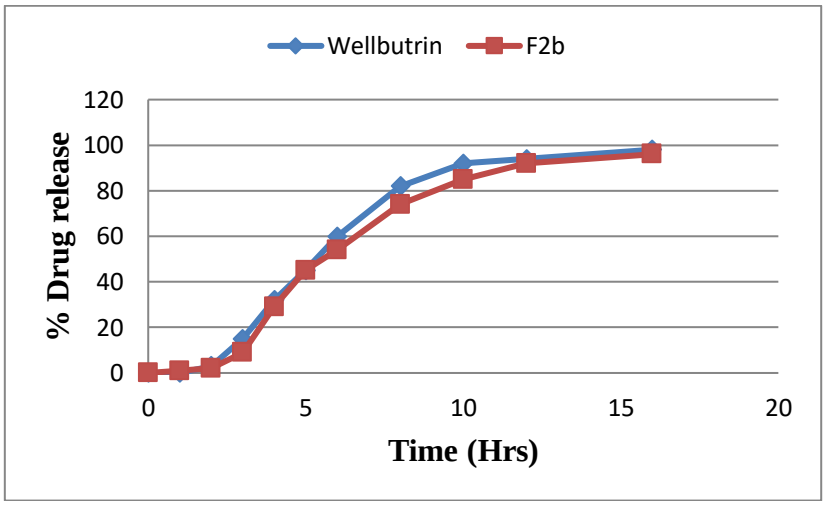


Fig 8: Comparison of drug release profile (Innovator and Test)

STABILITY DATA:

Table 14: Stability data of F2b (5.5% EC and 7% Eudragit):

RESULT→ TEST ↓	STABILITY SPECIFICATION	40 °C/75%RH				25 °C/60%RH
		INITIAL	30 DAYS	60 DAYS	90 DAYS	90 DAYS
Description	Off to off white, plain on both sides	Complies	Complies	Complies	Complies	Complies
% Drug release	NLT 80 % at the end of 16 hrs	96.07	96.08	96.01	96.00	96.01
Assay % w/w	NLT 90.0% and NMT 110.0% of the labeled amount	100.6	100.1	99.96	99.84	99.92

CONCLUSION:

Bupropion hydrochloride is an anti-depressant which is used to treat major depressive disorder and an aid to smoking cessation. In this study enteric coated tablets were prepared by using a hydrophobic polymer (ethyl cellulose) and a hydrophilic polymer (methacrylic acid copolymer). Various formulations were developed by preparing core tablets and varying the compositions of sub-coating (ethyl cellulose and hydroxyl propyl cellulose) and enteric coating (methacrylic acid copolymer). The core tablets were prepared by wet granulation method which were then divided into three portions for coating with different percentage of polymer. These three portions of sub-coat were again sub-divided into three portions each so as to give different percentage of enteric coating. Various quality control tests were performed. Of all the trials F2b (5.5 % ethyl cellulose and 7 % methacrylic acid copolymer) showed drug release similar to innovator's Wellbutrin XL. Stability study is carried out for 3 months at 25 ^{0}C / 60 % RH and 40 ^{0}C / 75 % RH according to ICH guidelines. The optimized formula shall be utilized for formulation development and other studies for successful launch of product.

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