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DEVELOPMENT AND EVALUATION OF MICROSPONGE-BASED CAPSULE CONTAINING LURASIDONE HCl BY BOX-BEHNKEN DESIGN

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ABASTRACT

The present study was aimed at formulating and evaluating a microsponge-based capsule containing Lurasidone HCl using a Box-Behnken Design (BBD) to enhance drug solubility, improve bioavailability, and ensure sustained drug release. Microsponges were prepared using the quasi-emulsion solvent diffusion method with ethyl cellulose and PEG 4000 as polymer and plasticizer, respectively. The optimization of microsponges was done by Box Behnken Design. The independent variables were drug-to-polymer ratio, plasticizer concentration, and stirring speed. The optimized batch showed improved drug entrapment, controlled release, and physical stability over time.

KEYWORDS: Lurasidone HCl, Microsponge, Capsule, Box-Behnken Design, Quasi-emulsion, Entrapment Efficiency, Schizophrenia.

INTRODUCTION

Schizophrenia is a chronic, severe mental disorder requiring long-term pharmacological treatment. Lurasidone HCl, an atypical antipsychotic, suffers from poor solubility and low oral bioavailability (9–19%). Microsponges—porous, polymer-based microspheres—offer benefits like enhanced solubility, stability, and controlled release. Capsule dosage forms provide an efficient vehicle for delivering these microsponges.

Box-Behnken Design (BBD), a statistical optimization technique, is ideal for pharmaceutical formulation development. It allows efficient screening of formulation parameters and their interactions with minimal experimental runs.

MATERIALS AND METHODS

Lurasidone HCl is provided as a gift sample ALMON Healthcare Pvt. Ltd. and exepients were Ethyl Cellulose, PEG 4000, PVA and Dichloromethane was provided by oxford lab fine chem LLP.

For Preformulation study, identification of drug- polymer compatibility by FTIR Fourier transform Infra-red (FT-IR) is the tool for solid state characterization of pharmaceutical solids. The identification of the drug was done by (FT-IR) spectroscopic method using Alpha Bruker FTIR spectrophotometer. The drug was mixed with suitable amount of KBr and converted into pellets using KBr press at 20 psi for 10 min. The disc thus prepared was placed in a sample compartment and scanned at transmission mode in the region of 4000 to 400 cm-1. The IR spectrum of the drug and drug with ethyl cellulose, polyvinyl alcohol, PVA thus obtained was compared with standard spectra of the drug.

Quasi-emulsion solvent diffusion method was employed. The drug-polymer mixture was dissolved in dichloromethane (internal phase), sonicated, and added to an aqueous PVA solution under continuous stirring. Formed microsponges were filtered and dried at 40°C.

Three variables (X1 = drug: polymer ratio, X2 = plasticizer concentration, X3 = stirring speed) were studied at three levels. Design Expert software generated 17 experimental runs.

Evaluation parameters of the prepared microsponges, organoleptic properties like color, odor, and taste.

PRODUCTION YIELD

Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of microsponges. Percentage yield can be calculated by using the formula:

$$Production\ Yield = Practical\ Yield\ /\ Theoritical$$

$$Yield\ x\ 100$$

DRUG CONTENT

To estimate the drug content in microsponges, 10 mg equivalent microsponges are precisely weighed and mixed in 10 millilitres of phosphate buffer solution (PBS) (pH 6.8). The mixture should be filtered through a 0.45-µm membrane filter and the samples are to be analysed at a suitable wavelength using ultraviolet–visible (UV) spectrophotometer. The drug content can be calculated using the following formula.

$$Drug\ Content\ (\%) = Amount\ of\ Drug\ /\ Total\ Weight\ of\ Microsponge \times 100$$

ENTRAPMENTEFFICIENCY

The solvent extraction method can be used to assess the drug entrapment efficiency. 10 mg of precisely weighed microsponge particles isdissolved in 5 mL of methanol using a magnetic stirrer for duration of 20 min. 20 mL of freshly prepared phosphate buffer solution (PBS) must be added and heated to a temperature range of 45–50 °C till the formation of a clear solution. Later, methanol is allowed to evaporate, cooled to 25 °C and filtered. Following appropriate dilutions, the drug's concentration is measured using UV spectroscopy. To compute drug encapsulation efficiency (DEE %), the following formula can be used. Entrapment Efficiency in microsponges.

$$DDE\% = Actual\ Drug\ Content\ of\ Microsponge\ /\ Theoretical\ Drug\ Content\ of\ Microsponge \times 100$$

PARTICLE SIZE ANALYSIS

Determination of the average particle size of Lurasidone HCl loaded microsponges was determined with an optical microscope using a calibrated ocular and stage micrometer. A minute quantity of microsponges was spread on a clean glass slide with a drop of liquid paraffin and a cover slip is placed on it. The average particle size was calculated by measuring 100 particles of each batch.

$$dav = \sum nd / \sum n$$

Where, dav is the average diameter of particles (µm), n is number of particles per group, and d is the middle value (µm).

SURFACE MORPHOLOGY

Scanning Electron Microscopy of optimized microsponge formulation was carried to determine the surface morphology. The sample was mounted directly onto the SEM sample holder using double sided sticking tape and images were recorded at different magnifications at acceleration voltage of 10 kV using scanning electron microscope.

In-vitro DRUG RELEASE STUDY

In-vitro release rate studies of microsponges were carried out by filling equivalent amount of microsponge in capsules placed in the basket containing phosphate buffer pH 6.8 was used as medium and rotated at 50 rpm. Samples was withdrawn and determined by spectrophotometrically at 315 nm.

Total 6 preliminary trial batches were prepared to select drug to polymer ratio and plasticizer and 3 preliminary trial batches for selection of stirring speed. Selection of Batch for Formulation and Optimization includes following tests for trial batches (T1-T6). Batch T1-T6 were checked with Practical Yield and Entrapment Efficiency and then the selected batch T2 was checked on three different speed to determine particle size.

Based on the results of the trial batches, a statistical design was applied to optimize the final formulation. It was observed that the Drug to Polymer ratio, Concentration of Plasticizer and Stirring Speed significantly influenced the physicochemical properties of the formulation. Hence, a Box Behnken Design was implemented, considering Drug to Polymer ratio, Concentration of Plasticizer and Stirring Speed and independent variables, while Practical Yield, Entrapment Efficiency and Particle Size were selected as dependent variables. The independent variables were studied at three levels: low (-1), intermediate (0), and high (1) to evaluate their impact on the critical quality attributes. Box Behnken design was applied as per below:

Independent Variables			**Dependent Variables**		
X1	**X2**	**X3**	**Y1**	**Y2**	**Y3**
Drug to polymer ratio	Concentration of PEG 4000 (%)	Stirring Speed	Practical Yield	Entrapment Efficiency	Particle Size

Coded values are as follows:

Levels	**Coded value**	**Independent Variables**		
		X1	**X2**	**X3**
Low	-1	1:1	50	400
Intermediate	0	1:2	100	600
High	1	1:3	150	800

Design Layout and Data Transformation for Batches

Batches	Coded Values			Real Values		
	X1	X2	X3	Drug to Polymer Ratio	Concentration of Plasticizer	Stirring Speed
F1	0	1	1	1:2	150	800
F2	0	0	0	1:2	100	600
F3	-1	0	-1	1:1	100	400
F4	0	0	0	1:2	100	600
F5	0	-1	-1	1:2	50	400
F6	0	0	0	1:2	100	600
F7	0	1	-1	1:2	150	400
F8	-1	1	0	1:1	150	600
F9	-1	0	1	1:1	100	800
F10	0	0	0	1:2	100	600
F11	1	1	0	1:3	150	600
F12	1	0	-1	1:3	100	400
F13	1	-1	0	1:3	50	600
F14	0	0	0	1:2	100	600
F15	-1	-1	0	1:1	50	600
F16	1	0	1	1:3	100	800
F17	0	-1	1	1:2	50	800

The optimized batch F16 was further formulated to capsules and its evaluation was performed, i.e. Bulk density, Tapped Density, Angle of Repose, Carr's Index, and Hausner's Ratio as Preformulation Evaluation.

Preformulation Studies for Capsules: Prepared microsponges are evaluated for Bulk density, Tapped Density, Angle of Repose, Carr's Index, and Hausner's Ratio.

Bulk Density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume.

Bulk Density: ρb = M/ Vb

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

Tapped Density: It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 500 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume.

Pt = M / Vt

Where, M and Vt are mass and tapped volume of the powder respectively. It is expressed in g/ml.

Angle of Repose: The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

Θ = tan-1 (h/r) Where, h = height of pile in cm; r = radius of pile in cm.

Carr's Index: It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by,

$$CI = \frac{\rho t - \rho b}{\rho t} X\ 100$$

Where, ρt and ρb are tapped density and bulk density respectively.

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

HR = ρt / ρb

Where, ρt and ρb are tapped density and bulk density respectively.

Formulation of Capsules: The optimised microsponges were filled into "0" sizes capsule each containing 40mg equivalent of Lurasidone HCl.

Optimised Formulation	Lurasidone HCl Microsponge (mg) (Equivalent to 40mg)	Lactose (mg)	Magnesium Stearate (mg)
F16	178.1 mg	22.3	0.96

Evaluation of capsules had Weight Variation, Disintegration Test, and Dissolution Test.

Weight Variation: The weight variation test was performed to ensure uniformity of capsule fill weight. A sample of at least **20 capsules** was individually weighed, and the average weight was calculated. The deviation of each capsule from the average was compared with pharmacopeial limits (±10% for capsules weighing ≤300 mg and ±7.5% for capsules >300 mg). Excessive variation indicated poor filling consistency in manufacturing.

Disintegration Test: The disintegration test was carried out to verify that capsules disintegrated within the required time frame for effective drug release. The USP disintegration apparatus was used, where capsules were placed in a basket and immersed in a dissolution medium such as 0.1N HCl (pH 1.2) for gastric release and phosphate buffer (pH 6.8) for intestinal release, maintained at 37±0.5°C. The time taken for complete disintegration (excluding shell fragments) was recorded, with a typical limit of ≤30 minutes for hard gelatin capsules.

Dissolution Test: The dissolution test was performed to determine the rate and extent of drug release. The test was conducted using the **USP dissolution apparatus** (Type I - Basket or Type II - Paddle) with a suitable dissolution medium at **37±0.5°C** and a set rotation speed (50–100 rpm). Samples were withdrawn at predefined intervals, filtered, and analyzed using **UV spectrophotometry.** The drug release profile was then compared with pharmacopeial standards to ensure proper bioavailability.

RESULT AND DISCUSSION

1. Organoleptic Properties

Property	Observation	Inference
Colour	White to Off–white	Matches standard, acceptable
Odor	Odorless	Complies, no unusual smell
Taste	Slightly Bitter	Consistent with standard
Appearance	Fine Powder	Meets specification

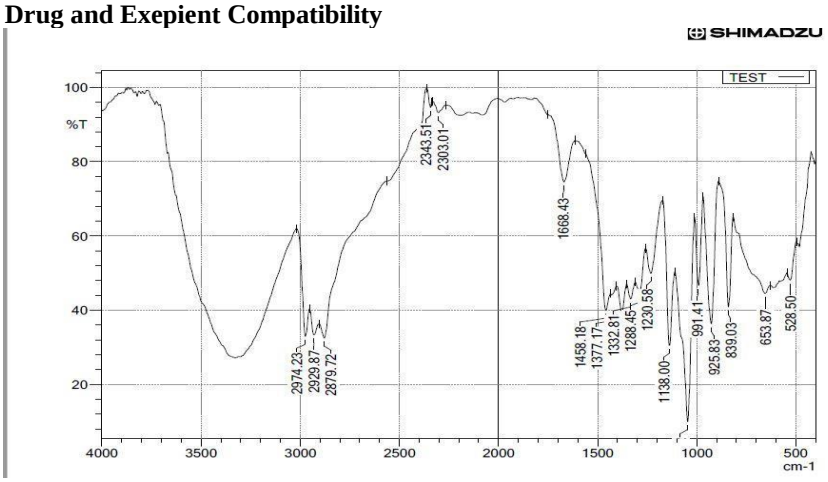
2. Melting point determination

Parameter	Observation	Reference Range	Inference
Melting Point (ºC)	253ºC	250ºC - 255ºC	Within range

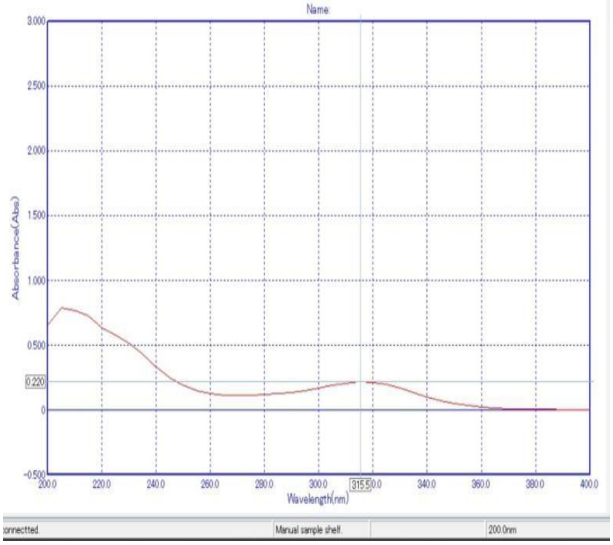
3. Solubility study

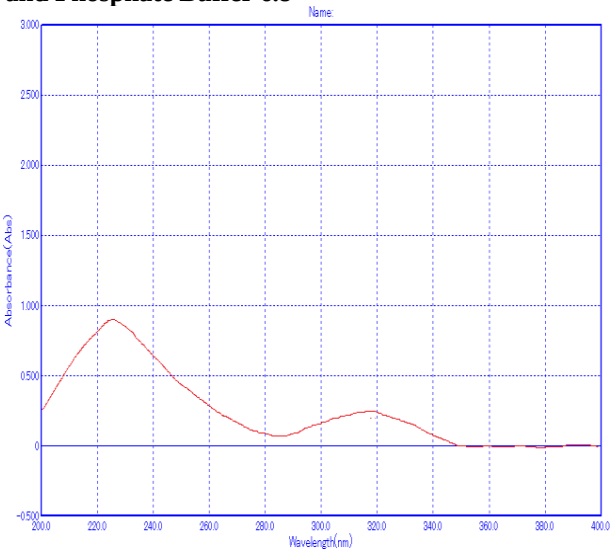
Solvent	Observation	Inference
Purified Water	0.0084 mg/ml	Practically insoluble
Methanol	~1.5mg/ml	Soluble
Dichloromethane	10.11mg/ml	Freely soluble
0.1N HCl	~ 0.3mg/ml	Slightly soluble
Phosphate Buffer (6.8)	~ 0.2 mg/ml	Slightly soluble

4. FTIR Study for Drug and Exepient Compatibility



5. Calibration Curve for Lurasidone HCl in 0.1N HCL and Phosphate Buffer 6.8

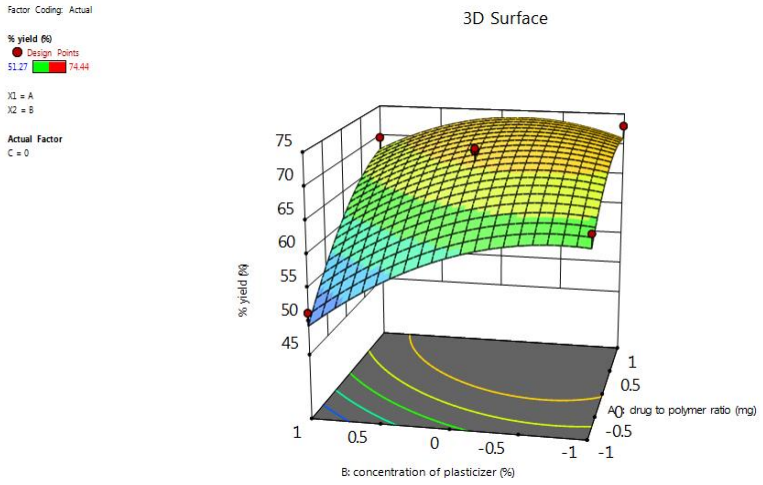




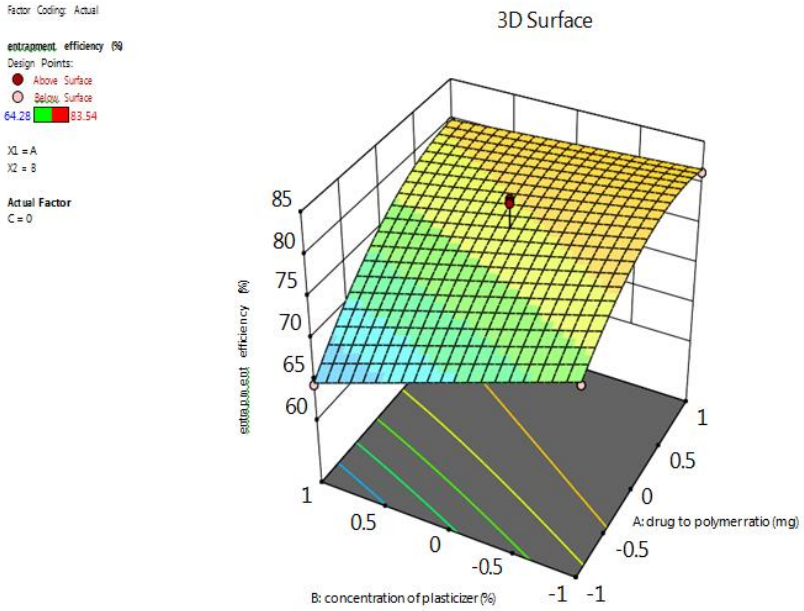
6. Results for the Box Behnken Design Batches

Batches	X1	X2	X3	Practical Yield (%)	Entrapment Efficiency (%)	Praticle Size (µm)
F1	0	1	1	67.68	78.32	32.11
F2	0	0	0	71.94	82.26	29.91
F3	-1	0	-1	51.47	64.28	43.85
F4	0	0	0	72.36	81.7	29.79
F5	0	-1	-1	65.44	76.51	33.15
F6	0	0	0	71.96	81.91	29.9
F7	0	1	-1	51.96	65.44	42.45
F8	-1	1	0	51.27	64.4	43.55
F9	-1	0	1	65.75	76.67	33.19
F10	0	0	0	71.96	81.91	29.9
F11	1	1	0	69.53	79.6	31.83
F12	1	0	-1	68.73	78.84	32.48
F13	1	-1	0	72.92	81.29	29.5
F14	0	0	0	71.96	81.91	29.9
F15	-1	-1	0	65.22	75.2	33.56
F16	**1**	**0**	**1**	**74.44**	**83.54**	**29.34**
F17	0	-1	1	71.14	80	29.34

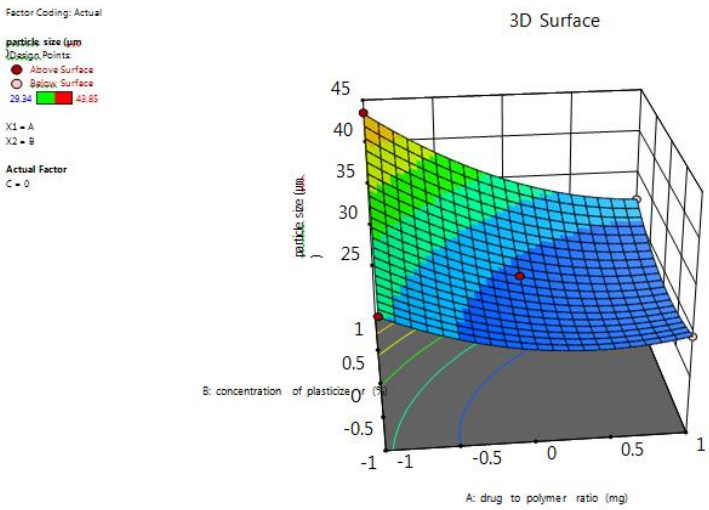
Validation of Statistical Model Response Y1



Validation of Statistical Model Response Y2



Validation of Statistical Model Response Y3



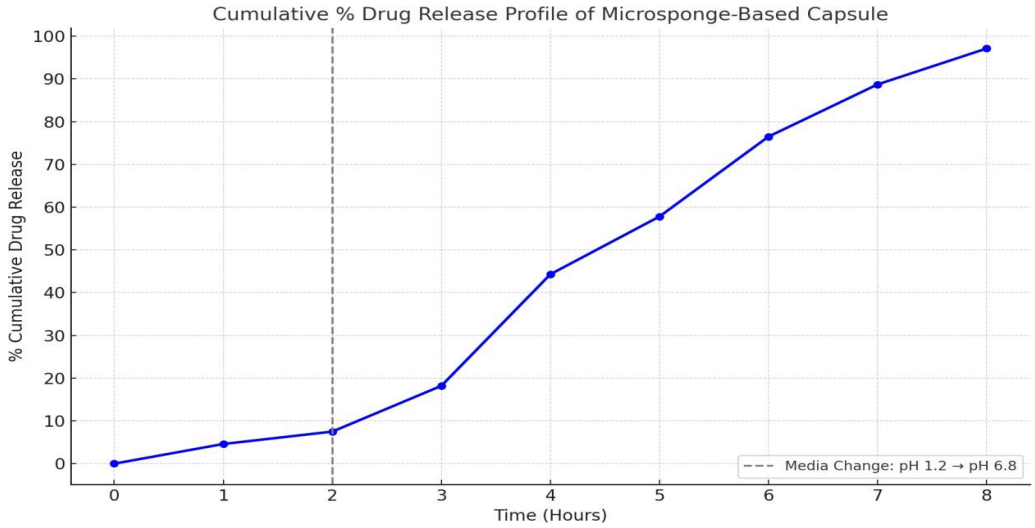
Preformulation Study Result for Capsules

Parameter	Result	Flow Characteristics
Angle of Repose (^{o})	25.6	Good Flow
Compressibility Index (%)	14.23	Fairly Compressible
Hausner's Ratio	1.17	Good Flow
Bulk Density (g/cm^2)	0.395	-
Tapped Density (g/cm^2)	0.489	-

Disintegration Time Result for Capsules

Batch	Disintegration Time (min)
F16	14.7

% Cumulative Drug Release in 900ml of Dissolution Medium, at 50rpm, 37.0ºC in USP Type I (Basket) Apparatus, (n=4)



CONCLUSION

Lurasidone HCl, a BCS Class II antipsychotic with poor water solubility and limited bioavailability, was formulated into a microsponge-based capsule using the quasi-emulsion solvent diffusion method to enhance solubility and provide sustained release. Ethyl cellulose and PEG 4000 were used as polymer and plasticizer, respectively, with PVA as a stabilizer.

Preformulation studies confirmed drug compatibility and purity, while preliminary trials identified optimal excipient ratios. A Box-Behnken Design was applied to optimize formulation variables, resulting in a batch with high entrapment efficiency, suitable particle size, and improved yield. The optimized microsponges were encapsulated and showed sustained in-vitro drug release, with stability confirmed under accelerated conditions. This novel capsule formulation offers a promising alternative to conventional tablets, enhancing therapeutic efficacy and patient compliance in schizophrenia management.