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Preparation, Characterization and *In Vitro* Evaluation of Nanosuspension for the Treatment of Schizophrenia

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ABSTRACT

The current study aims to construct a perphenazine oral nanosuspension utilizing the solvent evaporation technique with a variety of stabilizers and surfactants, including PVPK30, Pluronic F127, urea, and SLS. In order to obtain desired size and saturation solubility, several as well as process factors were tuned. Particle size, zeta potential, saturation solubility, dissolving rate, morphological study (SEM), and in-vitro dissolution study were all used to characterize the produced Nanosuspension. The improved formulation's (F12) zeta potential value was discovered to be -7mv, which was determined to be within acceptable bounds. It was discovered that the average particle size of optimal formulations (F12) in nanosuspension was 118 nm. According to the in vitro investigations, formulation F12 exhibits the greatest 98.65% of the medication is released within 30 minutes. The drug was not released for minutes by any of the other formulations. Understanding how the release of drugs via Nanosuspension functioned was aided by the application of mathematical formulae that included zero out, and first out, method equation. R^2 analysis revealed that the enhanced 1st order kinetics by F12.

Keywords: Perphenazine, PVPK-30, Poloxamer 184, Pluronic F127, Urea, SLS.

INTRODUCTION

As pharmaceutical scientists get a greater grasp of the physicochemical and biological characteristics important to their effectiveness, drug delivery devices are becoming more advanced. Despite enormous benefits in drug delivery, oral-administration-of-active agents continues to be the favoured route due to the low cost of treatment & convenience of administration, which results in high patient compliance. However, this high-throughput screening method hasn't done much to solve problem of oral medication candidates' low bioavailability.[1]

No of OD systems are been formed during the past 20years to serve as reservoir of drug from which active material may be delivered over a certain time period at a predefined and regulated pace.[1]

The primary goal of oral controlled DDS design should be to maximise bioavailability and make it more predictable. The majority of pharmaceutical experts nowadays are working to create the ultimate DDS. The benefit of a single dosage for the length of therapy would be a feature of the ideal system, and the active medicine would be delivered directly to the desired place[2]. Controlled release refers to

the capacity to predictably and repeatedly regulate the drug release, the concentration of the drug in the target tissue, and the optimization of a medication's therapeutic impact by regulating its release in the body at a lower and less frequent dose. However, there are a number of physiological challenges with this strategy, including the inability to constrain and identify the controlled drug delivery system in the targeted GIT area.

The oral route is preferred for many medications due to its various benefits (figure), especially when it comes to giving antibiotics like asatovaquone and bupravaquone[3].

Its solubility & bioavailability will enhance by making it nanoscale. In comparison to naproxen nanosuspension and naproxen tablets, oral-administration of naproxen-nanoparticles results in an area under the~curve(0-24 h) of 97.5 mg-h/l. The absolute bioavailability of danazole (a gonadotrophin inhibitor) in nanosuspension is 82.3, compared to 5.2% in traditional dispersion[4,5].

The current study aims to construct a perphenazine oral Nanosuspension utilizing the solvent evaporation technique with a variety of stabilizers and surfactants, including PVP K30, Pluronic F127, urea, and SLS.

MATERIALS AND METHODS

Perphenazine was obtained from Xenon Pharma Pvt Ltd. Urea, Pluronic F127, SLS and PVP K30 were procured from Rankem, Mumbai.

Studies of Pre-Formulation:

Preceding the making of the measurements structure, it is fundamental to decide a couple of principal physical and synthetic properties of the medication particle, both all alone and when joined with excipients. The goals of pre-formulation studies are: Analyze the drug substance and identify its most important characteristics to learn how successfully it capabilities with various excipients[5].

Capillary method:

The mp of a material is thought to be the temperature the first particle totally melts. The mp range is defined as the temperature range between first particle to start melting is the last one to finish melting[6].

Solubility studies:

Perphenazine's solubility was assessed in phosphate buffers with a pH of 1.2, 6.8, and 7.4 as well as in methanol and ethanol. Perphenazine was taken in excess and dissolved in various beakers of different solvents to conduct solubility investigations. mixes were agitated in a rotary shaker for 48 hours. After centrifuging the solutions for ten minutes at 1000 rpm, the supernatant was analysed using UV Spectrophotometry at 246 nm[6].

Drug-Excipient Interactions Studies:

Infrared spectroscopy is one of the most effective analytical techniques for chemical identification. The IR spectra were produced using the KBr pellet method. Perkin-Elmer Series 1615 FTIR Spectrometer)[5]

FORMULATION CALIBRATION CURVE OF PERPHENAZINE:

pH standard curve:

10 mg of perphenazine were broken up in 10 ml of pH 6.8 by a light shaking (1000 g/ml). Up to 10 ml of this solution, which had a pH of 6.8, had a concentration of 100 grams per milliliter (stock solutions). At a pH of 6.8, levels of 5, 10, 15, 20, 25, and 30 grams per milliliter were produced from the stock solution[6].

Methods of Formulation of Nano-suspension:

Using the solvent evaporation technique of emulsification Nanosuspension was produced using the emulsification and solvent evaporation process. Perphenazine has been dispersed in methanols. The solution is then emulsified with a number of stabilizers, all retained at room temperature, comprising PVP K30, SLS, Pluronic F127, and urea. injecting water-containing

stabilizing agents with organic solvents using a syringe, then agitating the mixture with a stirrer that is magnetic to permit the unstable dissolvable to dissipate[7]. Evaporation causes the medicine to precipitate (Table 1).

Table 1: Formulation chart

Drug + POLYME R	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Perphenazine (mg)	80	80	80	80	80	80	80	80	80	80	80	80
Urea	25	50	75	100								
P V P K-30					25	50	75	100				
Pluronic F 127									25	50	75	100
S L S	10	10	10	10	10	10	10	10	10	10	10	10
Methanol	5	5	5	5	5	5	5	5	5	5	5	5
Water(ml)	40	40	40	40	40	40	40	40	40	40	40	40

Criteria for evaluating nano suspension Perphenazine[8-11]:

Entrapment-efficacy:

Using a cold ultracentrifuge, the freshly made nano suspension was centrifuged 20 minutes at 20,000 rpm 5°C temperature. drug may be determined by measuring the absorbance of the appropriately dilute 5 ml of supernatant solutions 246 nm.

$$\%\text{Entrapment efficiency} = \frac{\text{drug content} * 100}{\text{Drug in dosage}}$$

Scanned electron microscope

It is used to examine the morphological characteristics of Perphenazine nanosuspension at various magnifications.

Particle size & shape:

Using water as the dispersing medium, the Malvern Zeta sizer ZS was used to measure the average size and shape of the synthesised nanosuspensions. To decide the molecule size, the example was checked multiple times.

***In vitro studies*:**

900 ml of 6.8 pH buffer was used as the dissolving medium in an experimental dissolution study conducted with a USP dissolving apparatus of type II. The temperature of the media was kept around 37 0.5 °C and the stirring speed was set at 50 rpm.

Five millilitre samples were obtained at specified intervals of time from the freshly made nanosuspensions in the dissolving solution, which were filtered via a 0.45 m filter cloth before being analysed at an intensity of 246 nm to ascertain their drug concentrations.

Zetapotential:

One of three systems exists for a strong particle (colloid) distributed in a fluid medium to get a surface charge. The first method involves the solution's electrons' attraction. Second, by ionizing practical gatherings that have been surface-addressed. Thirdly, since the particle and the medium have different dielectric constants. The development of an electric double layer at the solid-liquid boundary requires attention. It is defined as the diff in potential btw the solution's electro-neutral area and the firmly bonded layer's surface (shearplane). As you get further from the surface, the potential steadily drops.

The zeta potential rapidly decreases when the amount of electrolyte in the medium rises as a result. It can't be directly measure, but it may be derived experimentally obtained electrophoretic mobility data and theoretical models. The electrophoresis-based hypothesis is summarised as follows:

$\mu = \zeta\varepsilon/\eta$

RESULTS AND DISCUSSION

Study of Solubilzation:

at 25^0C by Methanol, Ethanol,0.1N HCL,6.8 phosphate buffer, and 7.4pH buffer.

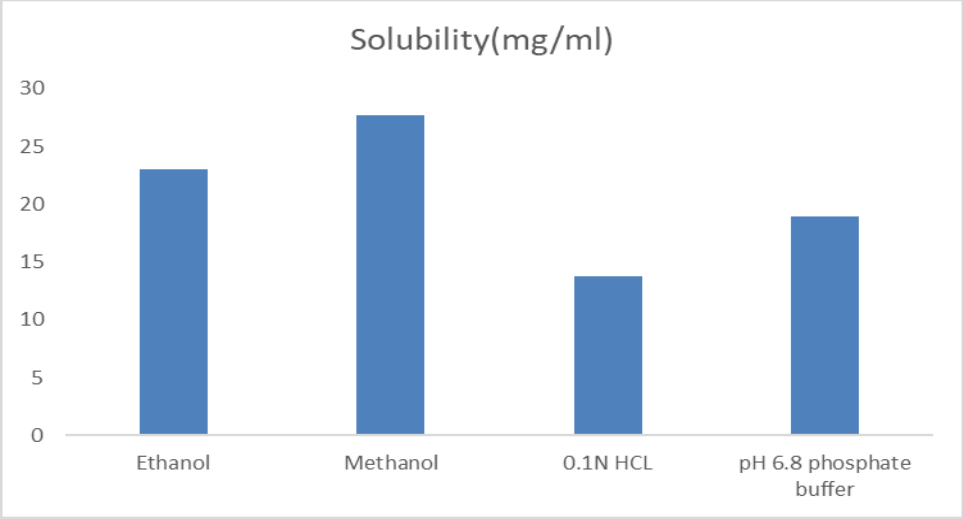

Figure 1: Solubility of Perphenazine

Discussion: According to the aforementioned solubility tests done in several buffers, pH 6.8 phosphate buffer is more soluble than other buffer solutions. Because methanol has a higher solubility than other organic solvents, it was chosen in the formulation of the nanosuspension. 6.8 pH buffer is used as the dissolving buffer.

Determining λ-max:

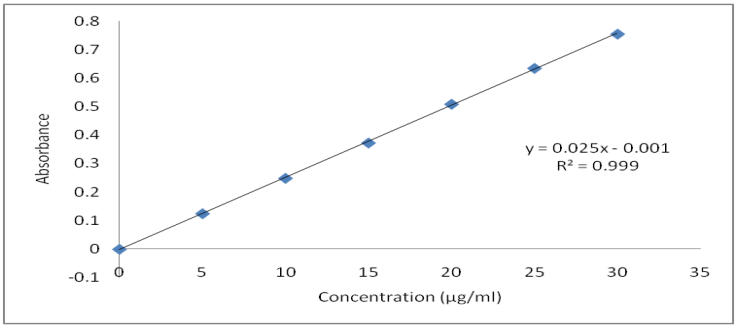

Figure 2: Determining the λ-max in pH6.8 buffer medium

The linearity was discovered to be between 5 and 30 g/ml in an acetone buffer at a pH of 6.8. As the regression value at 1.

Compatable studies the compatibility of the drug and excipient was established by comparing the spectra of the pure drug from the FT-IR analysis with those of the various excipients used in the formulation.

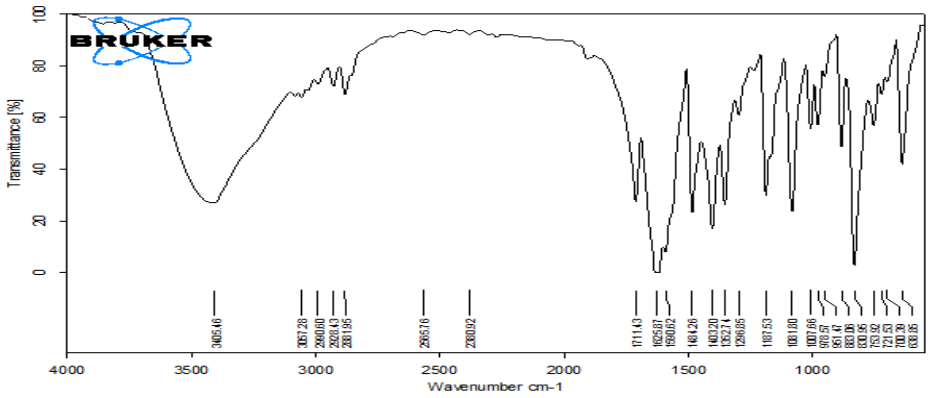

Figure 3: FTIR of Pure drug

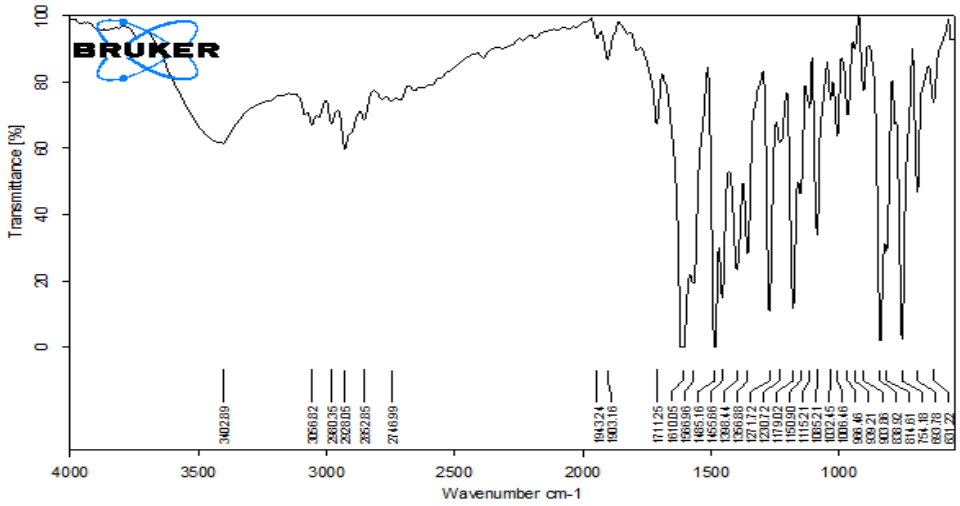

Figure 4: FTIR of Optimized drug

The findings of the study on the compatibility of drug excipients show that there are no interactions among the perfect formulation (Perphenazine+ excipients) and the pure drug (Perphenazine), which shows that no physical changes have taken place.

Entrapment Efficiency: -This was found in the range of 82.46%-98.52% respectively.

Table 2: %EE of the prepared formulations

Codes	% EE
F 1	83.23
F 2	85.15
F 3	87.45
F 4	89.63
F 5	88.23
F 6	97.14
F 7	93.26
F 8	95 .15
F 9	97 .26
F10	82.46
F11	98.52
F12	94.27

Discussion: Formulation-F1's entrapment effectiveness was determined to be 83.23%. F2 85.15%, F3 87.45%, F4 89.63%, F5 88.23%, F6 97.14%, F7 93.26%, F8 95.15%, F9 97.26%, F10 82.46%, F11 98.52%, F12 94.27%.

SCANNING ELECTRON MICROSCOPY:

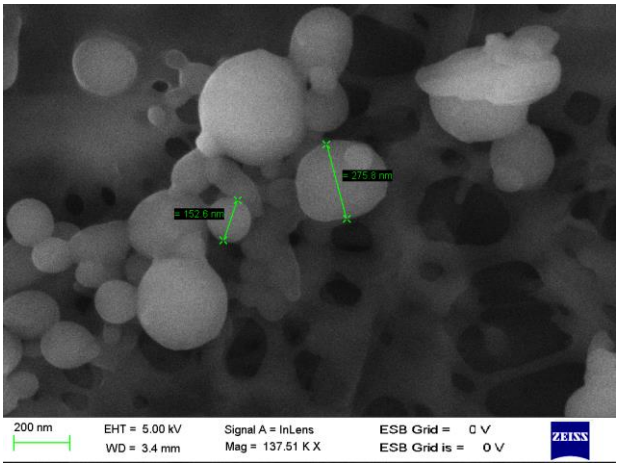

Figure 5: SEM of Optimized formulation

7.7. "zeta-potential":

The test is actually an electron electrophoresis, and the speed of the not entirely settled by the doppler shift of the dispersed laser light. The applied field strength was 20 V/cm. The Helmholtz-Smoluchowski equation was used to convert the electrophoretic mobility into the zeta potential in mV. This equation can be simplified to the form ZP in mV by multiplying the observed electrophoretic mobility (m/cm per V/cm) by an integer of 12.8, which occurs under typical measurement conditions (water, room at 25°C).

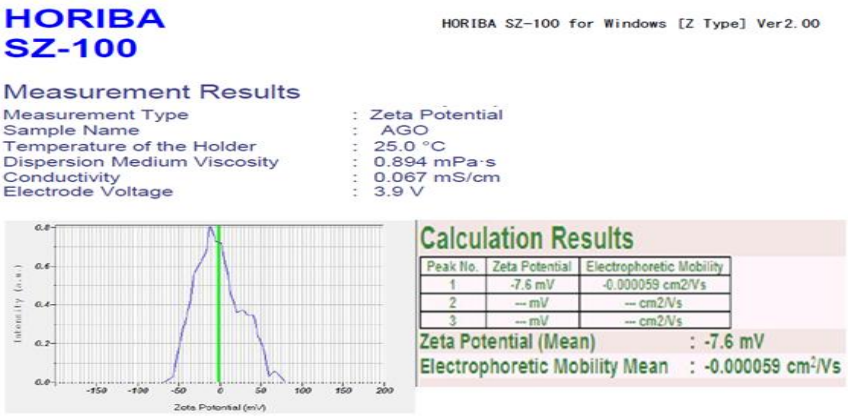

Figure 6: Zeta potential of Optimized formulation

Discussions: The optimized formulation's (F6) zeta potential value was determined to be within acceptable bounds.

Polydispersity index (PDI):

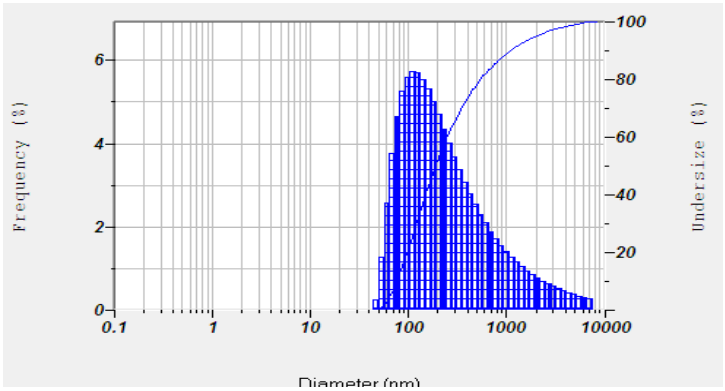

Figure 7: PDI of Optimized formulation

It was discovered that the average Nano-suspension particle size of the optimized formulations (F6) had the largest particles in a range of 118 nm.

Dissolution results:

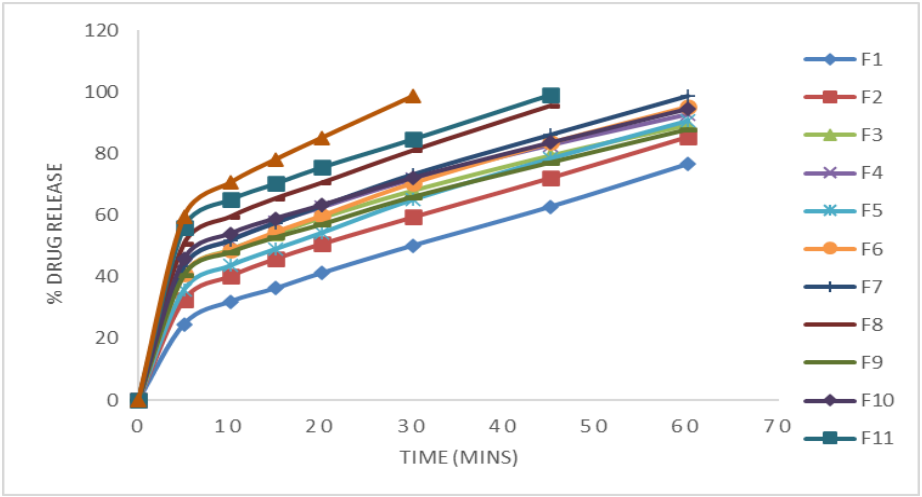

Figure 8: % drug release of prepared formulations

According to the aforementioned in vitro tests, all formulations' dissolving times decrease as polymer concentrations rise. We may infer from the aforementioned in vitro investigations that the drug release time was prolonged at low polymer concentrations. F12 is therefore regarded as an optimal formulation as it demonstrates drug release within 30 minutes. Comparing formulations made with PVP K30 and urea to those made with the other three stabilizers, we found that F12 including Pluronic F127 at a concentration of 1.0% results in the highest release at 30 minutes. Increase in Pluronic F127 stabilizer content reveals 98.65% of drug release, meaning formulations made with Pluronic F127 release more medication after 30 minutes than other stabilizers.

CONCLUSION

The current work, perphenazine nanosuspensions were made by evaporating the emulsification solvent. Due to their ease of manufacture and variety of applications, Nanotechnology suspension is a brand-new, possible target or controlled-release form of administration that have begun to appeal. Biodegradable polymer is now being employed more and more in drug development because to its accessibility and low toxicity.

Utilising a combination of urea, pluronic-F127, pvp-k30, SLS, a solution of & sufficient water, a nanosuspension containing medication was made using the emulsification solvent evaporation method. At 246 nm, the concentration of perphenazine was estimated spectrophotometrically.

The nanosuspension (FTIR) was evaluated using a variety of parameters, including the homogeneity of the drug content, sem, size of particles measurement, zeta potential, then in-vitro discharge, and drug-excipient interactions. Indicators were

According to the in vitro investigations, formulation F12 exhibits the best drug release, with a rate of 98.65% within 30 minutes, whereas none of the other formulations released the medication. Understanding how the Nanosuspension's drug release worked was made easier with the help of mathematical model equations like zero order, first order, and equation approaches. It was determined based on the regression data F12 i.e first order kinetics. utilized stability data as well.

The melting point for perphenazine was calculated using the capillary method and was discovered to be between 177°C and 178°C.

Immersion dissolvability was done at 250C utilizing 0.1N HCL, 6.8ph support, a 7.4 pH cushion, an answer of and ethanol.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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