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FORMULATION AND EVALUATION OF NANOSUSPENSION DRUG DELIVERY SYSTEM OF FLUCONAZOLE PRODUCED BY NANOPRECIPITATION METHOD

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Abstract:
The present research aimed to develop & Evaluation of Fluconazole Nanosuspension. Fluconazole is a medication used to treat fungal infections. The formulated Nanosuspension was subjected to various evaluation parameters like particle size, polydispersity index, zeta potential, drug content, saturation solubility studies, In vitro release studies. The polydispersity ranged from 0.40 PDI to 1.36 PDI and zeta potential ranged from -17.51 mV to -35.42 mV are the important evaluation parameters are responsible for the stability of nanosuspensions. In this result, F3 formulation shows spectacular drug content range of 76.89 % to 98.97 % it is the maximum drug content. Fourier transform infrared spectroscopy indicated that there was no possible interaction between drug and polymer. In dissolution studies F3 formulation showed maximum drug release compared with other formulation. Hence F3 formulation was considered as optimised formulation. From this study, it was concluded that in recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance, one such approach is Nanosuspension.

Keywords: *Fluconazole, Carbopol, Ethyl Cellulose, Na CMC and Nanosuspension.*

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1. INTRODUCTION:

Oral Drug Delivery System:

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.[6]

1.3. NANOSUSPENSION

Pharmaceutical industries are always looking for new methods in order to obtain adequate oral bioavailability, as most of the biological properties exhibiting NCEs are poorly Water-soluble. The increasing frequency of poorly water-soluble NCEs exhibiting therapeutic activity is of major concern to the development of new formulations in the pharmaceutical industry, which leads to low turnout in the development of new molecular entities as drug formulations are poor solubility and poor permeability of the lead compounds.[7]

Recently, the formulation of such drugs as nanoscale systems (which have a size below 1μm) has quickly grown as a new and novel drug delivery system. The major distinctive of these systems is the quick dissolution rate, which improves bioavailability after oral administration. The present article aims to review the nanosuspensions as an emerging and promising tool for the formulation of poorly soluble drugs.[8]

Nanotechnology is an emerging field in all areas of science, engineering and technology. It is a novel interdisciplinary area of comprehensive research that combines medicine and other life sciences. It offers a potential for unique and novel approaches with broad spectrum of application in cancer treatment including areas such as diagnostics, therapeutics and prognosis [9, 10]. The main advantage of particles in the nano-metric range is its improved physical and chemical properties. The major parameters in drug delivery include particle size, surface area, hydrophobicity, crystallinity and surface charge.[11] More than 40% of new chemical entities being generated through drug discovery programmes are poorly water soluble. The formulation of poorly water soluble drugs has always been a challenging problems faced by pharmaceutical scientists.[12] There are many conventional methods such as micronization, solubilisation using co-solvents, surfactant dispersions and precipitation technique has been developed for improving solubility of poorly water soluble drugs[13]. But these techniques show limitations to the drugs which are not soluble in both aqueous and organic solvents. Nanosuspension technology can be used to solve the problems associated with various approaches described earlier. Nanosuspension is colloidal dispersion of nano sized drug particles stabilized by surfactants. They can also define as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle. The diameter of suspended particle is less than 1μm in size.[14]

Need of Nanosuspension For bioavailability Enhancement:

Nevertheless, pharmacokinetic studies of BCS class-II drugs showed that they have a low oral bioavailability, which may be due to poor water solubility of drug. There are many classical pharmaceutical ways to improve drug dissolution rate such as dissolution in aqueous mixtures with an organic solvent, formation of ß-cyclodextrin complexes, solid dispersions and drug salt form. During last 20 years a new technology, reducing drug particle size, has been developed to increase drug dissolution rate.[15]

According to Noyes–Whitney equation, drugs with smaller particle size have enlarged surface areas which lead to increase dissolution velocity. Higher the dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation could further increase oral bioavailability of drugs. A nanosuspension is a submicron colloidal dispersion of drug particles which are stabilized by surfactants.[16]

MATERIALS AND METHODS:

LIST OF MATERIALS USED:

Fluconazole Provided by SURA LABS, Dilsukhnagar, Hyderabad.
Carbopol Purchased from Merck Limited, Mumbai (India)
Ethyl Cellulose Purchased from Merck Limited, Mumbai (India)
Na CMC Purchased from Merck Limited, Mumbai (India)
PVP k-30 Purchased from Merck Limited, Mumbai (India)

IST OF INSTRUMENTS USED:

Weighing Balance Sartourious
Dissolution Apparatus Labindia, Mumbai, India
UV-Visible Spectrophotometer Labindia, Mumbai, India
pH meter Labindia, Mumbai, India
FT-IR Spectrophotometer Bruker, Germany
Ultrasonic cleaner Remi Laboratories
SEM JEOL Ltd.,Japan
Homogenizer Kinematica AG(Poly tron PT2100)
Rotary evaporator Super fit Instruments, Mumbai
Vacuum Pump SH TID-75, Oil free diaphragm type
Lyophilizer Lyophilisation systems India PVT LTD
Particle size analyzer MALVERN
Zeta potential analyzer MALVERN

METHODS

Analytical method development for Fluconazole:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmax was found to be 210 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in 0.1 N HCl

100 mg of Fluconazole was dissolved in method 5ml, volumetric flask make up to 100ml of 0.1 N HCl., From primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of 0.1 N HCl, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of 0.1 N HCl, to produce 5, 10, 15, 20 and 25µg/ml respectively. The absorbance was measured at 210 nm by using a UV spectrophotometer.

Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

DIFFERENTIAL SCANNING CALORIMETRY (DSC):

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

PREPARATION OF FLUCONAZOLE NANOSUSPENSION BY NANOPRECIPITATION TECHNIQUE

The Nanosuspension was obtained by the Nanoprecipitation method. The drug Fluconazole was initially dissolved in 10 ml of methanol it is organic phase. The organic phase was slowly added drop wise with syringe in 10ml of Water aqueous phase containing carrier PVP k-30, and surfactants SLS kept at room temperature with speed of 900-1000rpm. Speeds using Magnetic stirrers until all the drug solution completely added in to surfactant solution and methanol completely evaporate from the solution.

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fluconazole (mg)	150	150	150	150	150	150	150	150	150
Carbopol (mg)	0.5	1	1.5	-	-	-	-	-	-
Ethyl Cellulose (mg)	-	-	-	0.5	1	1.5	-	-	-
Na CMC (mg)	-	-	-	-	-	-	0.5	1	1.5
PVP k-30 (mg)	20	20	20	20	20	20	20	20	20
Surfactant SLS (mg)	20	20	20	20	20	20	20	20	20
Methanol (mL)	20	20	20	20	20	20	20	20	20
Water (mL)	10	10	10	10	10	10	10	10	10

EVALUATION OF FLUCONAZOLE NANOSUSPENSION

Particle Size Analysis:

The particle size analysis was carried out using Microtac blue wave particle size analyzer. Before measurement the samples has to be diluted with de-ionized water to obtain a suitable Concentration for measurement. The results obtained for particle size distributions were used to confirm the formation of nano-sized particles.

Scanning Electron Microscopy (SEM):

Surface morphology of the specimen will be determined by using a scanning electron microscope (SEM), Model JSM 84 0A, JEOI, Japan. The samples are dried thoroughly in vaccum desicator before mounting on brass specimen studies, using double sided adhesive tape. Gold-palladium alloy of 120°A Knees was coated on the sample sputter coating unit (Model E5 100 Polaron U.K) in Argon at ambient of 8-10 with plasma voltage about 20mA. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage of about 15KV with load current about 80mA.The condenser lens position was maintained between 4.4-5.1. The objective lens aperture has a diameter of 240 microns and working distance WD=39mm.

Zeta potential measurement:

Zeta potential of the suspension is measured by Malvern Zetasizer. The zeta sizer mainly consists of laser which is used to provide a light source to illuminate the particles within the sample. For zeta potential measurements this light splits to provide an incident and reference beam. The incident laser beam passes through the center of the sample cell, and the scattered light at an angle of about 130 is detected. Zetasizer software produces a frequency spectrum from which the electrophoretic mobility hence the zeta potential is calculated.

Thermal Analysis by Differential Scanning Calorimetry (DSC):

DSC scans of the prepared lyophilized powdered drug sample and pure drug samples were recorded using DSC- Shimadzu 60 with TDA trend line software. All samples were weighed (8-10 mg) and heated at a scanning rate of 10°C/min under dry nitrogen flow (100 ml/min) between 50 and 300° C. Aluminum pans and lids were used for all samples. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

Drug entrapment efficiency (DEE)

The freshly prepared Nanosuspension was centrifuged at 20,000 rpm for 20 min at 5 C temperature using cool ultracentrifuge. The amount of unincorporated drug was measured by taking the absorbance of the appropriately diluted 25 ml of supernatant solution at 210 nm using UV spectrophotometer against blank/control Nanosuspension. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken. The experiment was performed in triplicate for each batch and the average was calculated.

The entrapment efficiency (EE %) could be achieved by the following equation:

$$\text{Entrapment efficiency}\,(\%) = \frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \times 100$$

Preformulation study:

8.1. Identification:

Organoleptic properties

Table: Organoleptic properties

S NO.	Properties	Results
1	State	Solid
2	Colour	White
3	Odour	Odorless
Melting point determination		
4	**Reported Melting Point**	**Observed Melting Point**
5	138 to 140	139.3

8.2. Solubility studies

Table: Solubility studies of drug in different solvents

S NO.	Solvents	Solubility of Fluconazole
1	Water	Freely soluble
2	Methanol	Sparingly soluble
3	Acetone	Freely soluble
4	Alcohol	Soluble
5	0.1N HCl	Soluble

Table: Solubility studies of drug in different media

S NO.	Solvents	Solubility of pure drug (µg/ml)
1	Water	0.512 ±0.01
2	0.1N HCl	0.256 ±0.02
3	Phosphate buffer pH 6.8	0.551 ±0.03

From the solubility studies it was observed that the Fluconazole have higher solubility in 6.8 pH buffer than the other buffers.

8.3. Analytical Method

Table: Observations for graph of Fluconazole in 0.1N HCl (210)

Concentration (µg/ml)	Absorbance
0	0
5	0.168
10	0.376
15	0.547
20	0.742
25	0.914

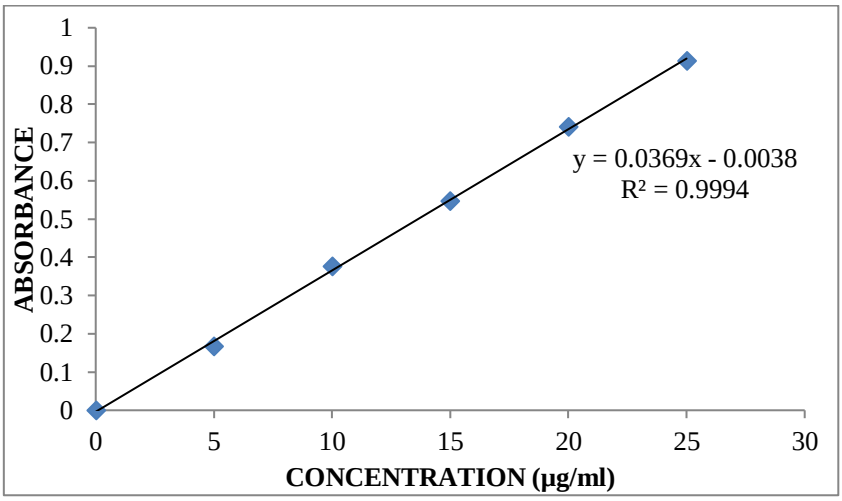

Figure: Calibration curve data of Fluconazole in 0.1N HCl

8.4. FTIR REPORTS

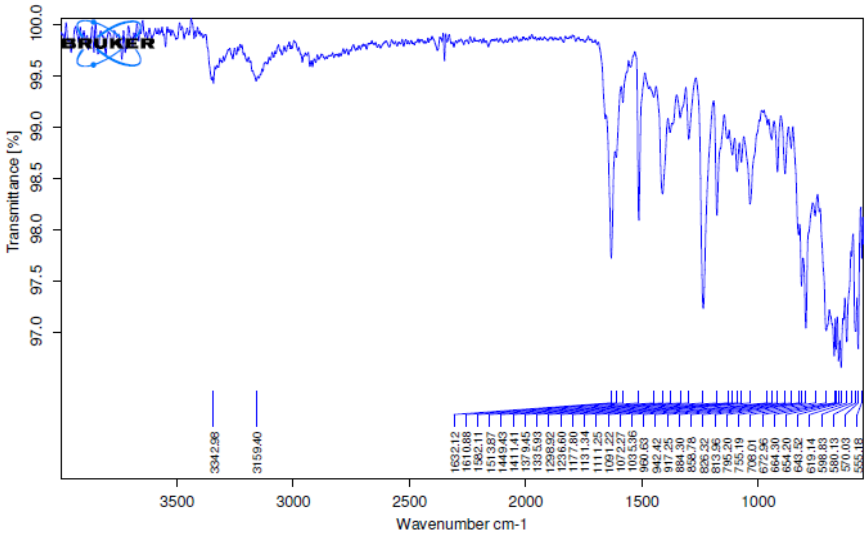

Fig: FTIR Peak of pure drug

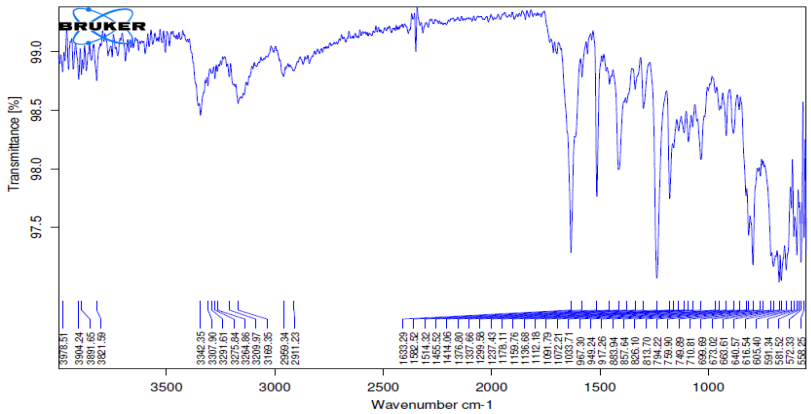

Fig: FT-IR Spectrum of Optimised Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Drug and excipients used in the preparation of different formulations.

8.5. DSC

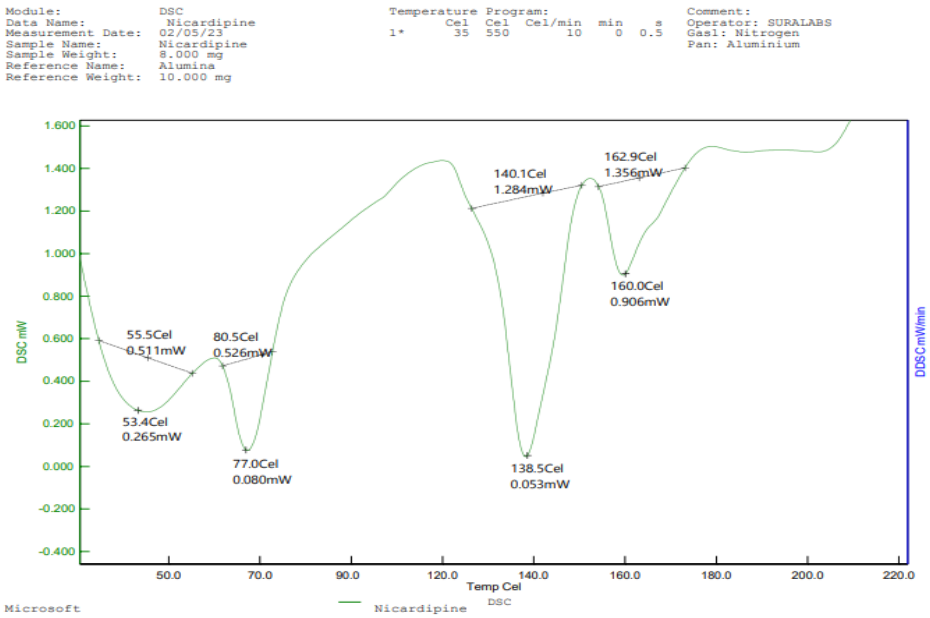

Fig: DSC spectra of pure drug

8.6. Characterization of Nanosuspension:

Table: Percentage yield, Drug Content, Entrapment Efficiency of all Nanosuspension formulations

FORMULATION	Entrapment Efficiency (%)	Drug Content (%)	Percentage yield (%)
F1	91.62	85.09	87.18
F2	93.06	92.50	90.15
F3	97.82	98.97	93.43
F4	82.06	82.14	73.34
F5	89.02	90.62	77.46
F6	93.89	91.71	85.24
F7	72.30	76.89	75.18
F8	84.81	85.60	83.05
F9	95.69	89.17	87.31

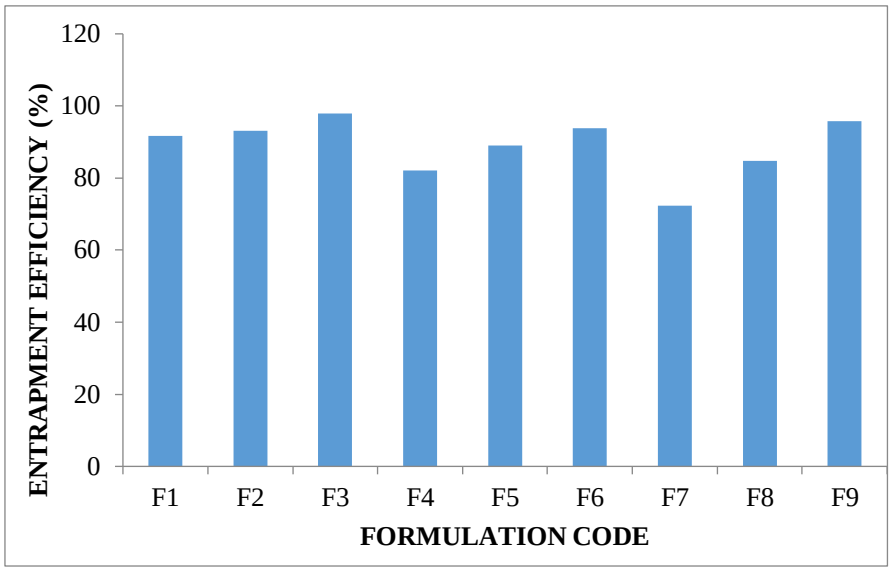

Figure: Entrapment efficiency of all Nanosuspension formulations

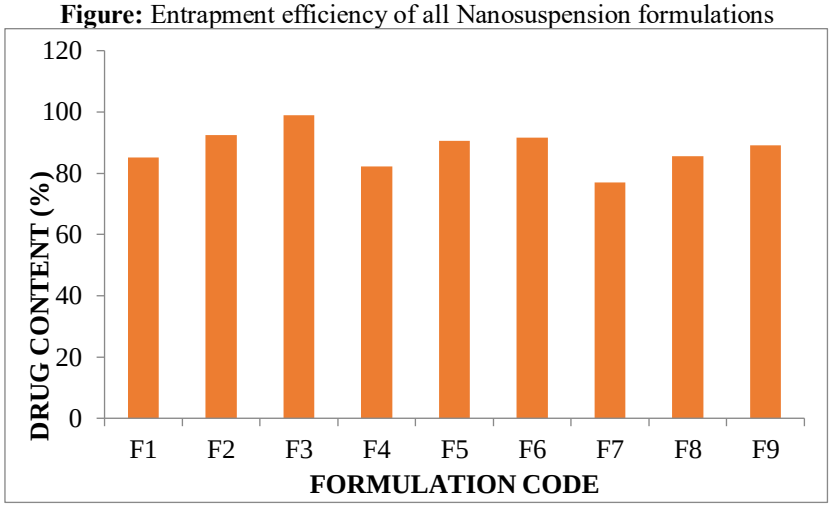

Figure: Drug content of all Nanosuspension formulations

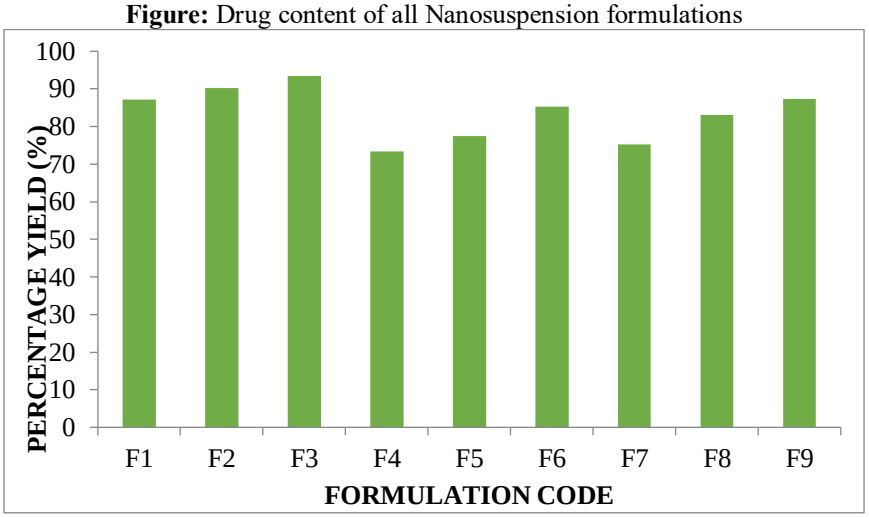

Figure: Percentage yield of all Nanosuspension formulations

Drug entrapment efficiency:

The formulations showed drug entrapment in the range of 82.06–97.82 %. Formulation (F3) containing drug concentration 16 mg/ml stabilized with Carbopol showed highest entrapment.

Table: Particle Sizes, PDI, Zeta Potential of all Nanosuspension formulations

FORMULATION	Particle Size (µm)	PDI	Zeta Potential (mV)
F1	5.0	0.81	-25.36
F2	4.1	0.60	-22.52
F3	3.2	0.40	-35.42
F4	4.5	1.15	-17.51
F5	5.2	0.68	-26.19
F6	4.5	0.56	-18.81
F7	6.2	0.58	-24.61
F8	8.9	1.24	-25.28
F9	9.5	1.36	-20.84

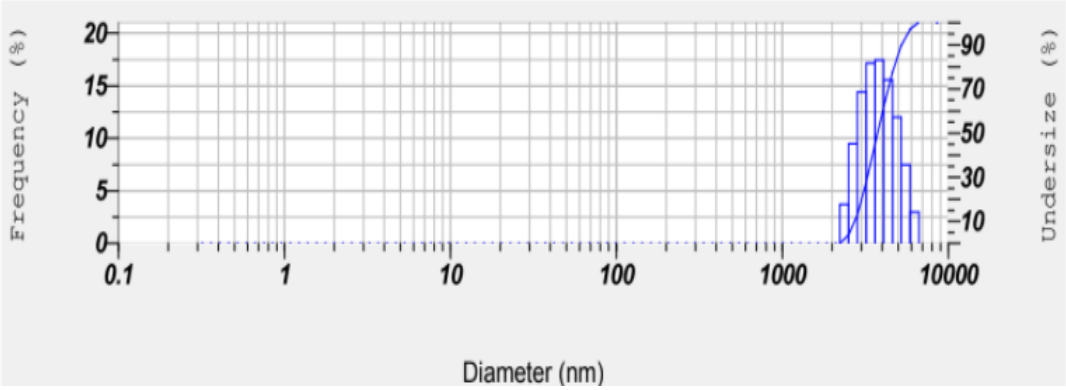

Fig: Particle Size of F3 Formulation

Particle Size Analysis:

The particle size distribution studies showed that all the formulation particle size was in the range of 3.8-9.5 nm. All the formulations having a particle size in the nanometer range and showing ideal surface morphology.

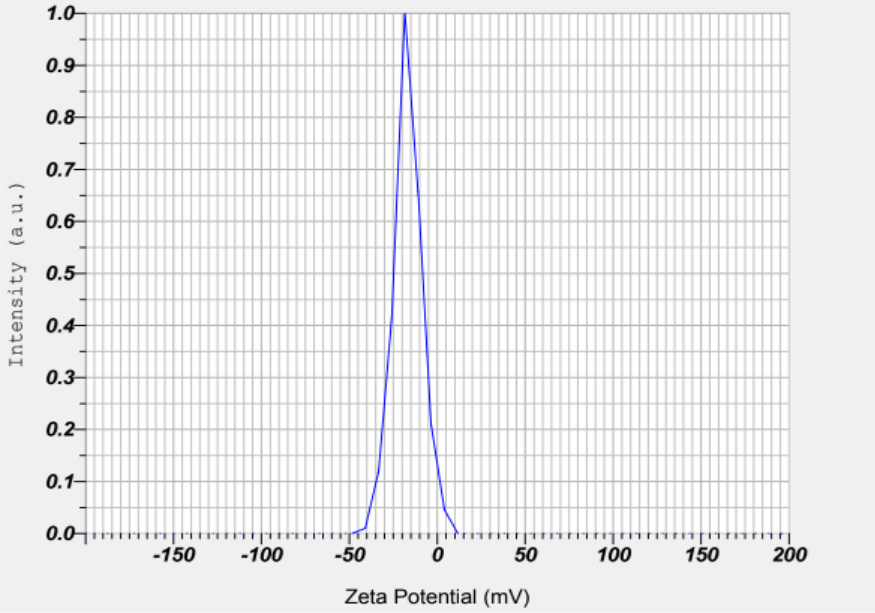

Fig: Zeta potential of F3 Formulation

Zeta potential is a term related to the stability of samples for molecules and particles that are small enough; high zeta potential will confer stability i.e.it resist aggregation. Here zeta potential of the prepared Nanosuspension was found to be -35.42, which would not allow aggregation.

Saturation Solubility and viscosity Determination

Table: Saturation Solubility and viscosity of various formulations

Formulations	Saturation solubility in water mg/ml	The viscosity of the dispersion medium
F1	0.782	0.893 mPa-s
F2	0.806	0.890 mPa-s
F3	0.864	0.898 mPa-s
F4	0.451	0.886 mPa-s
F5	0.595	0.871 mPa-s
F6	0.623	0.878 mPa-s
F7	0.501	0.873 mPa-s
F8	0.428	0.871 mPa-s
F9	0.642	0.872 mPa-s

8.4. IN-VITRO DRUG RELEASE CHARACTRISTICS OF FLUCONAZOLE NANOSUSPENSION

In-vitro release behavior of Fluconazole is summarized in tables; *in-vitro* drug release from the nanosuspensions in 0.1N HCL buffer was performed. The *in-vitro* drug release profile of nanosuspensions formulations obtained from experiment was shown in table.

TIME (MIN)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	20.92	27.90	53.06	21.15	33.54	41.03	10.43	13.14	17.41
10	24.86	36.98	68.19	30.25	48.22	53.19	16.96	20.94	23.75
15	40.78	47.56	71.47	41.76	52.19	65.42	23.09	28.37	31.14
20	45.05	54.71	79.99	50.91	54.59	69.71	32.14	35.19	38.43
25	50.11	65.98	86.03	56.24	65.32	74.86	38.27	42.24	45.18
30	54.59	70.35	90.38	62.86	71.73	79.90	43.19	48.83	51.27
45	58.62	89.99	96.60	65.34	78.81	84.61	49.34	60.14	65.54
60	71.14	92.47	98.12	70.63	82.62	87.55	60.15	67.72	73.78

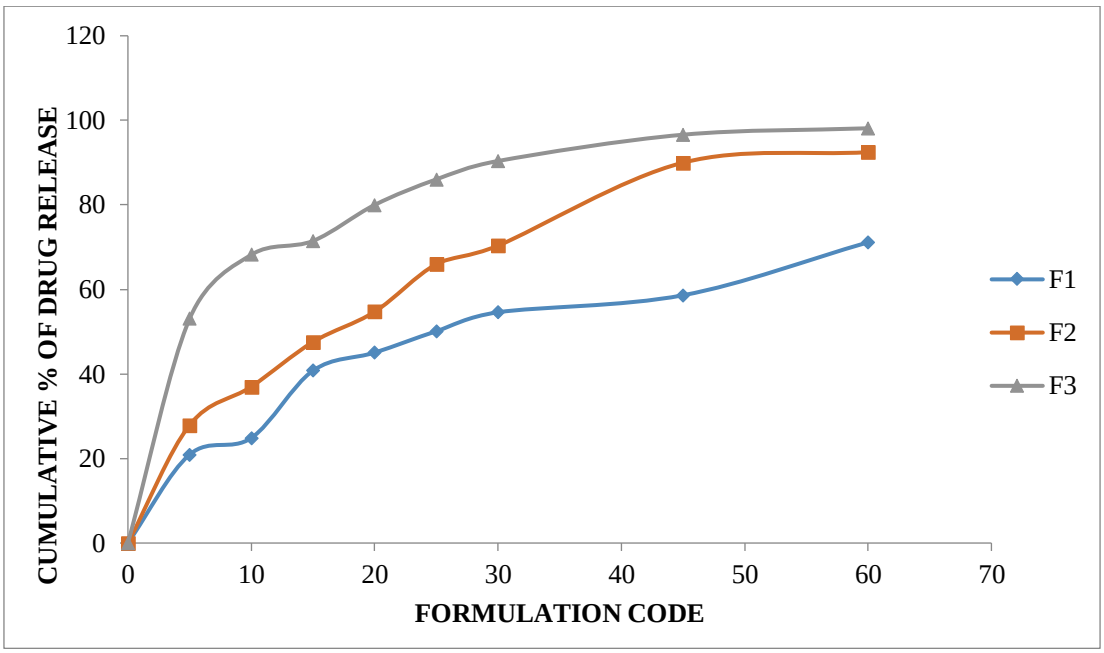

Figure: *In vitro* dissolution studies of F1-F3 Nanosuspension formulations

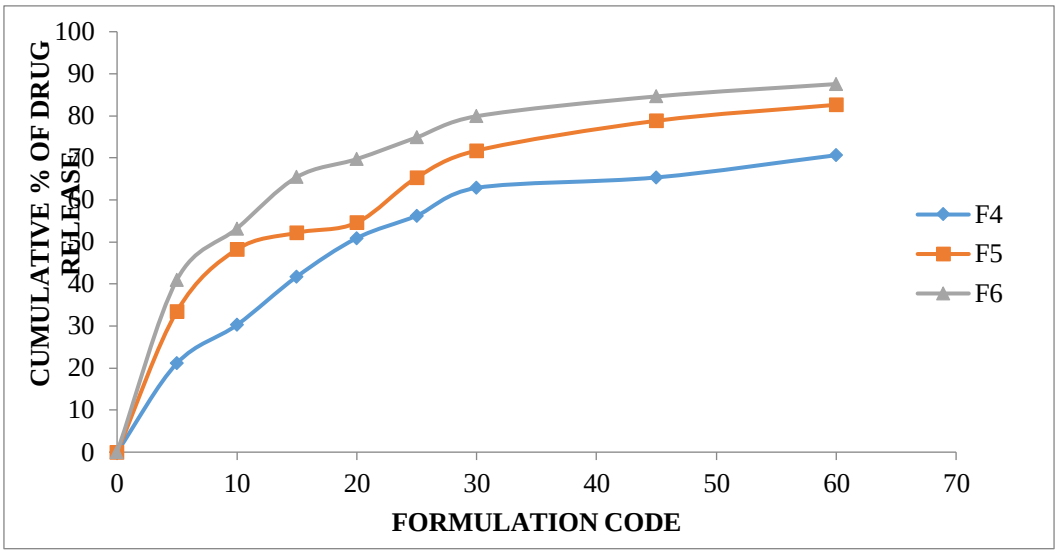

Figure: ***In vitro*** **dissolution studies of F4-F6 Nanosuspension formulations**

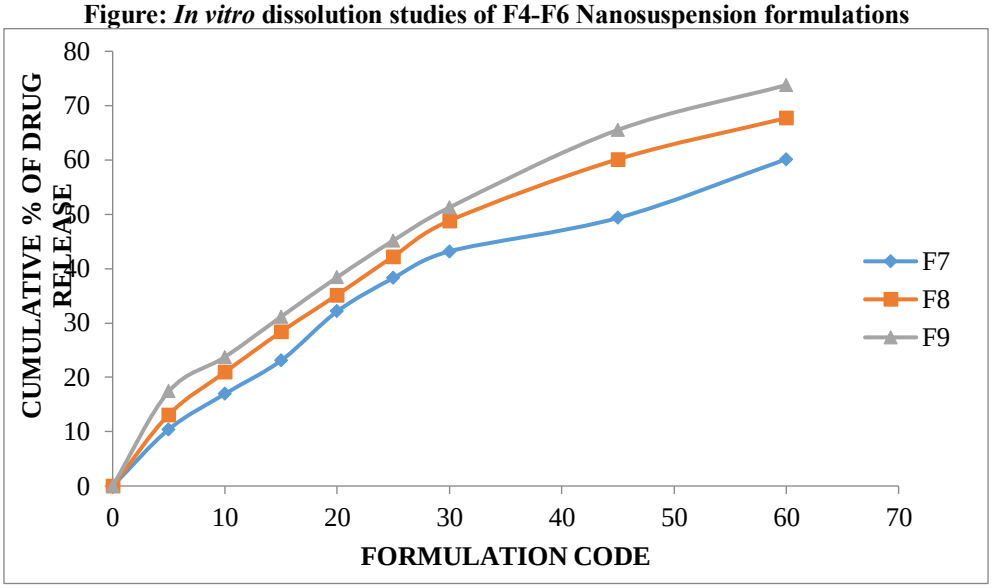

Figure: ***In vitro*** **dissolution studies of F7-F9 Nanosuspension formulations**

SEM

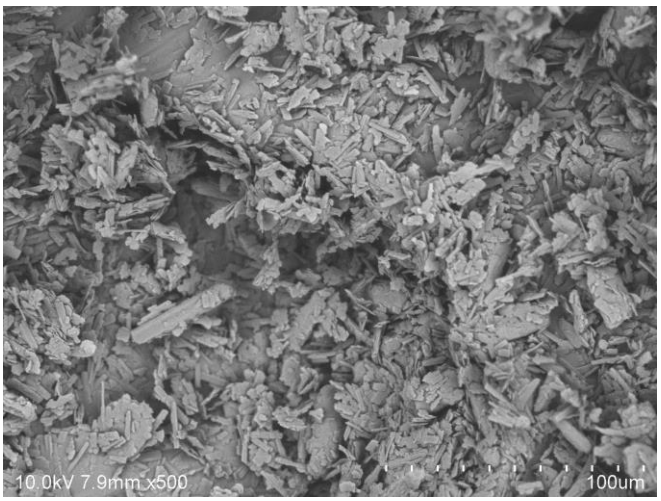

Figure: Fluconazole Nanosuspension optimised formulation (F3)

SEM studies showed that the Fluconazole - loaded Nanosuspension had a spherical shape with a smooth surface as shown in Figure.

9. CONCLUSION:

- ✓ Nanosuspension containing Fluconazole was prepared by Nanoprecipitation method using Carbopol, Ethyl Cellulose and Na CMC.
- ✓ Optimized Batch was subjected for % drug content, % Entrapment efficiency; Particle size Analysis, and *in vitro* drug release studies, indicate drug content was uniform and reproducible in all formulations.
- ✓ IR spectral analysis and DSC suggested compatibility between drug and formulation additive. Drug exists in original form and available for biological action.
- ✓ Nanosuspension which gave better physical, morphological and % encapsulation in either of Stabilizers and Excipients. Various Oral formulations with Fluconazole in free form and in Nanoparticulate delivery system were formulated and *in vitro* release studies were carried out.
- ✓ By considering all results of Check Point Analysis Nanosuspension It shows that saturation solubility of Nanosuspension is increased of Fluconazole. Also dissolution rate is increase therefore bioavailability of Fluconazole is increases.
- ✓ From the experimental result, it might be complete so the evaluation of your suspension, unconcealed that the following parameters for the customized formulation F3 are as follows saturation solubility, % Drug content 98.12%, average particle size 3.2 nm, polydispersity index 0.40, Zeta potential -35.42mv. The Carbopol used a polymer in F3 has shown effective cumulative drug release in 60min in comparison to any other formulations. The present study demonstrated successful preparation of Nanosuspension of Fluconazole.
- ✓ From study it can be concluded that it is possible to design Nanosuspension for Fluconazole may increase efficacy and patient compliance which are of prime importance.

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