IJPSR (2017), Vol. 8, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 August, 2016; received in revised form, 13 October, 2016; accepted, 19 October, 2016; published 01 March, 2017

FORMULATION AND OPTIMIZATION OF BUPROPION HCl MICROSPONGES BY 2^3 FACTORIAL DESIGN

P. Muralidhar *, E. Bhargav and B. Srinath

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli cross, Anantapuramu - 515721, Andhra Pradesh, India.

Keywords:

Microsponges, Quasi-Emulsion Solvent Diffusion Method, Ethyl Cellulose, Polyvinyl Alcohol, Dichloromethane.

Correspondence to Author:
P. Muralidhar

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, K.R. Palli cross, Anantapuramu-515721, Andhra Pradesh, India.

Email: muralip2016riper@gmail.com

ABSTRACT: The rationale of the present study was to formulate & optimize the floating Bupropion HCl microsponges by 2^3 factorial design. The concentration of ethyl cellulose (EC), polyvinyl alcohol (PVA) and Dichloromethane (DCM) were selected as independent variables. Floating lag time & % drug release were selected as independent variables. Factors, their levels (with values) were substituted in the design of experiment software (Sigma tech version 3.1). The effect of factors at different levels on response variable was predicted using poly nominal equations. FTIR studies revealed that no chemical interaction between drug & polymer used. DSC confirmed molecular dispersion of drug in the microsponges polymer matrix. Quasi emulsion solvent diffusion method was used to formulate microsponges. Bupropion HCl showed acceptable flow. The morphology of microsponges was studied using SEM and it was found that microsponges were spherical and porous. USP Type II dissolution apparatus with cellophane membrane was used to study *in vitro* drug release. Kinetic studies revealed that drug release from optimized formulation followed Higuchi's model and diffusion is the controlled release mechanism. From Polynomial equations it was found that increase in concentration of PVA decreased floating lag time and % drug release. Optimized formulation studies showed satisfactory *in vitro* drug release for more than 16 h with less than 1 min floating lag time. Based on simulation (by DoE software) most economical batch (optimized) decided which were in desired range. The results demonstrated the effectiveness of proposed design for development of Bupropion HCl microsponges for the treatment of psychosis.

INTRODUCTION: The oral route is promising route of drug delivery. Most of the drugs are given by oral route. Enhanced bioavailability and targeting, sustained drug delivery/reduced frequency of dosing, targeted therapy for local ailments in the upper GIT,

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(3).1134-44

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (3).1134-44

Reduced fluctuations of drug concentration, improved selectivity in receptor activation, reduced counter-activity of the body, extended time over critical (effective) concentration are the advantages of gastro retentive drug delivery systems (GRDDS) that have a bulk density lower than gastric fluids and thus remain buoyant in the stomach, for a prolonged period of time, without affecting the gastric emptying rate.

A Microsponge Delivery System (MDS) is potent, highly cross-linked, porous, polymeric microspheres that can entrap wide range of actives

and then release them over a time and in response to trigger. Bupropion HCl is the most commonly prescribed antidepressant by physicians for treatment of Psychosis. Bupropion HCl, (±)-1-(3-chlorophenyl)-2-[(1,1 dimethylethyl) amino]-1-propanone hydrochloride an antipsychotic drug, was selected as a model drug for this study. Selected Bupropion HCl belongs to BCS Class I drug i.e. high solubility and high permeability. To maintain the drug in plasma it has to be administered thrice a day which results in severe side effects especially in case of slow acetylators. These side effects are highly dose-dependent; if frequency of dose administration is reduced side effects can be minimized hence the Bupropion HCl is proved to be a suitable candidate for controlled release dosage forms. Factorial designs are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated. These are the design of choice for simultaneous determination of the effect of several factors and their interaction. If there are three factors, each at two levels, eight experiments are necessary which are situated at the corners of an orthogonal cube in a 3-dimensional space [1-3].

MATERIALS AND METHODS:

Materials: Bupropion hydrochloride obtained as a gift sample from Aurobindo Laboratory, Hyderabad. Ethyl cellulose, polyvinyl alcohol, dichoromethane, Glycerol were purchased from SD fine chemicals, Mumbai.

Methods:

Preformulation studies:

FT-IR Studies: [2] The physical mixture of pure drug sample, other polymers were taken in the ratio 1:1 and were subjected to IR spectral studies using FTIR spectrophotometer (FT IR Spectrometer Bruker ALPHA).

Differential scanning calorimetry: [4-5] The DSC measurements were carried out on a Mettler Toledo DSC – 822e model. The accurately weighed sample was placed in an aluminium pan. An empty aluminium pan was used as reference. The experiment was carried out in a nitrogen atmosphere at a scanning rate of 10ºC / min in the range of 30 - 220ºC.

API characterization: [6-9]

Organoleptic properties: Organoleptic properties such as description, color, Odour, taste of the drug were studied.

Determination of Melting point: The melting point of the drug was determined using capillary tube. One end of the capillary tube was sealed. The sample was filled and placed in the melting point apparatus. The melting point of the drug was noted and the obtained value was compared with the literature value.

Solubility analysis: The solubility of API was determined by dissolving the highest unit dose of the drug in 250 mL of buffer adjusted between pH 1.0 and 8.0.For this purpose 0.1N HCl, pH 4.6 buffer, pH 6.8 buffer and purified water were used . Highest dose of the drug i.e., 400mg was dissolved in 250 mL of medium and was kept untouched for 6 h. Later on the insoluble drug was filtered off and the solution was analyzed by UV Spectroscopic technique.

Analytical method -Standard Calibration curve by Ultraviolet Visible Spectroscopy: [10] An accurately weighed amount of 100 mg drug was transferred into 100 ml volumetric flask and then the volume was made up to the mark with 0.1N HCl. From the stock solution 0.6, 0.8, 1.0, 1.2, 1.4, and 1.6 ml of sample was taken diluted up to 100 ml using 0.1N HCl in a 100 ml volumetric flask resulting in concentrations of 6, 8, 10, 12, 14, 16µg/ml solutions. These were analyzed at 252 nm and calibration curve was plotted taking concentration in µg/ml on X-axis and absorbance units on Y-axis.

Flow properties: [9, 11]

Angle of repose: A funnel was kept vertically in stand at a specified height above a paper placed on the horizontal surface. The bottom was closed and the weighed quantity of API was filled in funnel. The funnel was opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured using the scale [11]. A border heap was marked circularly and its diameter was measured at four points. The average diameter was calculated and radius was found out from it. Angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h= height of the powder heap, r= radius of the powder heap, θ=the angle of repose

Determination of bulk and tapped density:

Bulk Density: A sample powder of API was introduced in 50 ml graduated cylinder. The volume of material was noted on graduated cylinder. The bulk density was calculated by the formula given below:

$$Db = M/Vb$$

Where, M is the mass of powder. Vb is the bulk volume of the powder.

Tapped Density: It was measured by tapping the powder by many times (approximately 750-1000) and tapped volume was noted. From this tapped density calculated according to the formula mentioned below:

$$DT = M/VT$$

Where, DT=Tapped density, M=Weight of powder in grams, VT=Tapped volume of powder.

Hausner's Ratio: It is calculated by the formula as follows:

$$HR = \text{Tapped density} / \text{Bulk density}$$

Carr's index: Carr's index was calculated as follows:

$$CI = DT-DB/DT \times 100$$

Where, DT is Tapped density of powder, DB is the Bulk density of the powder.

Optimization by 2^3 factorial design: In present investigation 2^3 factorial design with 4 replicates were selected for the design of experimentation of microsponges. The amount of ethyl cellulose, polyvinyl alcohol, dichloro methane were selected as independent variables, floating lag time and % drug release were selected as dependent variables. (**Table 1**)

TABLE 1: EXPERIMENTAL DESIGN OF TABLETS AS PER 2^3 FACTORIAL LEVEL

S.no	Code	Name of variable	Unit	-1 (Low level)	0 (Mid-Point)	1 (High level)
1	X1	Ethyl cellulose	gm	3.25	5.5	7.75
2	X2	Polyvinyl alcohol	%	4	5	6
3	X3	Dichloro methane	ml	0.625	0.75	0.875

Formulation of Bupropion Hydrochloride Microsponges by Quasi-Emulsion Solvent Diffusion Method: [12] The internal phase of drug-polymer solution prepared in a volatile solvent dichloromethane and then it was added to external phase comprising of aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Glycerol (1 ml) was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called Quasi-Emulsion globules. The stirring was continued up to 6 h till the insoluble, rigid microparticles i.e. microsponges were formed. Then it was filtered to separate the microsponges. The microsponges were then dried in an hot air oven.

TABLE 2: FORMULATION DESIGN OF BUPROPION HCL MICROSPONGES

Formulation	Combination	Drug (mg)	Ethyl cellulose (gm)	Polyvinyl alcohol (%)	Dichloro methane (ml)	Glycerol (ml)	Water (ml)
F1	1	150	3.25	4	0.625	1	100
F2	X1	150	7.75	4	0.625	1	100
F3	X2	150	3.25	6	0.625	1	100
F4	X1X2	150	7.75	6	0.625	1	100
F5	X3	150	3.25	4	0.875	1	100
F6	X1X3	150	7.75	4	0.875	1	100
F7	X2X3	150	3.25	6	0.875	1	100
F8	X1X2X3	150	7.75	6	0.875	1	100
F9	Mid-point	150	5.5	5.0	0.75	1	100
Optimized formulation (F10)		150	5.5	6	0.625	1	100

Evaluation of Microsponges: [2, 5, 8]

Morphology: For assessing morphology and surface topography, prepared microsponges were examined under scanning electron microscope (LEO 440i, UK) operated at 30 kV. By means of double adhesive tape, samples were mounted on a metal stub coated with platinum/palladium alloy under vacuum.

Particle size: Particle size analysis of prepared microsponges was carried out by dispersing in double distilled water before analyzing under optical microscopy. By counting 225 particles and particle size analyzed by using below formula

$$\sum f\, m/\sum f$$

Where, f is number of particles in each size, m is mean particle size

Loading efficiency: The loading efficiency (%) of the microsponges can be calculated using following equation Loading efficiency= (Actual drug in microsponges/Theoretical drug concentration)*100

Production yield: The product yield of microsponges can be calculated by the following formula

Product yield= (Practical mass/Theoretical mass)*100

Floating lag time: The test was performed by placing 150mg equivalent of microsponges in 250 ml beaker containing 0.1N HCl, maintained at pH 1.2 and temperature 37±0.5^{0}C in water bath. The time between introduction of dosage form and its bouncy is floating lag time.

Dissolution study: Dissolution study performed in USP-II dissolution apparatus with 0.1N HCl at pH 1.2 by maintaining temperature 37°C ± 0.2°C with 75 RPM. Sample was included in sigma membrane[8]. At 2, 4, 8, 16 h intervals samples were collected and replaced with fresh media. Collected samples were analyzed by UV Spectrophotometrically.

Comparison of estimated results with predicted values: The estimated value is compared with practical value by selecting one experiment among varies experiments. Standard error calculated using formula

Standard error of mean=s/SQRT n

Where, s=sample standard deviation, n=size of sample

RESULTS:

Drug- Excipient compatibility studies:

FTIR studies:

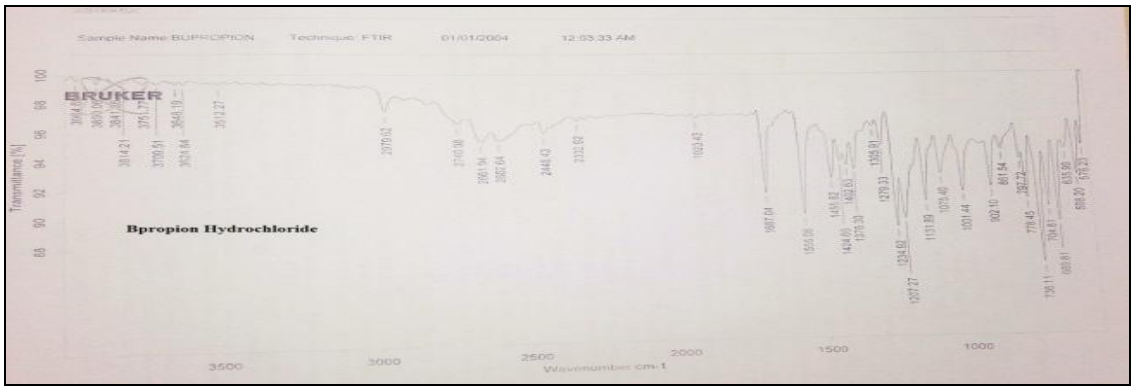

FIG. 1: FT-IR SPECTRUM OF BUPROPION HCL

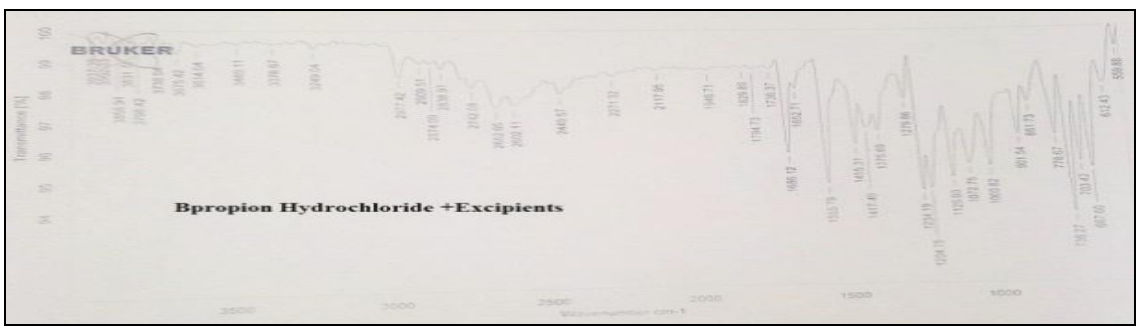

FIG. 2: FT-IR SPECTRUM OF DRUG WITH EXCIPIENTS

DSC studies:

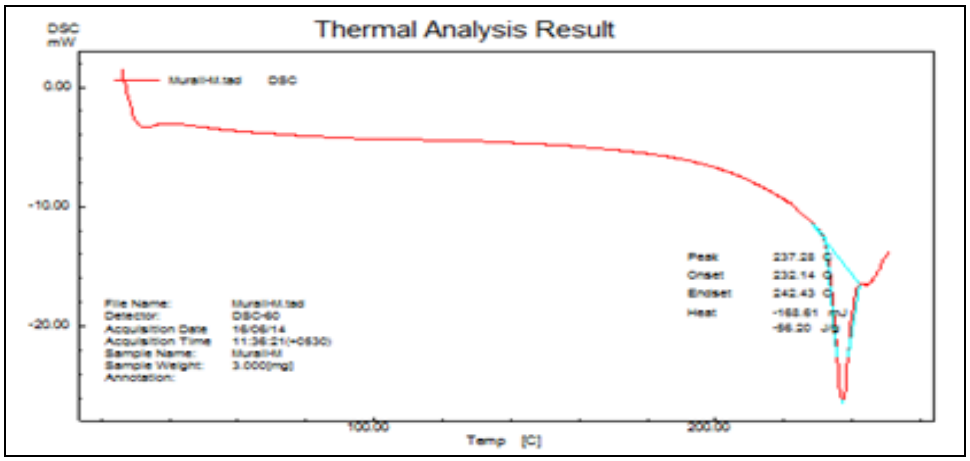

FIG.3: DSC THERMOGRAM OF DRUG

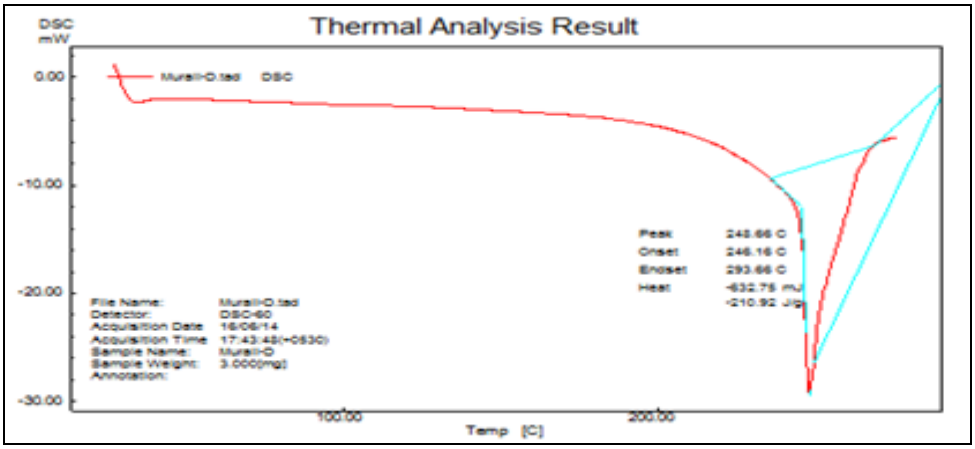

FIG.4: DSC THERMOGRAM OF DRUG-EXCIPIENTS

API Characterization:

TABLE 3: SOLUBILITY PROPERTIES OF DRUG

S. No.	Medium	Approximate pH	Solubility (mg/ml)	Dose/solubility Ratio
1	0.1N HCl	1.2	310.36	0.966
2	pH 4.5 Acetate Buffer	4.5	1197.58	0.250
3	pH 6.8 Phosphate Buffer	6.8	273.78	1.095
4	pH 7.4 Phosphate Buffer	7.4	364.56	0.822
5	Purified water	6.02	272.97	1.099

Calibration curve of Bupropion HCl:

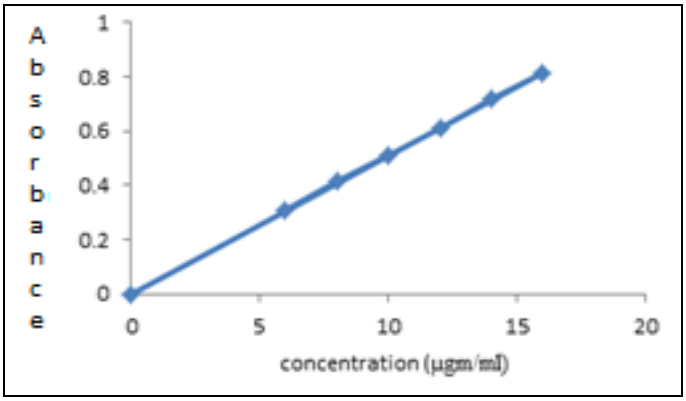

FIG. 5: STANDARD PLOT OF DRUG IN 0.1N HCL

TABLE 4: FLOW PROPERTIES OF DRUG

S.No.	Characteristics	Results
1.	Physical appearance	A white powder
2.	Bulk density(gm/ml)	0.403 ± 0.12
3.	Tap density(gm/ml)	0.675 ± 0.26
4.	Compressibility index (%)	40.296 % ± 0.15
5.	Hausner's ratio	1.6749 ± 0.20
6.	Angle of repose	35^0 ± 0.19

*All values are mean ± SD, n=3

Evaluation of Microsponges:

Morphology:

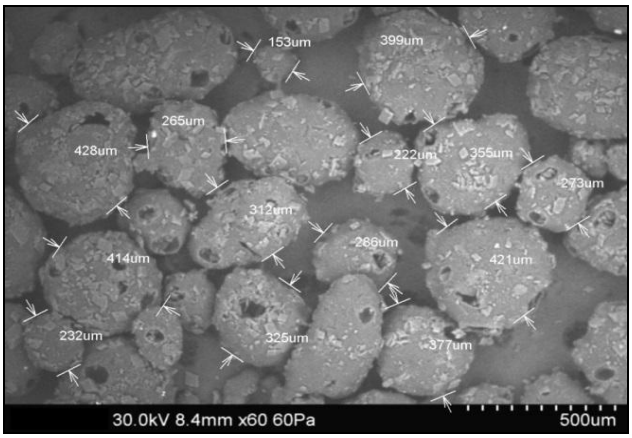

FIG.6: SEM PICTURE OF MICROSPONGES

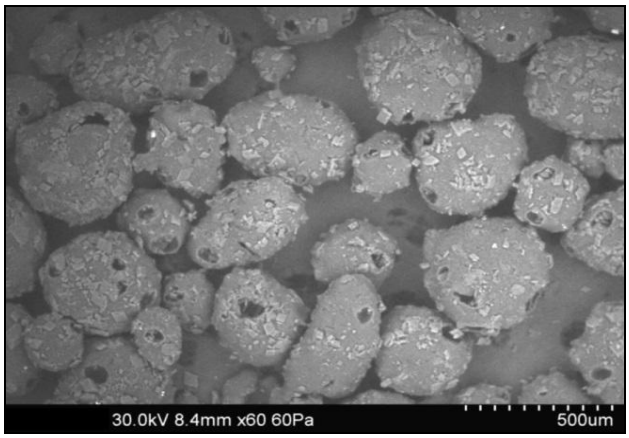

FIG.7: SEM PICTURE OF MICROSPONGES

Particle size:

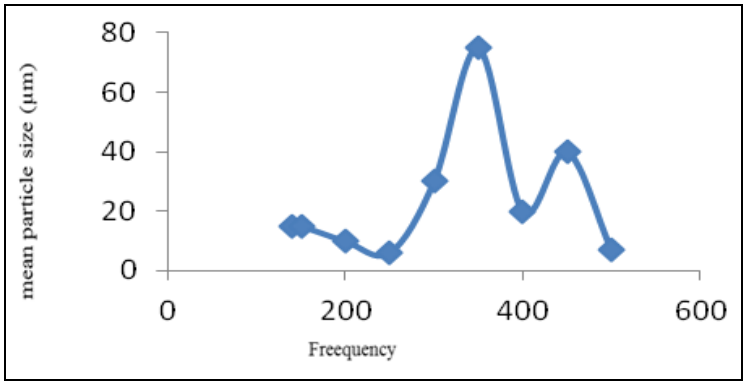

FIG. 8: PARTICLE SIZE DETERMINATION PLOT

TABLE 5: RESULTS OF LOADING EFFICIENCY, PRODUCT YIELD, AND FLOATING LAG TIME

Formulation	Loading Efficiency* (%)	Product Yield* (%)	Floating lag Time*(sec)
F1	71.5	84.7	45
F2	70.2	81.2	42
F3	73.6	80.4	39
F4	74.4	86.3	41
F5	69.3	79.5	42
F6	70.9	82.3	48
F7	68.7	78.6	39
F8	72.6	82.8	42
F9	71.8	85.4	45
Optimized formulation (F10)	73.4	83.6	40

*All values are mean ± SD, n=3

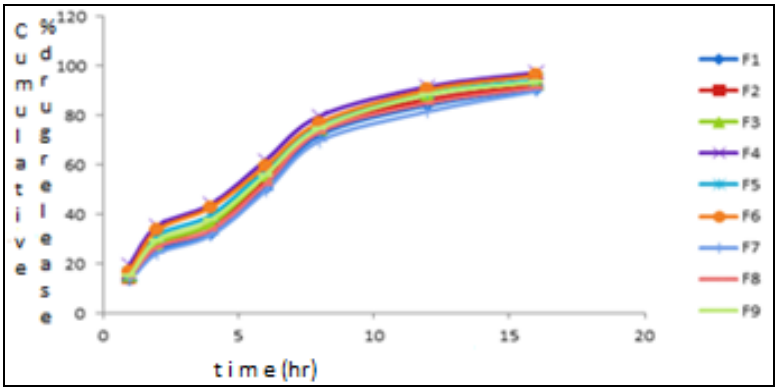

FIG.9: % DRUG RELEASE FROM FORMULATIONS F1- F9

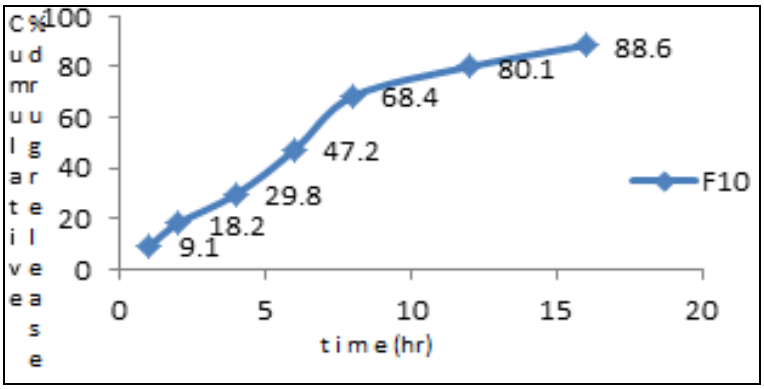

FIG.10: %DRUG RELEASE FROM OPTIMISED FORMULATION F10

TABLE 6: KINETIC ANALYSIS OF *IN VITRO* DRUG RELEASE DATA

Formulation code	R^2				n value
	Zero order	First order	Hixoncrowell	Higuchi	
F1	0.9275	0.9834	0.9389	0.9645	0.3068
F2	0.9191	0.9846	0.9438	0.9677	0.3215
F3	0.92	0.9857	0.9425	0.9685	0.2903
F4	0.914	0.9824	0.9532	0.9725	0.2554
F5	0.9175	0.9871	0.9422	0.9729	0.3295
F6	0.9188	0.9873	0.9327	0.9761	0.3080
F7	0.9369	0.9871	0.9329	0.9721	0.2919
F8	0.924	0.9842	0.9428	0.9661	0.2821
F9	0.9202	0.9869	0.9423	0.9718	0.3175
F10	0.9342	**0.9976**	0.9293	**0.9748**	0.3985

Evaluation of critical formulation variables on Response variables:

Floating lag time (Y1): $422.5 + 1.0\ X_1 - 2.0\ X_2 + 0.25\ X_3 + 0.5X_1X_2 + 1.25\ X_1X_3 - 0.25\ X_2X_3 - 0.25X_1X2X3$ (1)

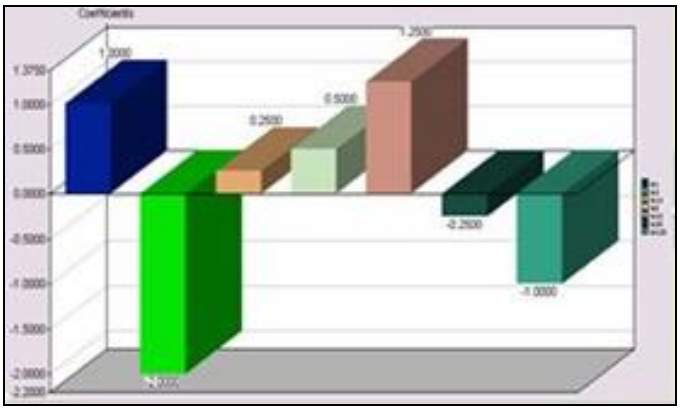

FIG. 11: BAR GRAPH SHOWING CONTRIBUTION OF FACTORS TO Y1

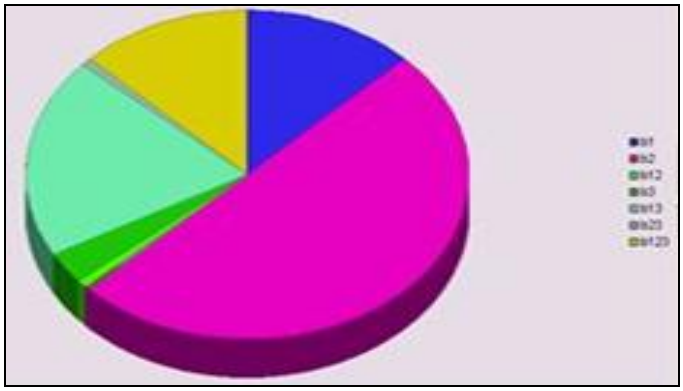

FIG.12: PIE DIAGRAM CONTRIBUTION OF FACTOR WITH RESPECT TO Y1

TABLE 7: ANOVA RESULTS FOR FORMULATION VARIABLES OF BUPROPION HCL MICROSPONGES (Y1)

SNO	Src of Vari	SS	DF	MS	F-valu	Fstd at0.1p	Fstd at0.05p	Fstd at0.01p
1	Model	55.5	6	9.25	5.7813	3.4	4.95	10.7
2	error	8.0	5	1.6				
3	Total	63.5	11					

OK

Standard Deviation : 1.4142
Curvature Effect : 2.75
95% Confident Level Of Currvature Effect
F Standard value at 0.05 p : 10.1
F Standard value at 0.01 p : 34.1
FROM : -0.0049 TO : 5.5049
Linear

***In vitro* drug release: (Y2)**: $93.185 + 1.15X_1 - 0.185X_2 + 0.235\ X_3 - 0.28X_1X_2 - 0.26X_1X_3 - 2.11X_2X_3 - 0.385X_1X2X3$ (2)

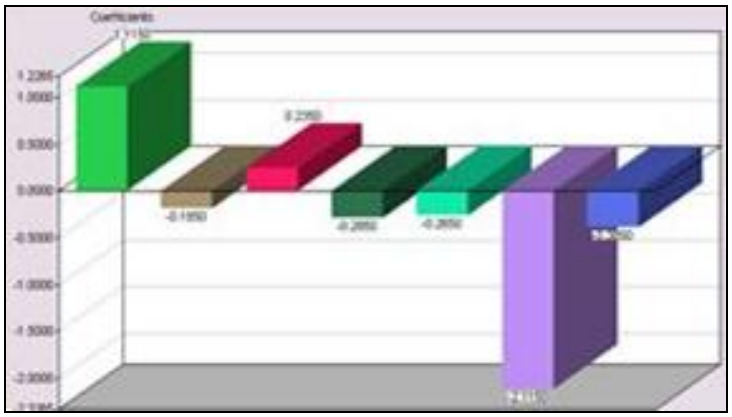

FIG.13: BAR GRAPH SHOWING CONTRIBUTION OF FACTORS TO Y2

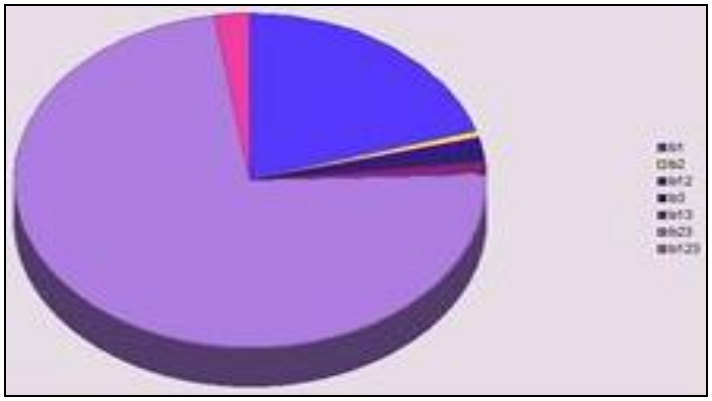

FIG.14: PIE DIAGRAM CONTRIBUTION OF FACTOR WITH RESPECT TO Y2

TABLE 8: ANOVA RESULTS FOR FORMULATION VARIABLES OF BUPROPION HCL (Y2)

SNO	Src of Vari	SS	DF	MS	F-valu	Fstd at0.1p	Fstd at0.05p	Fstd at0.01p
1	Model	47.6588	6	7.9431	33.4869	3.4	4.95	10.7
2	error	1.1858	5	0.2372				
3	Total	48.8446	11					

OK

Standard Deviation : 0.3512
F Standard value at 0.05 p : 10.1
Curvature Effect : 0.665
F Standard value at 0.01 p : 34.1
95% Confident Level Of Currvature Effect FROM : -0.0191 TO : 1.3491
Linear

Comparison of estimated results with practical values

TABLE 9: COMPARISON OF ESTIMATED AND PRACTICAL VALUES

S.no	X1	X2	X3	Estimated value of Y1 (sec)	Practical value of Y1 (sec)	Estimated value of Y2 (%)	Practical value of Y2 (%)
1	3.25	6	0.625	39	32	89.9	81.5
2	**5.5**	**6**	**0.625**	**40**	**43**	**90.95**	**88.6**
3	6.625	6	0.625	40	33	90.6	82.6

DISCUSSIONS: Critical Quality Attributes (CQAs) based on their strong correlation to Total Quality Product Profile (TQPP) were considered for Design of experimentation to ensure a predefined quality of the product. In order to define the "design space" the critical formulation variables (independent variables) and the dependent variables able to measure the product quality were defined based on prior knowledge and preliminary studies. The independent variables considered for Microsponges formulation were ethyl cellulose, Poly vinyl alcohol, dichloromethane since they were considered critical in determining responses Floating lag time & % drug release. Microsponges were prepared by Quasi emulsion solvent diffusion method. On comparison of FT-IR spectrums it was observed that there is no appearance of new peaks and shifting of already existed peaks (**Fig. 1** & **2**). The endothermic peak observed at 233ºC, this is attributed to the melting point of pure Bupropion HCl shown in **Fig 3**. In **Fig. 4** peak observed at 231ºC this indicates that there is no much difference in the melting point of the drug in the thermographs of drug and that of with excipients. It may be concluded that, the drug is compatible with the excipients.

By observing the organoleptic properties, the Bupropion HCl was found to be white powder, highly bitter, odorless and colorless. The melting point of the Bupropion HCl was determined by capillary tube method and it was found to be 233.5°C. Solubility of drug is shown in **Table 3**. From the above data it was observed that Bupropion HCl found to be soluble over the observed pH (1.2 to 7.4). Analytical method developed in 0.1N HCl of pH1.2 which is shown in **Fig 5.** The λ_{max} of Bupropion HCl was observed at 252 nm. Considering this λ_{max}, a calibration curve of Bupropion HCl was plotted. The standard graph constructed conferred that the concentrations of drug ranging from 6 to 16µg/ml obeyed the beer lambert principle.

Moreover, the calibration curve of Bupropion HCl exhibited a good correlation between the concentrations and the absorbance in this range (R^2 = 0.981). Flow properties like bulk density, tapped density, compressibility index, Hausners ratio and angle of repose are shown in **Table 4**. Based on the flow properties it was observed that the flow was acceptable. Morphology of microsponges determined by SEM and results were shown in **Fig. 6** and **7.** Scanning Electron Microscopic studies revealed that microsponges are spherical and porous. Particle size was determined by using optical microscopy and results were shown in **Fig. 8.** The Mean particle size of formulated microsponges was found to be 325µm for 225 particles. Results of loading efficiency, product yield and floating lag time for formulations F1-F10 is shown in **Table 5**. From the data loading efficiency ranges from 68.7% - 74.4% and product yield ranged from 78.6-85.4% and floating lag time

from 39-45 sec. *In vitro* drug release (**Fig 9** and **10**) and release kinetics for formulations F1-F9, optimised formulation (F10) shown in **Table 6.** F1 shows 90% of drug release at the end of 16th hour, whereas formulations F3-F9 shown 92.3, 93.4, 94.4, 94.2, 96.2, 89.9, 91.3 and 93.6% respectively. All formulations matched with the USP criteria of bupropion HCl oral controlled release formulation. R^2 values and n values for formulations F1-F9, optimised formulation (F10) shown in **Table 6**. All formulations shown high R^2 values for first order release (0.9834-0.9873) than zero order (0.9191-0.9369) hence drug release mechanism is first order i.e., concentration dependent. Higuchi kinetics showed highest of R^2 value (0.9654-0.9761) when compared to hixoncrowell (0.9327-0.9532) so drug release is controlled by diffusion mechanism. Drug diffusion follows ficks law of diffusion i.e. fickian diffusion because all the formulations shown n value less than 0.4 (**Table 6**).

From Polynomial equation (1) it was observed that floating lag time decreased with increase in concentration of PVA where as it is reverse in case of ethyl cellulose and DCM (**Fig 11** and **12**). The calculated F value and P value for response (Y1) indicates a significant effect of three factors. Since the obtained F ratio (10.7) is larger than critical value F (4.95) **Table 7**. From Polynomial equation (2) it was observed that % drug release increased with increase in concentration of ethyl cellulose where as it is reverse in case of PVA and DCM (**Fig 12** and **13**). The calculated F vale and P value for response (Y2) indicates a significant effect of three effects. Since the obtained F ratio (10.7) is larger than critical value F (4.95) **Table 8**. Based on simulation given by Sigma tech Software optimised formulation was selected. Standard Error for Y1 was 1.5 and Y2 showed 1.775, there is no much difference between estimated value and practical value (**Table 9**). Optimised formulation F10 followed first order release and Higuchi model. Ethylcellulose by osmotically driven release and diffusion through the polymer and/ or aqueous pores showed action, PVA prevented aggregation of Bupropion HCl in Microsponge formation and DCM as a solvent showed sustained release action.

CONCLUSION: The basic goal of the present work is to achieve a steady state blood drug concentration level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. One such area of research is design of targeted Floating drug delivery System. Bupropion HCl is one of the most important CNS stimulant agents used in the treatment of acute to chronic psychosis with a half-life of 8-16 h and requires multiple daily doses to maintain adequate plasma concentrations which results in severe side effects. More over the side effects are dose dependent. Hence Bupropion HCl can be regarded as a suitable candidate for controlled release dosage forms. Bupropion HCl floating microsponges were prepared by Quasi-Emulsion Solvent Diffusion Method with 2^3 factorial design by using ethylcellulose, PVA & Dichloromethane.

Among all the formulations (F10) optimized formulation showed 88.6% controlled drug release at the end of 16 hours and 40 sec of floating lag time. Hence it can be concluded that bupropion HCl floating microsponges formulated and optimized by 2^3 full factorial design is expected to provide clinician with a new choice of safe and more bioavailable formulation in management of psychosis. The present study has got future scope for the further pharmacokinetic and pharmacodynamic evaluation.

ACKNOWLEDGEMENT: The authors are thankful to Raghavendra Institute of Pharmaceutical education and Research, for providing opportunity to conduct the above research.

CONFLICT OF INTEREST: The authors report no conflict of interest.

REFERENCES:

1. Ujjwal Nautiyal, Meenakshi Jassal. A review: Gastroretentive drug delivery system. Ind J of Pharm and Biological Res 2015; 1:82-92.
2. Sonali, Rahul Pratap Singh, Sunil Kumar Prajapati. Formulation and Evaluation of Prednisolone loaded Microsponges for Colon Drug Delivery: *in-vitro* and Pharmacokinetic study. Int J Pharm Sci Res (IJPSR) 2014; 5(5): 1994-2005.
3. Sinai Kakodkar, Sharmada S. Pharmaceutical Quality-by-Design (QbD): Basic Principles. Int. J. Res. Methodol. 2015; 1: 1-19.
4. Ravi R. Microsponges drug delivery system: A review. Int J Pharm Sci Rev Res 2013; 3: 6-11.
5. Bargal JS, Dhawale SC, Landage SN, Kulkarni RV. Formulation and Evaluation of Eudragit RS 100 Loaded

microsponges of Flutrimazole. Int J Pharm Sci Res (IJPSR) 2013: 4(8): 3039-3045.
6. Yerram Chandramouli. Preparation and evaluation of microsponge loaded controlled release topical gel of acyclovir sodium. Int J Biopharm 2012; 3: 96-102.
7. Yerram Chandramouli. Microsponges: A novel drug delivery system for controlled delivery of topical drugs. Int J Pharm Res & Analysis 2013; 2: 79-86.
8. Rekha U. Formulation and evaluation of microsponges for topical drug delivery of mometasone furoate. Int J Pharm Pharm Sci 2011; 3: 133-137.
9. Lachman L, Liberman HA and Kanig JL. The Theory and practice of industrial Pharmacy. Fourth Edition. Mumbai: Varghese Publishing house; 2013: 171-194, 293-342, 346-360.
10. Hitesh V. Chavda Microsponge as Novel Topical Drug Delivery System. Journal of Global Pharma Technology 2010; 9: 19-29.
11. Jaiswal. S.B, Brahmakar D.M. Biopharmaceutics and pharmaceutics: A treatise Vallabh Prakashan. Second Edition. Delhi: 2011: 335-371.
12. Nawal A, Mohammad S Jawad. Formulation and *in vitro* evaluation of Piroxicam Microsponge as a tablet. Int J Pharm Pharm Sci 2016; 8(2): 104-114.

How to cite this article:
Muralidhar P, Bhargav E and Srinath B: Formulation and optimization of bupropion HCl microsponges by 2^3 factorial design. Int J Pharm Sci Res 2017; 8(3): 1134-44.doi: 10.13040/IJPSR.0975-8232.8(3).1134-44.