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Research Article

Innovative Nanosuspension Formulation for Prochlorperazine and *In-vitro* Evaluation

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Abstract

Prochlorperazine is a dopamine antagonist and is used to control nausea and vomiting. It is a BCS class II drug which has low aqueous solubility and high permeability. The present study is aimed to formulate and evaluate prochlorperazine nanosuspension to improve solubility and enhance dissolution of Prochlorperazine with varying concentrations of stabilizers such as Tween 80, PVP K30, Poloxamer 188 by using nanoprecipitation method. The developed formulations were characterized for particle size and polydispersity index, total drug content, SEM, Zeta Potential and FTIR. The invitro drug release studies and invitro drug release kinetics were performed for all formulations. FTIR studies revealed that drug is compatible with the excipients. The particle size and poly dispersity index of optimized formulation was found to be 162nm and the zeta potential was found to be -30.2 mV and concluded that the system had sufficient stability. The invitro drug release was found within their acceptable ranges. The rate of dissolution of best batch was enhanced to 93.24 in 120min. Stability studies proved that nanosuspensions were more stable with no significant changes in particle size distribution. Thus the formulated nanosuspension of prochlorperazine offers a superior conventional dosage forms for drug release

Keywords: Prochlorperazine, Nanosuspension, Solubility, Dissolution

INTRODUCTION

Amongst the various routes of administration, the oral route is the one commonly used and most convenient for the Drug delivery. Oral drug delivery system has received more attention in the pharmaceutical field, because of its more Flexibility in designing the dosage form than other drug delivery system[1]. More than 40% of the new chemical Entities being generated through drug discovery programmes are faced the problem for aqueous solubility and become a hurdle for the formulation [2]. Nanotechnology can be used to solve the problems associated with these Conventional approaches for solubility and bioavailability enhancement [3]. Nanosuspensions are basically Suspension where the particle size of the suspended material is within the range of 10-1000 nm [4, 5].

Nanosuspension platform is an efficient and intelligent drug delivery system for water insoluble drugs, as the Saturation solubility and the surface area available for dissolution increased [6,7]. Generally, the biopharmaceutical Advantages of water insoluble drugs formulated as nanosuspensions including improvement in formulation Performance, such as high drug loading, reproducibility of oral absorption, improved dose-bioavailability Proportionality, reduced toxicity and side effects and increased patient compliance via reduction of number of oral Units to be taken [8]

Prochlorperazine, a phenothiazine derivative; it is known as typical antipsychotic medication, whose effect through blocking dopamine receptors. Prochlorperazine and its salts are in general utilized in the avoidance and treating of nausea and vomiting resultant of radiotherapy, chemotherapy, surgery and acute migraine. The half-life of prochlorperazine maleate is 4 to 8 h and has about 12.5%oral bioavailability. The aim of the study was to prepare prochlorperazine nanosuspension in an attempt to improve drug solubility, bioavailability and patient compliance.

MATERIALS AND METHODS

Drug was purchased from Lupin Pharmaceuticals. Poloxamer 188 was procured from Merck Limited, Mumbai, India, and employed in the research. PVP k-30, an essential component in the study, was also purchased from Merck Limited in Mumbai, India. Tween80, Methanol was sourced from Merck Limited in Mumbai, India.

Methods:

Preformulation Study

Determination of melting point

A small amount of drug powder was placed into a fusion tube. That tube is set in the melting point determining apparatus containing liquid paraffin[9]. The temperature of the drug put in a capillary was gradually increased mechanically and read the

temperature at which powder started to melt up to all powder gets melted and temperature is calculated by the thermometer[10].

Determination of Prochlorperazine Solubility

For determining the saturated solubility of the drug in dis. H2O, methanol, DMSO, phosphate buffer PH6.8 (5ml) each were taken in a 100ml conical flask each containing excess amount of drug. These flasks were kept for shaking in an orbital shaker at room temperature[11]. Samples were collected at specified time intervals and filtered using filter paper (Whattman), followed by dilution with respective solvent. Then the concentration was analyzed by UV spectroscopy[12].

Drug-Excipients compatibility studies:

Drug-excipient compatibility was performed to examine any feasible interactions linked with drug and other excipients in formulation.

FTIR Spectroscopy

Spectroscopy is an analytical technique used to identify drug substances by monitoring the functional groups exist in the compound.

FTIR spectra of Prochlorperazine (pure) and its mixtures were done by using FTIR spectrometer (Bruker, Germany). The samples were mixed thoroughly with KBr and the spectrum was analyzed in resolution of 4/cm and frequency range of 4000 to 400cm^{-1}.[13]

Analytical method development Using UV spectroscopy

Preparation of 0.1 N HCl:

Dissolve 8.5 ml of concentrated HCl in 1000 ml of distilled water.

a) Determination of absorption maxima

Stock 1(1000mcg/ml) - 100mg of drug was measured and dissolved in 100ml of methanol

Stock 2 (100 mcg/ml) - Pipette out 5ml from stock 1 and dilute to 50ml with 0.1N HCL.

From the above sol. Pipette out 0.2, 0.4, 0.6, 0.8, 0.10 and 0.12 ml into 10ml volumetric

Flask and makeup the volume with 0.1NHCL to give concentrations 2,4,6,8,10,12 µg/ml.

Scan for absorption maxima using UV spectroscopy in range between 200-400nm. From this scan the spectral data was used for the formulation of calibration curve.[14]

Calibration curve of prochlorperazine

Preparation of standard stock solution in 0.1N HCL

Stock 1(1000mcg/ml) will be prepared and then stock 2 (100mcg/ml) will be formulated from stock 1.

Preparation of sample solution in 0.1NHCL

From the above solution various concentrations such as 2,4,6,8,10 and 12 µg/ml will be prepared and absorbance will be detected at 254nm by UV spectrophotometry. Then calibration curve will be obtained by plotting the graph by taking concentration (mcg/ml) and absorbance value (nm) on X-axis and Y-axis respectively.[15]

DESIGN OF EXPERIMENT AND FORMULATION

Further designing of experiment for oral nanosuspension is done to obtain formulations by high pressure homogenization method and to optimize a most stable oral nanosuspension with high drug content & drug release.

- For PCP nanosuspension development and optimization, a two-factor, two-level central composite design (CCD) using Sigma Tech software was chosen
- 2 factors for this study were labeled as A (PVP), B (Tween 80) with high and low values coded as +1, -1 respectively.
- Organic solvent, surfactants and co-surfactants were selected based on their solubility.
- Independent variables or factors were selected as (A) PVP, (B) Tween 80
- Dependent variable or responses was selected as % Drug Release.
- A total of 9 experiments with 1 midpoint were suggested by the software and the experiments were done in random order.
- Table 3.3 shows the independent variables. Formulations were developed and further analyzed for the nine batches generated.
- After the formulations were prepared, they were subjected to evaluation studies for the optimization process[16,17].

Table 1 Low and High Values of independent variable

Variable Index	Independent variable	Low	High
X1	PVP	15	30
X2	TWEEN 80	1.5	2.5

Table 2 software generated formulation

Formulation	Prochlorperazine	PVP (mg)	TWEEN 80	Poloxamer 188(mg)	Methanol	Water
F1	10	15	1.5	1	2	50
F2	10	30	1.5	1	2	50
F3	10	15	2.5	1	2	50
F4	10	30	2.5	1	2	50
F5	10	22.5	2	1	2	50
F6	10	7.5	2	1	2	50
F7	10	37.5	2	1	2	50
F8	10	20.5	1	1	2	50
F9	10	20.5	3	1	2	50

METHOD OF PREPARATION OF NANOSUSPENSIONS

The software generated Nanosuspension formulations were prepared by using a high pressure Microfluidizer (Microfluidizer LM-20).

1. Firstly, measured quantity of drug (10mg) was dissolved in a methanol in a separate beaker
2. Then, the above solution was added dropwise with a syringe into a beaker containing PVP, Poloxomer, Tween 80 which is a aqueous phase placed on a magnetic stirrer (SAI038, Remi), to form a total of 50ml Nano suspension.
3. The above suspension was further sonicated using a probe sonicator (GOC 3) for 5 min to form a coarse suspension. Then the coarse suspension was placed on a ice bath
4. Finally, the coarse suspensions of all the 9 formulations were poured one by one into the feed reservoir of Microfluidizer for proper mixing of two Phases by gradually increasing pressure from 5000 to 25000 psi for 5-15 cycles by careful visual observation, time 1 min/ cycle, to obtain nano sized suspensions. After the completion of desired cycles the samples were collected from the outlet.[18,19]

Figure 1 Formation of coarse suspension

Figure 2 Formation of Nanosuspension

CHARACTERIZATION OF NANOSUSPENSION

PARTICLE SIZE, PDI AND ZETA POTENTIAL

The particle size, polydispersity Index (PDI) and zeta potential of prepared formulation were analyzed by photon correlation spectroscopy utilizing Zeta sizer (Malvern Zetasizer.). The method was based on the concept of Photon correlation spectroscopy that calculates the light scattering due to Brownian motion of the fragments where 1ml of the sample is observed at 25°C at a scattering angle of 90°.[20]The samples were suitably diluted with solvent that is not soluble with the sample and placed in quartz/plastic disposable cuvette having two electrodes. The samples analyzed for particle size and zeta potential analysis in triplicate.[21]

DETERMINATION OF DRUG CONTENT

For this study, 1ml of sample taken in a 10ml volumetric flask and was diluted with methanol to produce required drug concentration. It was then centrifuged at 3500 rpm for 30 mins. Supernatant obtained was filtered and the drug content of was analyzed by UV spectrophotometer.[22]

***IN-VITRO* DRUG RELEASE STUDIES**

The dissolution study of prochlorperazine nanosuspension formulation was performed using the USP Apparatus II (paddle method with a paddle speed of 50 rpm, 37 C ± 0.5 C temperature and 0.1 N hydrochloric acid as a dissolution medium. Pipette was used to collect samples (5 ml) For a period of 2 hours after addition of the formulations to the dissolution vessels. Filtered samples with 0.22 mm Millipore filter(Whatman) were analyzed by UV (254 nm). 5 ml of fresh dissolution medium was replenished after each sample withdrawal.[23]

***IN-VITRO* DRUG RELEASE KINETICS STUDY**

Kinetic model had described drug dissolution from Nano suspension where the dissolved amount of drug is a function of test time. In order to study the exact Mechanism of drug release from the Nanosuspension, drug release data was analyzed According to zero order, first order, Higuchi square Root, Korsmeyer- Pappas model. The criteria for Selecting the most

appropriate model were chosen on the basis of goodness of fit test.[24]

Zero order kinetics: it expresses the complex where the drug released rate is independent of concentration

C=K0 t

where,

K0= Zero-order rate constant(hr^{-1})

When the data is put as cumulative percent drug release vs time, the data obeys

zero-order kinetics if the plot is linear.

First order kinetics: expresses the release from complex where release rate depends on concentration

First order kinetics could be predicted by the given equation:

Log C= log C0-Kt / 2.303

The constant 'Kt'can be gained by multiplying 2.303 with the slope value.

Higuchi's model: (1963) based on Fickian diffusion it expresses the release of drugs from insoluble matrix as a sq. root of time dependent process.

Drug release from the matrix devices by diffusion has been described by following equation:

Q= [DЄ/τ (2A-ЄCS) CSt]1/2

The equation is simplified as if we assume that 'D', 'CS', and 'A' are constant.Then equation becomes:

Q= Kt1/2

Where, KH is the constant reflecting the design variables

Peppas model: A simple relationship which showed drug release from a polymeric system equation was derived by Korsmeyer et al. (1983). To know the mechanism of drug release, 60% DR data were fitted in Korsmeyer Peppas model.[25]

Mt / M∞ = Ktn

SEM

The surface morphology of Nanosuspension was evaluated using a scanning electron microscope (JEOL,USA) at a voltage of 20 kv. Afew drops of the freshly prepared nanosuspensions were spread on stubs using double side carbon tape and then sputtered with gold using a sputter.[26]

PHYSICAL STABILITY

The physical stability of optimized nanosuspension F4 was evaluated at 4°C and 25°C for a period of 1 month. Small aliquots of nanosuspension Were withdrawn at 0,1,5,12,20,30 days for analysis of particle size and drug content. Each sample was analyzed in triplicate.[27]

RESULTS AND DISCUSSION

The present study was aimed to developing Nanosuspension of Prochlorperazine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

PHYSICO-CHEMICAL PROPERTIES OF PROCHLORPERAZINE

Appearance: Prochlorperazine was observed for physical evaluation such as state, color, odor and taste and the observations are reported below.

Table 3 Organoleptic properties

S. NO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odorless
4	Taste	bitter

Melting point of prochlorperazine

The M.P of Prochlorperazine was found to be 226° C

Table 4 M.P of PCP

Pure Drug	Reference Range	Observed Range
Prochlorperazine	225-228 °C	226 °C

Solubility studies

The absorbance of the drug was measured with UV Visible Spectrophotometer at 254 nm and its concentration was calculated, the highest solubility was found to be in methanol i1.152±0.00 mg /ml

Table 5 solubility of drug in different solvents

S.NO	SOLVENTS	Concentration(mg/ml)
1	Water	0.002±0.01 mg /ml of drug
2	Methanol	1.152±0.00 mg /ml of drug
3	Phosphate buffer PH 6.8	0.231±0.023 mg /ml of drug
4	DMSO	0.16± 0.019 mg /ml of drug
5	0.1N HCL	1.026± 0.01 mg /ml of drug

Results are expressed as mean ± S.D (n = 3)

Discussion Solubility of Prochlorperazine in various solvents was accomplished and the highest solubility was found to be in methanol i.e. 1.152±0.00 mg /ml of drug

UV-SPECTROSCOPIC EXAMINATION OF DRUG

Determination of λ max for prochlorperazine in 0.1N HCL by UV Solution of Prochlorperazine in concentration 10 µg/ml was screened in the wavelength range of 200-400 nm which revealed significant absorbance at 254 nm. The absorption spectrum was deemed to be sharp and maximum at 254nm, therefore it was chosen as wavelength of detection in 0.1N HCL

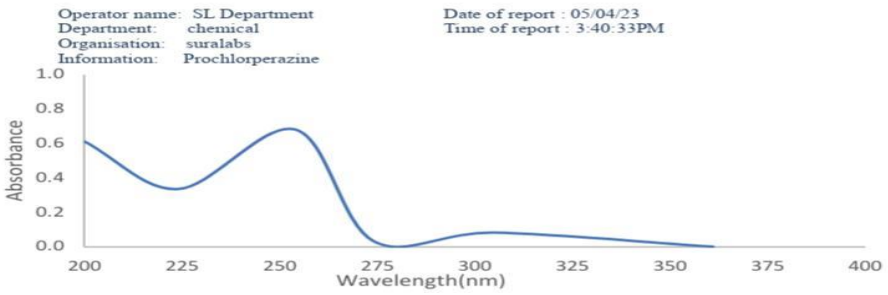


Figure 3 Spectra for Prochlorperazine wavelength optimization

Table 6 absorbance values at different concentration

Concentration (µg/ml)	Absorbance
0	0
2	0.163±0.02
4	0.308±0.03
6	0.468±0.06
8	0.607±0.01
10	0.787±0.04

All values are expressed as mean ± S.D (n = 3)

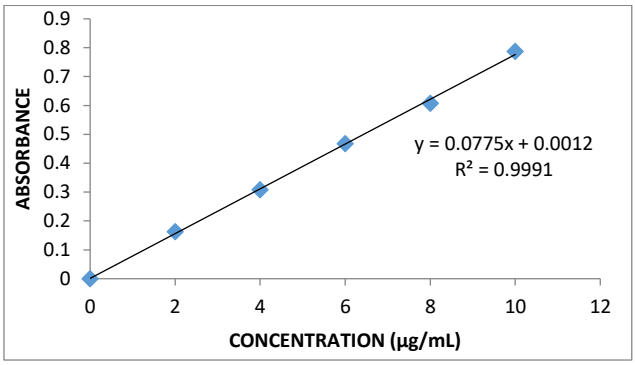


Figure 4 Calibration curve data of Prochlorperazine in 0.1N HCl

From the prepared stock solution, various dilutions of the sample solutions were prepared and analyzed at 254 nm. The different dilutions showed absorbance values and the standard graph was obtained by taking concentration on X-axis and Absorbance on Y-axis. R^2 value was ascertained to be 0.9991

FTIR REPORTS:

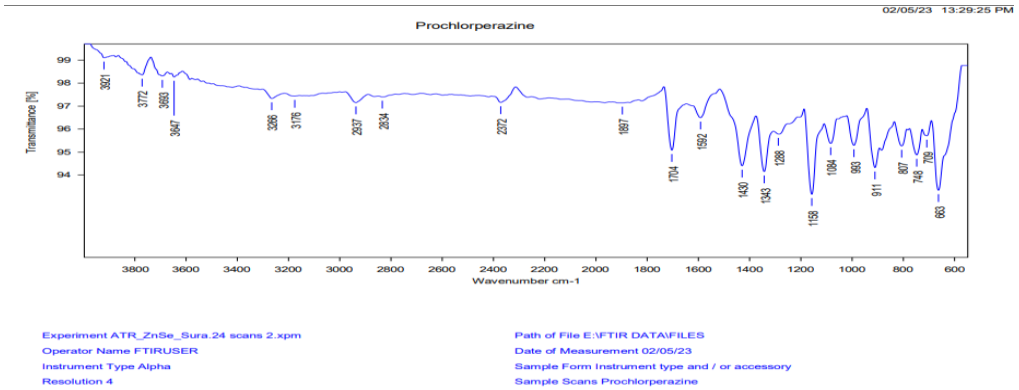


Figure 5 FTIR graph of pure

Table 7 FTIR peaks of pure drug

Functional groups	Standard IR values (cm-1)	Observed IR values (cm-1)
Hydroxyl (OH)	3100-3700	3693
(C-H) of aliphatic groups CH3 and CH2	3000-2840	2937
Ar. C-Cl	885-550	807
C=O	1710-1680	1704
Ar. C=C	1670-1600	1638.47

The purity of Prochlorperazine procured was confirmed by FTIR. The spectrum of Prochlorperazine showed a characteristic sharp peak at 3693,2937,807,1704,1638.47 cm^{-1} corresponding OH ,C-H, Ar.C-Cl, C=O, Ar.C=C

FTIR SPECTRA OF PURE PROCHLOROERAZINE ALONG WITH Poloxomer- 188,PVPK-30,Tween-80

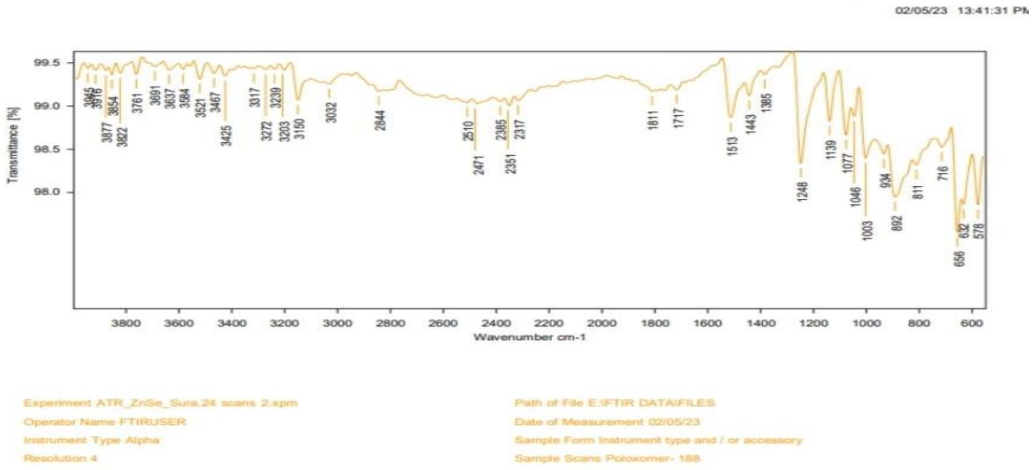


Figure 6 FTIR graph of pure drug with excipients

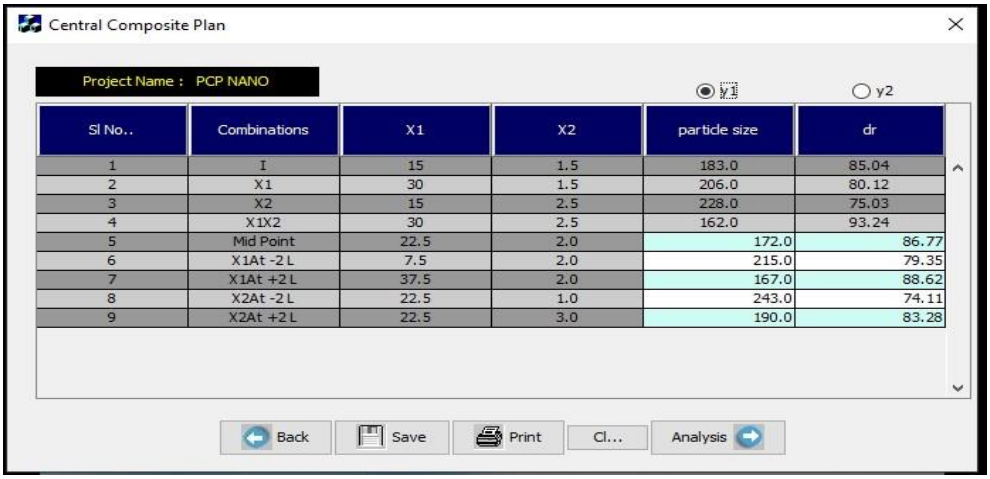
Discussion: The spectral data indicated that the major peaks for drugs acquired nearer value and there were no significant changes in IR peaks in all physical mixtures of drug and excipients. This demonstrates that the drug was molecularly dispersed in the excipients inevitably specifying the compatibility between drug and excipients and also the absence of any interactivity.

DESIGN OF EXPERIMENT RESULTS:

After the coarse suspension were formed using the software generated formulas, the nanosuspension formed as a result of high energy microfluidization are shown in **fig no7** All these formulations showed acceptable transparency but the highest transparency was seen in the formulation F4.

Figure 7 PCP nanosuspension obtained by high energy microfluidization

For the designing of experiment first the high and low value of PVP & Tween80 were determined through literature. These values were entered into the SIGMA TECH software. The High and low values of independent variables in mg & ml is shown in **figure 4.6** which shows the input variables of the DOE.



Sl No..	Combinations	X1	X2	particle size	dr
1	I	15	1.5	183.0	85.04
2	X1	30	1.5	206.0	80.12
3	X2	15	2.5	228.0	75.03
4	X1X2	30	2.5	162.0	93.24
5	Mid Point	22.5	2.0	172.0	86.77
6	X1At -2 L	7.5	2.0	215.0	79.35
7	X1At +2 L	37.5	2.0	167.0	88.62
8	X2At -2 L	22.5	1.0	243.0	74.11
9	X2At +2 L	22.5	3.0	190.0	83.28

Figure 8 Formulation, Particle size, Drug release table of F1-F9 Formulations

The results and observations were confirmed from the contour plot observed for the % Drug Release.

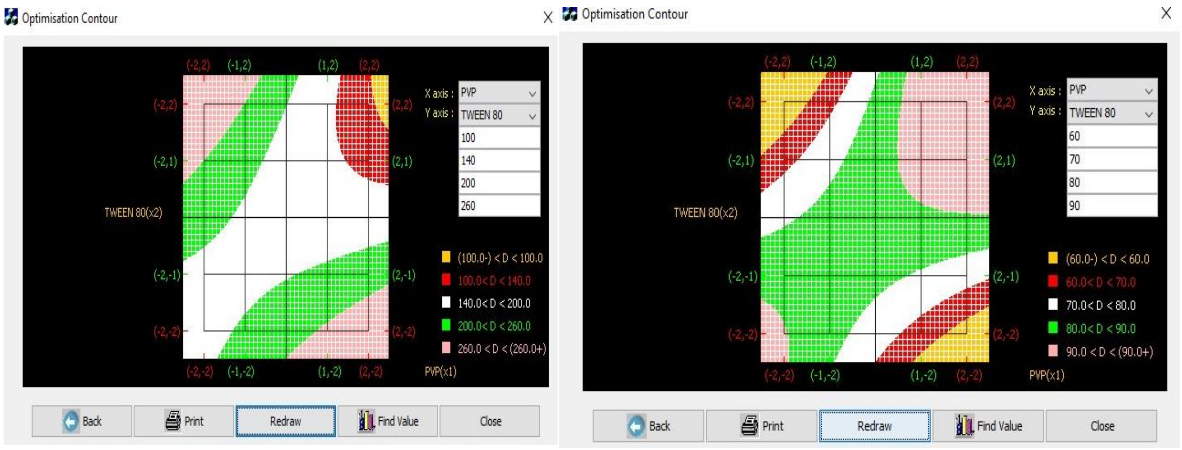


Figure 9 Optimization Contour Plot

EVALUATIONS

Average Particle size & polydispersity index (PDI) analysis:

Particle size :

The size ranged from (162nm) to (243nm) . From the data obtained through particle size analysis, it was deemed that all prepared prochlorperazine nanosuspension have a particle size less than 300 nm. Although all formulations were within the range, PCP1 and PCP showed least particle size i.e. 162 nm and nm respectively.

Polydispersity Index: PDI of almost all formulations was found to be within the limit i.e. <0.5, indicating the uniformity of formulations.

Table 8 Particle size and PDI values of all the formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
P. Size (nm)	183	206	228	162	172	215	167	243	190
PDI	0.389	0.479	0.538	0.266	0.359	0.507	0.265	0.585	0.465

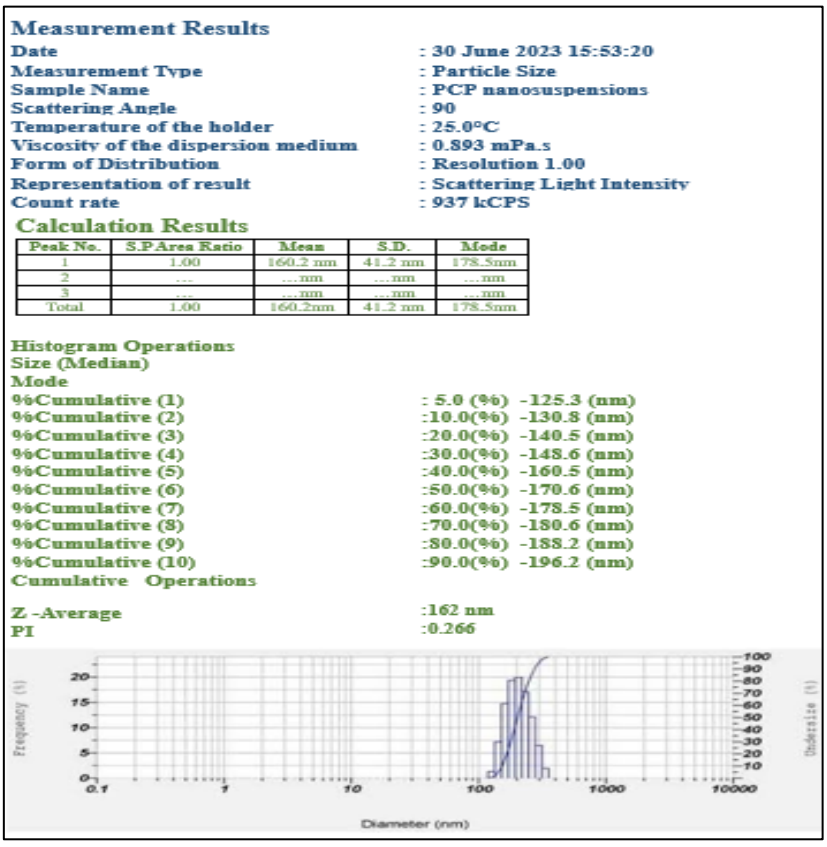


Figure 10 particle Size & PDI of Optimized Formulation F4

2. Zeta potential: In General, zeta potential value of ± 30 mV is sufficient for the stability of nanosuspension. Zeta potential of optimized formulation was observed -30.2 mV, which Complies with the requirement of zeta potential. Almost all formulations were found to be stable owing to their zeta potential

Table 9 zeta potential values

Formulation	Z.P (mv)
F1	-25.9
F2	-22.2
F3	-20.2
F4	**-30.2**
F5	-27.4
F6	-21.7
F7	-28.9
F8	-19.4
F9	-24.7

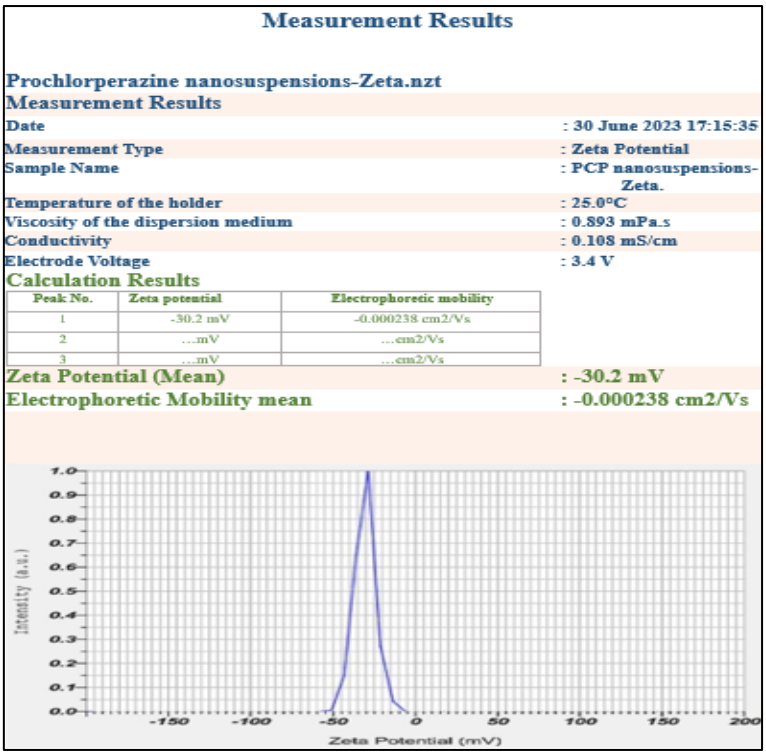


Figure 11 Zeta potential of optimized formulation F4

% Drug content

The total drug content of the formulated Nanosuspension was in the range of 78.21 to 94.15% respectively, which indicates that loss of drug was lower during preparation process. The total drug content of the optimized formulation F4 was found to be 94.15%. The results were shown in table

Table 10 %DC

Formulation	%Drug content
F1	86.31
F2	82.65
F3	79.31
F4	94.15
F5	87.54
F6	80.15
F7	89.98
F8	78.21
F9	84.13

***IN-VITRO* drug release**

The most important feature of nanoparticles is the increase in the dissolution velocity, not only because of increase in surface area but also because of increase in saturation solubility. In-vitro drug release data from the nanosuspension were carried out for 120 min and graphically represented as % drug release v/s time profile **(Fig. 4.14).** The percentage drug release curve of formulation F4, showed the desired rate in 0.1 N hydrochloric acid up to 120min. From that study it was found that formulation of F4 batch gave faster release behaviour compared to other formulation. The drug release of optimized batch(F4) was found to be 93.24% . Thus, from the above results it was found that as the particle size is decreased drug release is increased.

Table 11 *IN VITRO* drug release of PCP nanosuspension

Time (MINS	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	16.24 ±0.26	17.52 ±0.32	21.23 ±0.15	24.63 ±0.41	21.89 ±0.22	18.05 ±0.09	18.63 ±0.20	20.54 ±0.61	21.92 ±0.01
30	30.54 ±0.56	32.36 ±0.13	36.52 ±0.66	32.14 ±0.82	39.45 ±0.44	32.48 ±0.65	35.13 ±0.64	35.24 ±0.87	40.46 ±0.72
45	58.36 ±0.34	39.49 ±0.70	44.39 ±0.25	50.47 ±0.27	47.21 ±0.04	39.27 ±0.19	49.21 ±0.48	49.62 ±0.24	47.38 ±0.05
60	60.45 ±0.78	55.64 ±0.64	50.15 ±0.53	58.32 ±0.69	59.14 ±0.71	55.72 ±0.84	53.45 ±0.12	58.21 ±0.24	59.75 ±0.31
90	76.21 ±0.52	69.86 ±0.84	68.41 ±057	79.84 ±0.04	79.32 ±0.56	70.25 ±0.41	74.18 ±0.67	69.04 ±0.23	79.56 ±0.14
120	85.04 ±0.67	80.12 ±0.85	75.03 ±0.64	93.24 ±0.24	86.77 ±0.5	79.35 ±0.12	88.62 ±0.83	74.11 ±0.47	83.28 ±0.05

Results are expressed as mean ± S.D, n=3

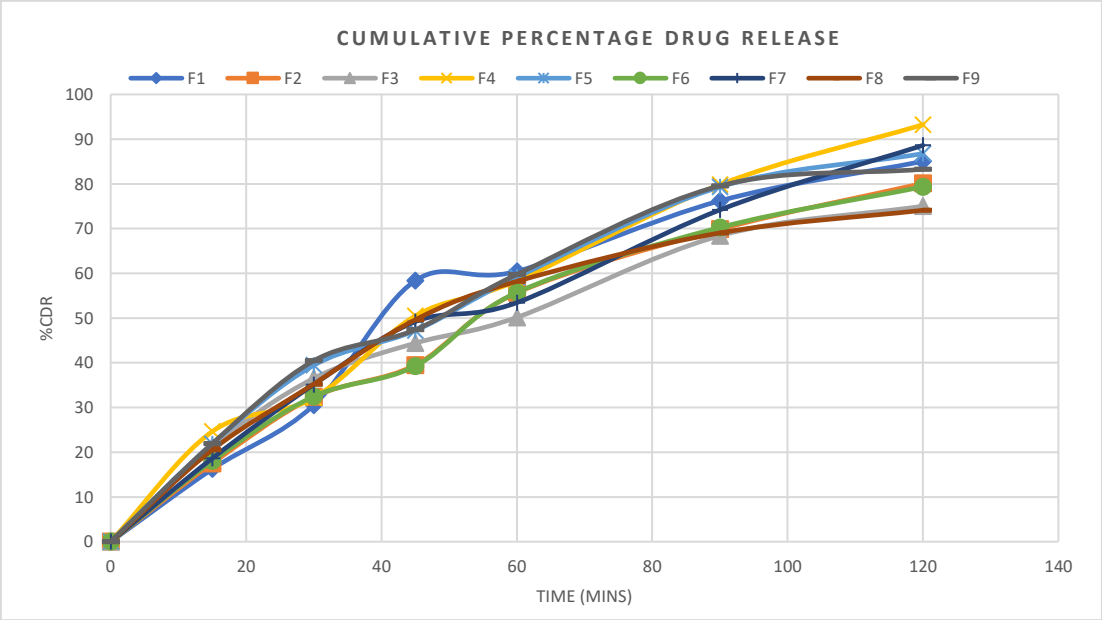


Figure 12 %CDR graph

Kinetic Release Profiles

The release data of optimized Nanosuspension F4 was fitted to various kinetic Models such as zero order, first order in order to Conclude the mechanism of release of PCP from the nanoparticles. The drug release pattern of the Formulations F4 shows best fit with the highest Correlation coefficients in first order.

Table 12 Release kinetics for optimized nanosuspension

PLOT	SLOPE	INTERCEPT	CORRELATON	R^2
ZERO % CDR Vs T	0.754203593	10.16095808	0.979346761	0.959120079
FIRST ORDER Log% Remain Vs T	-0.00937516	2.069898053	-0.986868276	0.963534748

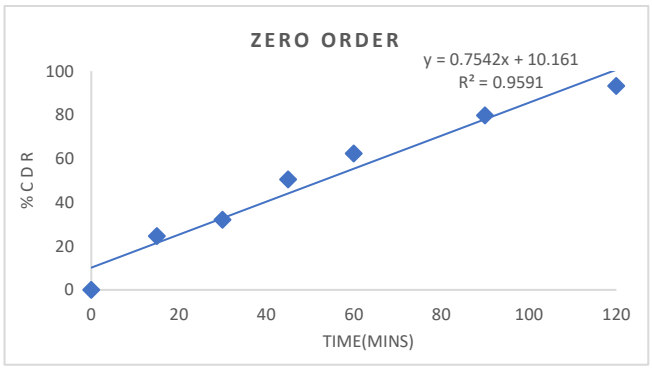


Figure 13 zero order kinetics

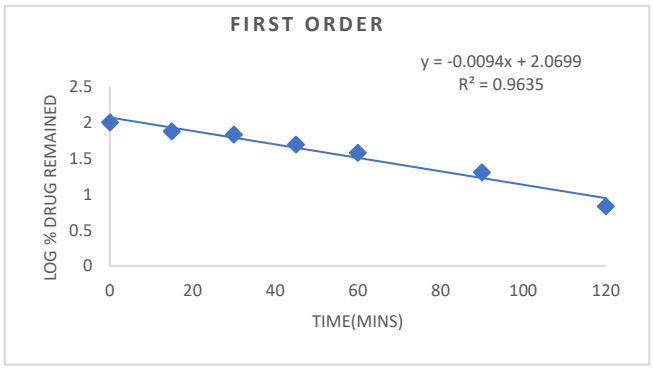


Figure 14 First order kinetics

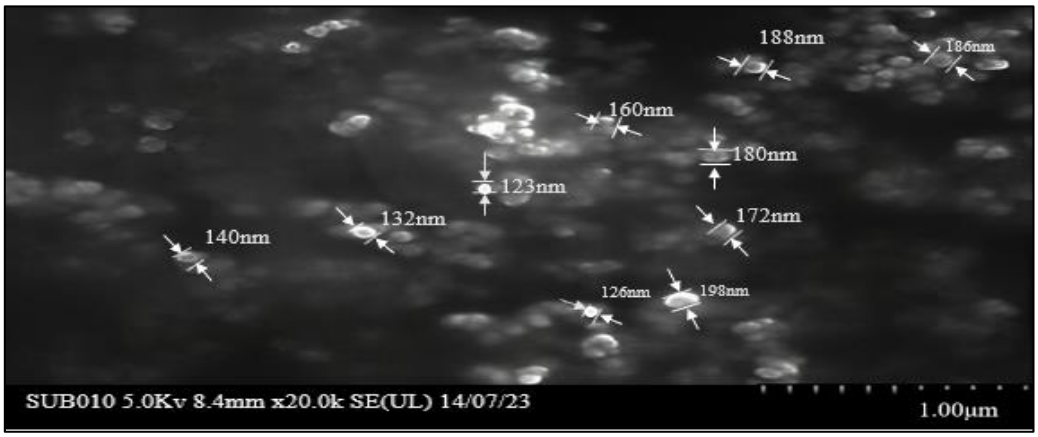


Figure 15 SEM of optimized Nanosuspension

Surface morphology and shape of optimized formulation studied utilizing SEM (JEOI, Japan). The nanoparticles showed smooth surface **(fig. 4.17**). The nanoparticles were observed to be, with a smooth surface and almost spherical and uniform. In a SEM study, the nanoparticles' surface morphology and patterns visualized

STABILITY STUDIES

The stability of PCP nanosuspension-F4 in terms of droplet size & % DC was estimated at 0, 1, 5,12, 20 & 30 days upon storage at specific temperatures of 4 ˚C & 25 ˚C, the droplet size and % drug content showed slight change over time but it was found to be negligible.

Table 13 stability of nanosuspension at 4 ˚C and 25 ˚C

Assessment Parameter	Temperature	Number of days					
		Day 0	Day 1	Day 5	Day 12	Day 20	Day 30
Droplet Size (nm)	4 ˚C	162.0	162.2	162.8	163.2	164.3	164.2
	25 ˚C	162.0	163.2	169.4	174.2	181.2	190.6
% Drug Content	4 ˚C	94.15	94.15	94.10	94.8	93.8	93.5
	25 ˚C	94.15	94.10	94.10	94	93.6	93.4

CONCLUSION

In the present research work a central composite design was utilized to optimized Prochlorperazine Nanosuspension to enhance its low dissolution rate. Prochlorperazine is an antiemetic drug belongs to BCS class-II (Low Solubility and high permeability). It has poor bioavailability and low solubility. In the current work, we had prepared Nanosuspension using nanoprecipitation method by using different concentrations of PVP-K30, tween 80. In this method the particle size of PCP was obtained in nano-size by incorporation of suitable concentration of surfactants and stabilizer. The dissolution of nanosized PCP suspension is significantly enhanced by the used nanoprecipitation method. Stability study of optimized formulation F4 was proven to be stable after storage at different temperature condition. Thus the method is simple and effective to develop submicron particles of poorly water soluble drugs.

FUTURE SCOPE

In the future, the PCP formulations can be further evaluated for in-vivo studies

Prepared formulation can be compared with marketed formulations.

Stability studies can be further extended as per ICH guidelines.

IVIVC correlation can be done.

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