RESEARCH PAPER

FORMULATION, DEVELOPMENT AND OPTIMIZATION OF PROCHLORPERAZINE LOADED MICROSPHERES

Ms Niyati S. Shah[1], Dr. Payal N. Vaja[2], Dr. Hardik L. Varu[3], Dr. Chetan H. Borkhataria[4]

[1]Research Scholar, School of Pharmacy, Dr. Subhash University, Junagadh (362001), Gujarat, India

[2]Associate Professor, School of Pharmacy, Dr. Subhash University, Junagadh (362001), Gujarat, India

[3]Assistant Professor, School of Science, Dr. Subhash University, Junagadh (362001), Gujarat, India

[4]Assistant Professor, Department of Pharmaceutics, BK Mody Government Pharmacy College, Rajkot (360003), Gujarat, India.

Correspondence to:

Dr. Payal N. Vaja

Associate Professor, School of Pharmacy, Dr. Subhash University, Junagadh (362001), Gujarat, India. (M) 8780541846, Email Id: payalvaja55@gmail.com

ABSTRACT

Aim: The present study was undertaken to formulate and evaluate sustained-release microspheres of Prochlorperazine with the objective of improving drug release characteristics and extending therapeutic efficacy.

Materials and Method: Microspheres were prepared using the ionic gelation technique employing different drug-to-polymer ratios to optimize the formulation variables. Preformulation studies, including drug–excipient compatibility assessment, were carried out using Fourier Transform Infrared (FTIR) spectroscopy to ensure the absence of significant chemical interactions between the drug and excipients. The prepared microspheres were evaluated for production yield, entrapment efficiency, particle morphology, and in vitro drug release behavior.

Result & Discussion: Among the developed formulations, the optimized batch was selected based on superior production yield, high drug entrapment efficiency, and desirable sustained-release characteristics. Further characterization of the optimized formulation was performed using FTIR and Scanning Electron Microscopy (SEM). FTIR spectra confirmed the compatibility of prochlorperazine with the selected polymers, while SEM analysis demonstrated the formation of discrete, spherical microspheres with a smooth surface morphology. In vitro drug release studies indicated prolonged drug release over an extended period, suggesting effective sustained-release performance. The release kinetics of the optimized formulation were analyzed using various mathematical models, and the drug release pattern was found to follow the Higuchi model, indicating diffusion-controlled drug release.

Conclusion: A short-term stability study was conducted under accelerated conditions (40 ± 2°C and 75 ± 5% relative humidity) for one month. The optimized microspheres exhibited no significant changes in physical appearance, entrapment efficiency, or drug release profile, confirming their stability. The study further demonstrated that the drug-to-polymer ratio and the concentration of Eudragit RS 100 significantly influenced entrapment efficiency and drug release behavior. Overall, the developed prochlorperazine microspheres showed promising sustained-release properties, satisfactory stability, and potential for improving patient compliance through prolonged drug delivery.

Keywords: Prochlorperazine, Sustained release, Carbopol 974, Eudragit RS100, Ionic Gelation method

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INTRODUCTION

By localizing the drug to the site of action, lowering the required dose, or ensuring consistent drug delivery, sustained delivery systems aim to either decrease the frequency of dosage or increase the efficacy of the treatment. Therefore, a sustained release dosage form is one that releases one or more medications to a specific target organ either continuously in a predetermined manner or systemically over a predetermined length of time.[1] Sustained release dosage forms offer higher efficacy, less frequent dosing, less adverse effects, improved management of plasma drug levels, and dependable administration.[2] Additionally, these systems offer a consistent release of the medication over a prolonged period of time and may control the drug's distribution throughout the body either geographically, temporally, or both.

In other words, the system does a good job of keeping the target tissue or cells at constant drug levels. Sustained release is defined as a progressive release over a long period of time, followed by an initial release shortly after administration.[3] Highly cross-linked, porous polymeric microspheres known as Microsphere Delivery Systems (MDS) have the ability to absorb a variety of active substances and release them gradually.

2. MATERIALSANDMETHODS

2.1 Materials

Vaikunth Chemicals, Ankleshwar, Gujarat India, Ltd. provided a gift sample of prochlorperazine, while Signet Chemical Co., India, sent a gift sample of Eudragit RS. The remaining ingredients were all of analytical quality.

2.2 Method of Preparation

2.2.1 Preparation of microspheres by Ionic Gelation Method

After dissolving a predetermined amount of sodium alginate in enough distilled water to create a

homogenous polymer solution, a predetermined amount of HPMC was added and well stirred using a magnetic stirrer. Finally, the drug Prochlorperazine was mixed with polymer solution to create a smooth, viscous dispersion. Using a 20G needle, the resulting dispersion was added dropwise to a 5% CaCl2 solution. The droplets were kept in the CaCl2 solution to finish curing the reaction and create a hard, spherical particle. After that, it was dried and filtered [5,6,7].

2.2.2 Composition table for optimization of CaCl2 Concentration

The table below lists the amount of ingredients needed for the ionic gelation process.

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
ACB : Eudragit RS 100	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
Sodium Alginate (%)	2	2	2	2	2	2	2	2	2
Calcium chloride (%)	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5

3. EVALUATION STUDY

Preformulation Parameters

Drug's initial characteristics can be used to identify a specific material. The physicochemical properties of prochlorperazine were investigated. i) Color ii) Smell

Identification of drug by FTIR

The pressed pellet method with a KBr press was used for the FTIR investigations. To remove any last traces of moisture, the KBr was placed in a hot air oven for two hours. The previously mentioned dried KBr was used to create medication pellets and an optimized batch of microspheres. The produced pellet was placed in the instrument's sample holder and scanned in the 400–4000 cm-1 wave number range. The finished finger print was then compared to the reference standard.[6]

Solubilty Studies of drug

Drug solubility analysis:

The drug solubility investigation was conducted in water and several buffer solutions with pH values of 1.2 and 6.8. To create a saturated solution, the extra medication was added to the buffer solution. Saturated medication solutions were then sonicated three times for ten minutes each. Prochlorperazine solutions were left overnight to achieve solvent equilibrium. WhatMan filter paper number 42 was used to filter the prepared solutions. The same medium was used as the blank for spectrophotometric analysis of the filtrate at 271 nm. The calibration curve was used to calculate the amount of medication dissolved.

FORMULATION PARAMETERS

Flow Properties

All prepared microspheres were evaluated for their flow properties.

Particle Size Analysis

A calibrated ocular lens is used in optical microscopy to determine the microspheres' particle size distributions. A smear of the product dispersed in light liquid paraffin is examined under a compound microscope. Every time, the size of 100 microspheres is measured in micrometers using a calibrated eyepiece.

% Practical yield

By comparing the total weight of the microspheres produced to the total weight of the copolymer and medication, the yield of microspheres was calculated. Instead of calculating the total weight of the copolymer and drug, the practical yield is determined by dividing the mass of microspheres obtained by the total weight of the drug and poly microspheres generated [8].

Drug entrapment efficiency

For evaluation, microspheres containing 20 mg of the medication were consumed. By repeatedly crushing the microspheres and extracting with aliquots of 6.8 phosphate buffer, the amount of drug entrapped was calculated. Following the transfer of the extract to a 100 ml volumetric flask, 6.8 PB was used to adjust the volume. The solution was filtered after the appropriate dilution, and the absorbance was measured spectrophotometrically at 294 nm using 6.8 phosphate buffer as a blank. The following calculation was used to determine the percentage of medication trapped in the microspheres:

Drug Entrapment = (Theoretical Drug Content/Calculated Drug Content) x 100

The following formula was used to determine drug loading: %Drug Loading = (Drug Weight in Microspheres/Microspheres Weight) x 100

***In vitro* drug release studies**

USP dissolution test equipment (Type 1) was used for in vitro drug release investigations. The dissolution investigations were conducted using a pH progression approach in 900 milliliters of dissolving medium that was agitated at 50 rpm at 37±0.5°C. For example, pH 1.2 for the first two hours and pH 6.8 for the remaining research. Periodically, aliquots were removed and replaced with new media.[9]

Release Kinetics

The release data is analyzed using the following mathematical models to investigate how drugs are released from microspheres: zero-order, first-order, and Higuchi and Korsmeyer Poppas' model investigations. Aliquots were taken out and replaced with fresh media on a regular basis.

Optimization of microspheres by using 3^2factorial design method

For the purpose of optimization,

X_1=Concentration of Eudragit RS100(%)

X_2= Concentration of $CaCl_2$ (%)

Y_1=Entrapment Efficiency(%)

Y2= Drug release (%) [10,11]

Characterization of optimized batch of microspheres by using different techniques

FTIR: Prepared Optimized batch of microspheres were characterized by FTIR as described

Scanning electron microscopy

The surface structure of microspheres was examined using scanning electron microscopy (SEM-JSM 5000). SEM images were taken at the required magnification after the generated microspheres were coated with gold palladium at room temperature in an argon atmosphere.

Stability Study

Batch B2 of manufactured microspheres underwent a stability investigation in accordance with ICH guidelines. They were kept in a stability chamber for 30 days at 40 ±2°C and 75% relative humidity. The optimized batch of microspheres was contained in USP type-1 flint vials that were hermetically sealed with bromo butyl rubber plugs and aluminum lids.The entrapment efficacy and drug release of the formulation were evaluated after a month.[12, 13, 14, 15, 16].

Table 1. Optimization using factorial design method

Variables	-1	0	+1	Responses
X1=Concentration of Eudragit Rs100 (%)	40	50	60	Y1=Entrapment Efficiency (%)
X2=Concentration of Carbopol 974(%)	200	250	300	Y2=Drug release (%)

4. RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic properties

Table 2.Organoleptic properties of Prochlorperazine

Properties	Results
Description	White Crystalline Powder
Odor	Odorless
Color	White
State	Solid

Identification of drug by FTIR

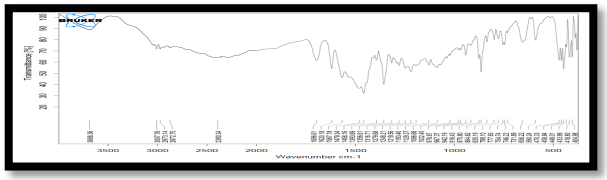

Fig.1.FTIRof Prochlorperazine

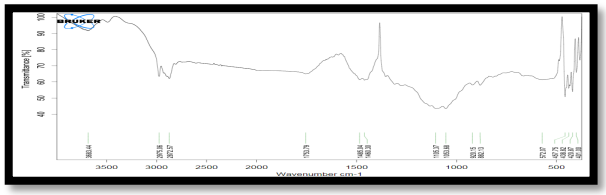

Fig.2.FTIR spectra of physical mixture of Eudragit RS 100

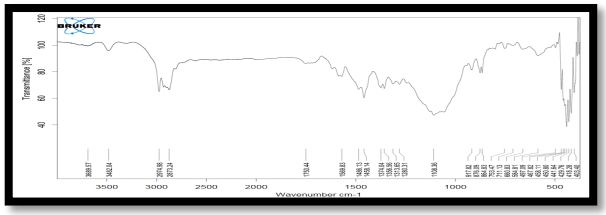

Fig.3.FTIR spectra of physical mixture of Drug+ Mixture

Interpretation

Table 3.Interpretation of FTIR graphs

Sr No.	Functional Group	Wave No. (cm^{-1})	
		Reported Value	Observed Value
1)	C-S	1200-1280	1279.68
2)	C-N amine	1300-1350	1316.71
3)	C=C (aromatic)	1420-1600	1458.16 and 1567.18
4)	CH (aromatic)	2900-3	2973.14
		000	

Table 4: Physical properties of drug

Experiment	Properties	Observations
Physico-mechanical properties	Bulkdensity	0.26±0.005 7g/cm^3
	Tappeddensity	0.413±0.028g/cm^3
	Hausner'sratio	1.45±0.577
	Angle of repose	18.11
	Compressibilityindex	29.6±0.57%
	MeltingPoint	217.39ºC
Solubility(mg/ml)	Water	0.011±0.16
	0.1NHCl	**11±0.12**

Formulation Parameters

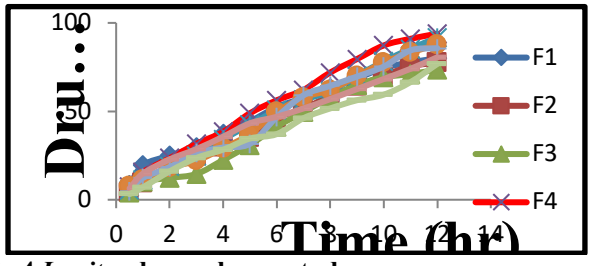

Fig 4 *In-vitro* drug releases study

From the above evaluation study, it was concluded that with increase in Eudragit RS100, concentrations, sustained release pattern was obtained.

Table 5 Release kinetic profile of optimized batch

Optimized formula	Higuchi (R^2)	Zero ord	First ord	Korsmeyer peppas	Hixone Cro

tion		er (R^2)	er (R^2)	(R^2)	well (R2)
B2	0.960	0.906	0.923	0.961	0.839

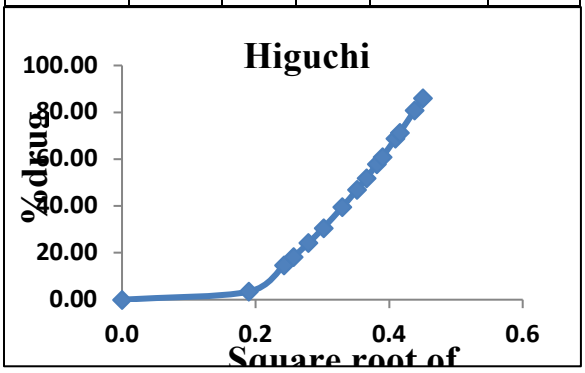

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Fig 5 Release Kinetics

According to the higuchi model formulation followed first burst release and then gives the sustained release effect.

Optimization of microspheres by using 3^2 factorial design method

Layout of optimization (A)

Variables		-1	0	+1	Responses
X1=Concentration of Eudragit Rs100(%)	Numeric	1	2.5	3	Y1=Entrapment Efficiency (%)
X2=Concentration of $Cacl_2$(%)	Numeric	2.5	5	7.5	Y2=Drug release (%)

Table 6 Layout of optimization (B)

Run	Coded Value		Actual Value	
Batch Code	X1	X2	X1	X2
B1	-1	-1	1	2.5
B2	0	-1	2	2.5
B3	+1	-1	3	2.5
B4	-1	0	1	5
B5	0	0	2	5
B6	+1	0	3	5
B7	-1	+1	1	7.5
B8	0	+1	2	7.5
B9	+1	+1	3	7.5

ANOVA for % entrapment efficiency(responseY1)

Table 8. ANOVA table for response Y1:Entrapment Efficiency

Source	Sum of square	Df	Mean square	F-value	P-value	
Model	82.25	2	41.12	20.92	0.0020	Significant
A-EudragitRs100	48.17	1	48.17	24.50	0.0026	
B-$CaCl_2$	34.08	1	34.08	17.34	0.0059	
Residual	11.79	6	1.97			
Cor Total	94.04	8				

Contour plot of % entrapment efficiency(response Y1)

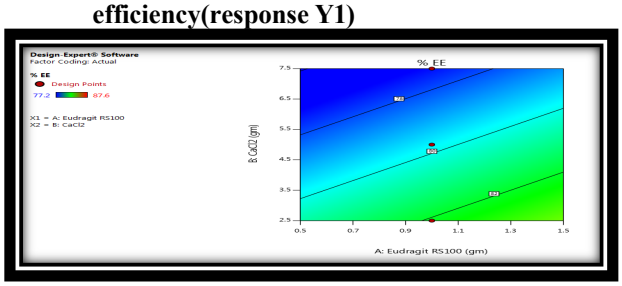

Fig.6.Contour plot showing the effect of Eudragit RS100(X1) and $CaCl_2$(X2) on response Y1 (% Entrapment Efficiency)

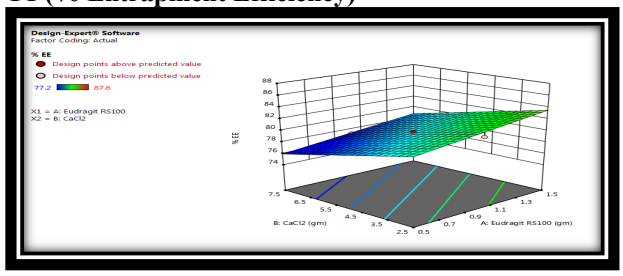

Fig.7.Response surface plot of % entrapment efficiency(ResponseY1)

ANOVA for % CDR (responseY2)

Table 9. ANOVAtablefor%CDR(responseY2)

Source	Sum of squa re	D f	Mea n squa re	F-val ue	P-valu e	
Model	256. 70	2	128. 35	23. 46	0.00 15	Signific ant
A-EudragitRs 100	178. 21	1	178. 21	32. 57	0.00 13	
B-$CaCl_2$	78.4 8	1	78.4 8	14. 35	0.00 91	
Residual	32.8 3	6	5.47			
Cor Total	289. 52	8				

Counter plot of % drug release(response Y2)

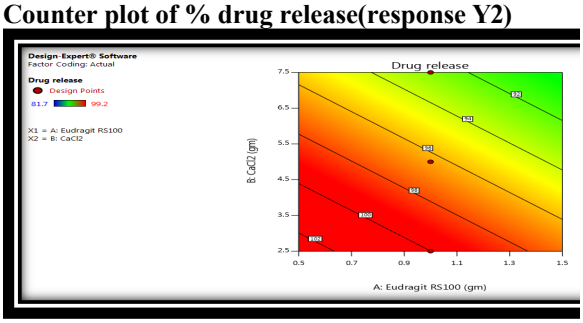

Fig.8.Contour plot showing the effect of Eudragit RS100(X1) and Carbopol 974(X2) on responseY2 (% Drug release)

Response surface plot of % Drug release(Response Y2)

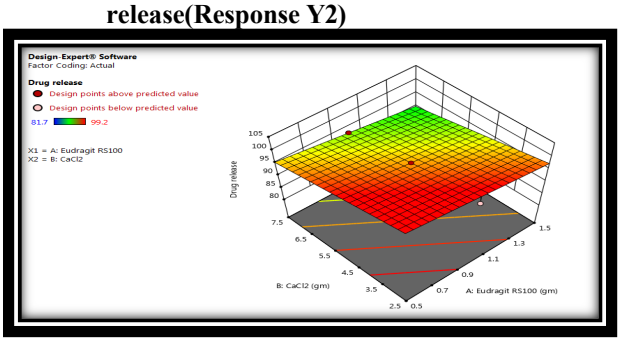

Fig.9.Response surface plot of %drug release(Response Y2)

Overlay plot

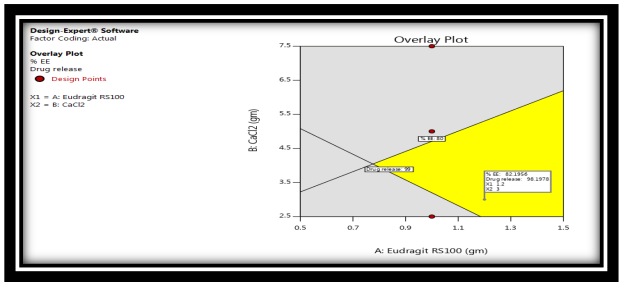

Fig.10.Ovelay plot of Eudragit RS100 & $CaCl_2$

Table 10. Predicted & observed values of check point batch B2

Name	X_1	X_2C	Response	Predicted	Observed	%Error
M_1 553.7 200			Y_1(Entrapment efficiency) (%)	82.19	85.3	3.7
			Y_2 (% Drug	98.19	99.2	1.02

	releas e)			

Predicted error (%) = (observed value − predicted value)/predicted value × 100%

From the results of checkpoint batch B2 (optimized batch), the predicted values of responses were found to be near to the observed value. By this, the validity of the optimization procedure was proven

Characterization of Optimized Batch of Microspheres by using Different Techniques

FTIR of optimized batch of microspheres

Fig.11.FTIR spectra of optimized batchB2

Scanning Electron Microscopy of optimized batch

From the above figure it was observed that microspheres were spherical in shape

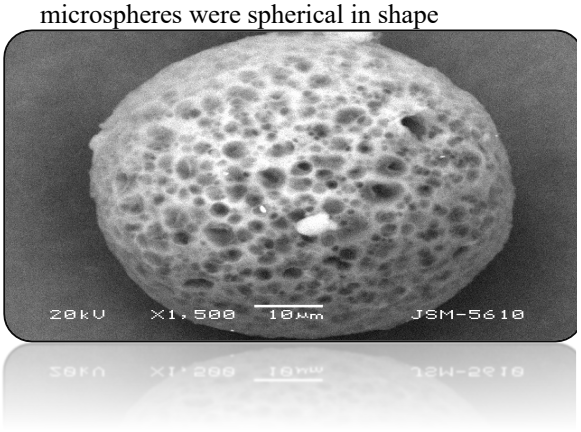

Fig.12 SEM of optimized batch

Stability Study

Short term stability conditions of temperature and relative humidity (45 ± 2°C/75% ± 5% RH).

Table 11.Characterizationof optimized Batch after stability

Parameters	Initial	After1month
Particle size	84.3 µm	83.9
%Entrapment Efficiency	87.6	86.3
% CDR	99.2	98.1

Table15.Characterizationof optimized Batch after stability

The formulation did not significantly alter appearance, particle size, entrapment efficiency, or drug release, according to the above results. Thus, it was discovered that the produced formulation was stable at speed.

5. CONCLUSION

Sustained release microspheres that retain the formulation for an extended amount of time were developed for this investigation.The Ionic Gelation Method was used to create microspheres.When making the microspheres, a number of parameters were taken into account, including drug release, trapping efficacy, and production yield. To ensure that the medication and polymer were compatible, pre-formulation experiments were conducted. SEM analyses showed that the microspheres had a spherical shape. Stability tests were conducted for a month at 40 ± 2°C and 75% relative humidity to find out how temperature and humidity affected the percentage of entrapment efficiency and drug release. Stability testing showed that the improved formulation's entrapment efficiency and in vitro release studies did not significantly change, indicating that the formulation is stable.

6. CONSENT

Not applicable

7. ETHICAL APPROVAL

Not applicable.

8. COMPETING INTERESTS

Authors have declared that no competing interests exist.

9. AI DISCLOSURE

AI was used for grammar checking and improving sentence clarity. he author(s) declare that artificial intelligence (AI) tools were used solely for language refinement, grammar correction, and formatting assistance during the preparation of this manuscript.

10. AUTHOR'S CONTRIBUTION

Research Work, Drafting of Manuscript : Niyati Shah

Final Correction and Formatting: Dr Payal Vaja

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