INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD
ISSN(O): 2455-0620 [Impact Factor: 9.47]
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value : 86.87
Volume - 10, Issue - 6, June - 2024

DOIs:10.2015/IJIRMF/202406018 --:-- Research Paper / Article / Review

Preparation & Evaluation of Ziprasidone HCI Solid lipid Nanoparticle

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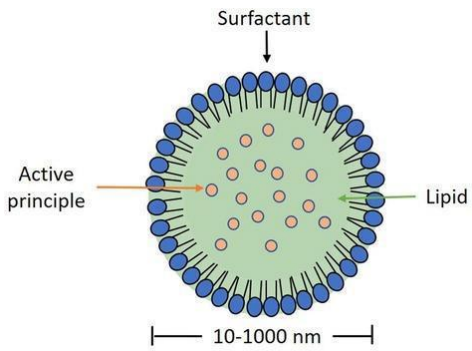
Abstract: *Solid lipid nanoparticles (SLN) have an average diameter ranging from 1 nm to 1000 nm, and they are usually spherical. It is a substitute for conventional colloidal carriers like polymeric micro and nanoparticles and liposome emulsions. Atypical antipsychotic drugs ziprasidone (ZP) are used to treat schizophrenia. It has about a 60% oral bioavailability. Since ZP is a class II medication, its solubility in water is low. The preparation of ziprasidone's solid lipid nanoparticles solves that issue and boosts its bioavailability. Formulation batches are created by adjusting the lipid concentration, surfactant concentration, stirring speed, and stirring duration using a custom experiment design. The SLN was prepared by using Solvent Injection Technique. Particle size analysis, drug entrapment efficiency, drug diffusion, and an in vitro drug release study were used to characterize. The results of this study suggest that ZP loaded solid lipid nanoparticles can deliver ZP more effectively and with fewer side effects. And the SLN preparation was turned into a unit solid dosage form that is capsule. To offer an appropriate method of SLN administration, SLN was combined with the excipient and fill the capsule. Following that, the prepared dried SLN stabilizes at room temperature.*

Key Words: *Ziprasidone, SLNs, Solvent injection technique, ZP SLNs Capsule.*

1. INTRODUCTION :

The four basic pathways of drug transport and modification in the body—absorption, distribution, metabolism, and excretion—determine a drug's therapeutic efficacy. Therapy failure can be attributed to a variety of factors, such as poor drug solubility, rapid metabolism and elimination, high fluctuations in plasma levels due to unpredictable bioavailability, and insufficient drug concentration caused by poor absorption[1].Creating an appropriate drug colloidal carrier system is a viable approach to solving these issues. Solid lipid nanoparticles are one of the colloidal carrier systems with numerous advantages over other colloidal carrier systems[2].Solid Lipid Nanoparticles (SLN) have garnered considerable interest lately as a possible substitute colloidal drug delivery method for liposomes and lipid emulsions. The benefit of SLN is that it shields the components inside the capsule from deterioration and offers greater control over drug release. Moreover, it provides improved bioavailability, selective biodistribution, and drug stability in vivo and in vitro[2,3]

Figure 1.1: general structure of solid lipid nanoparticle



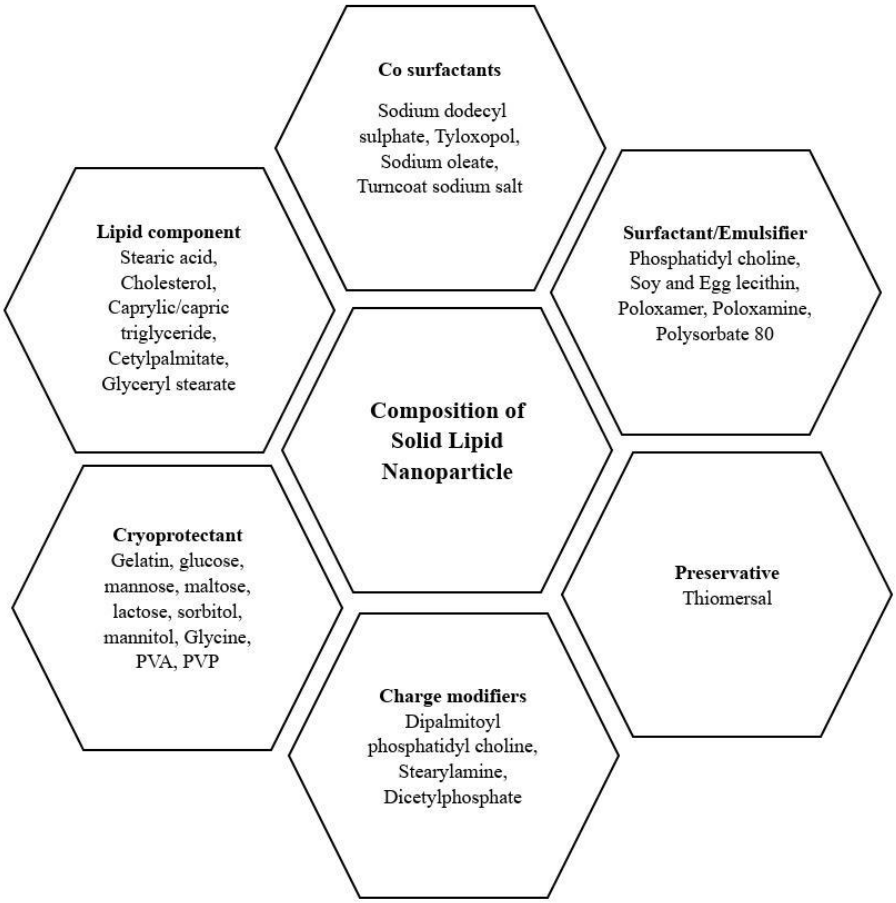
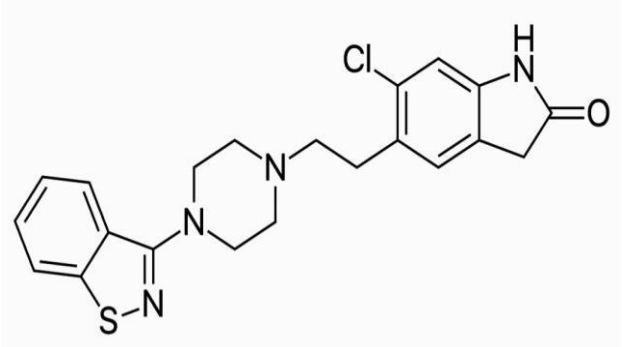


Figure 1.2 : composition of SLN

Despite developments in the field of neurology, schizophrenia is still a major global public health concern that negatively affects a person's ability to function in their personal, social, academic, and professional lives[4].Long-term mental illness called schizophrenia is characterized by a number of symptoms, such as hallucinations, delusional behaviour, disorientation in speech and behaviour, and cognitive impairment. Additionally, due to its negative and cognitive symptoms, schizophrenia is viewed as a disabling condition for both patients and caregivers due to its early onset and chronic nature[5, 6].Ziprasidone is used in schizophrenia. It is derivative of benzo-thiazolyl piperazine. Ziprasidone (ZP) is an antipsychotic. ZP is a type 2 dopamine (D2) blocker, a selective monoaminergic inhibitor with affinity for the type 1 and type 2 adrenergic receptors, the H1 histaminergic receptor, and serotonin type 2 (5HT2)[7,8].Drug transport to the brain is hampered by numerous factors, even though cerebral blood flow is comparatively high. The brain and its blood supply are separated by two physiological barriers that control drug delivery: the blood–cerebrospinal fluid barrier and the blood–brain barrier (BBB) [9].Ziprasidone belongs to BCS Class II.As it is belong to BCS Class II it have the poor solubility & high permeability. It is poor water soluble drug, which required a method which can enhance it's solubility.



2. MATERIAL & METHOD :

2.1. Material:

Ziprasidone HCL(Amepurva Forum Nirant Institute of Pharmacy), Lactic acid (LOBA CHEMIE PVT.LTD),Stearic acid(LOBA CHEMIE PVT.LTD), Magnesium stearate (LOBA CHEMIE PVT.LTD), Polysorbate 80 (LOBA CHEMIE PVT.LTD).

2.2 Method:

2.2.1: PREPARATION OF SLN

SLNs is prepared by using solvent injection method. This method contain mainly three step. First step is preparation of organic phase, second is preparation of aqueous phase, Third phase is drop wise addition of organic phase into aqueous phase. To prepare the first phase, Drug is dissolved in suitable organic solvent (in which drug is very soluble). And that solvent must be water miscible. Then add the lipid matrix in it & properly dissolve the lipid in it. Afterwards add required excipients. If drug have low solubility then apply the external force to it by providing sonication ,sonicate the organic phase for 10-15 min. In second phase water is mixed with surfactant & cosurfactant Or stabilizers & properly mixed. The third phase have dropwise addition of organic phase into aqueous phase , drug with lipid matrix is dropwise added into water & surfactant mixture with the continuous stirring on the magnetic stirrer at 1500 rpm, like that way SLNs was prepared. To obtain SLNs In solid form evaporate the organic solvent at some extend using magnetic stirrer at 350 rpm then centrifuge ,from which layers get separate .Remove the supernant & get the sample . Kept the sample 24hr in Desiccator & get dried SLNs.

2.2.2 : FORMULATION TABLE

	Drug(gm)	Lactic acid(ml)	Stearic acid(gm)	Polysorbate 80(ml)	Ethanol(ml)	Water(ml)
F1	0.6	5	-	1	40	40
F2	0.8	-	1.2	0.5	35	35
F3	0.8	-	1.2	1	40	40
F4	0.8	-	1.2	1	40	40

Table 2.1 : Formulation Table

2.2.3: EVALUATION OF SLNs

2.2.3.1: Particle Size Analysis

Sample is diluted in the proportion of 1: 10 in methanol. Sonicated for 10 minutes and filtered through Whatman filter paper. Filtrate is taken for analysis. Light from the laser light source illuminates the sample in the cell. The scattered light signal is collected with detectors, at a 90 degree (right angle). Keep sample in cuvette. Go to condition set and fill name of sample, Run time for 120 seconds and select glass cuvette as sample holder. Start measurement and view the report in nanometers for particle size. Result will show value of Mean, Mode, median, SD, PD and z Average for particle size with graph contains mean value.

2.2.3.2: Entrapment Efficiency

The entrapment efficacy (EE) of Solid lipid nanoparticles dispersion was determined by centrifugation method. The SLN dispersion was centrifuged at 2000 rpm for one hour and then collected the supernatant liquid of that dispersion. Then collected liquid was filtered to measure the free drug concentration after making the dilutions with freshly prepared phosphate buffer pH 7.4. The absorbance was measured at 266 nm. Following formula was used for the calculation of EE:

EE (%) = Amount of drug in NP (mg)/ Amount of drug added (mg) × 100.

2.2.3.3: Drug content

Take a known volume (e.g., 1 mL) of the prepared SLN formulation. Dissolve the SLNs by adding an appropriate solvent (e.g., methanol) & filter the solution. Use a UV spectrophotometer to measure the concentration of the drug in

the solution. Set the wavelength range 400nm to 200nm & check the absorbance at 266nm. & Calculate the total drug content using Beer's Law.

2.2.3.4:In vitro drug release :

In vitro drug release of ZP SLN was determined using type II Apparatus of IP(Basket) . The cellophane membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer (pH 7.4) at 37°C. The solution was stirred at 75 rpm. The ZP SLN was placed on cellophane membrane and the compartments were clamped together. One ml of sample was withdrawn at predetermined time for 1.5hours, from receptor compartments and immediately replaced using phosphate buffer after filtering through 0.45µm filter and appropriate dilutions, the sample were analysed for drug content at 318nm.

3. RESULT :

3.1: Preformulation study

3.1.1: FTIR of Ziprasidone HCL

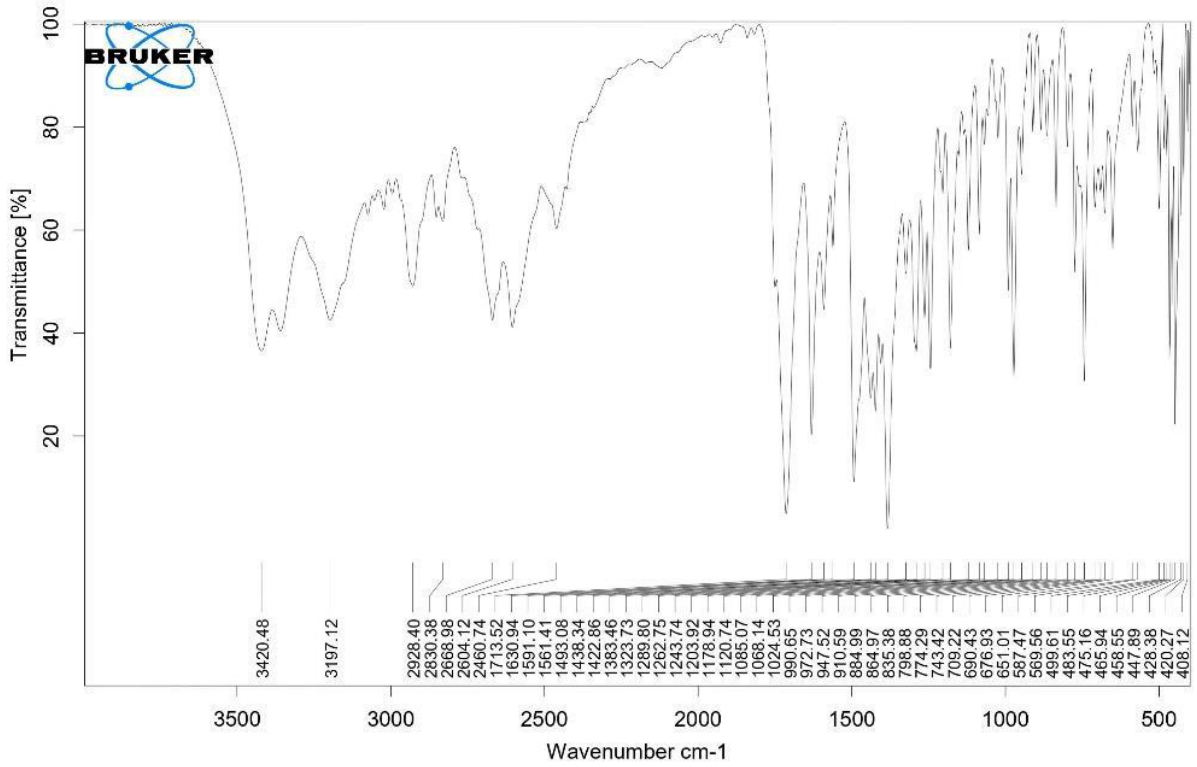


Figure 3.1: Systematic Representation of FTIR of Ziprasidone HCL

Sr. No	Reported range cm-1	Observed range (cm-1)	Functional group
1	3500-3400	3420.48	N-H stretch (1° Amine)
2	3000-2840	3197.12	N-H stretch (amine salt)
3	3000-2840	2928.40	C-H stretch (Alkane)
4	2830-2810	2830.38	C-H stretch (Aldehyde)
5	2600-2550	2668.98	S-H stretch (Thiols)
		2604.74	
6	1725-1710	1713.52	COOH stretch (Carboxylic acid)
7	1680-1620	1630.94	C=C stretch (Conjugated alkene)
8	1390-1310	1383.34	OH stretch (Phenol)

		1323.73	
9	995-905	990.65	C=C bend
		972.73	
		947.52	
10	850-550	835.38	C-Cl stretch (Halo compound)
		774.29	
		690.43	

Table 3.1: Interpretation of FTIR of Ziprasidone HCL

3.1.2: Drug Excipient Compatibility

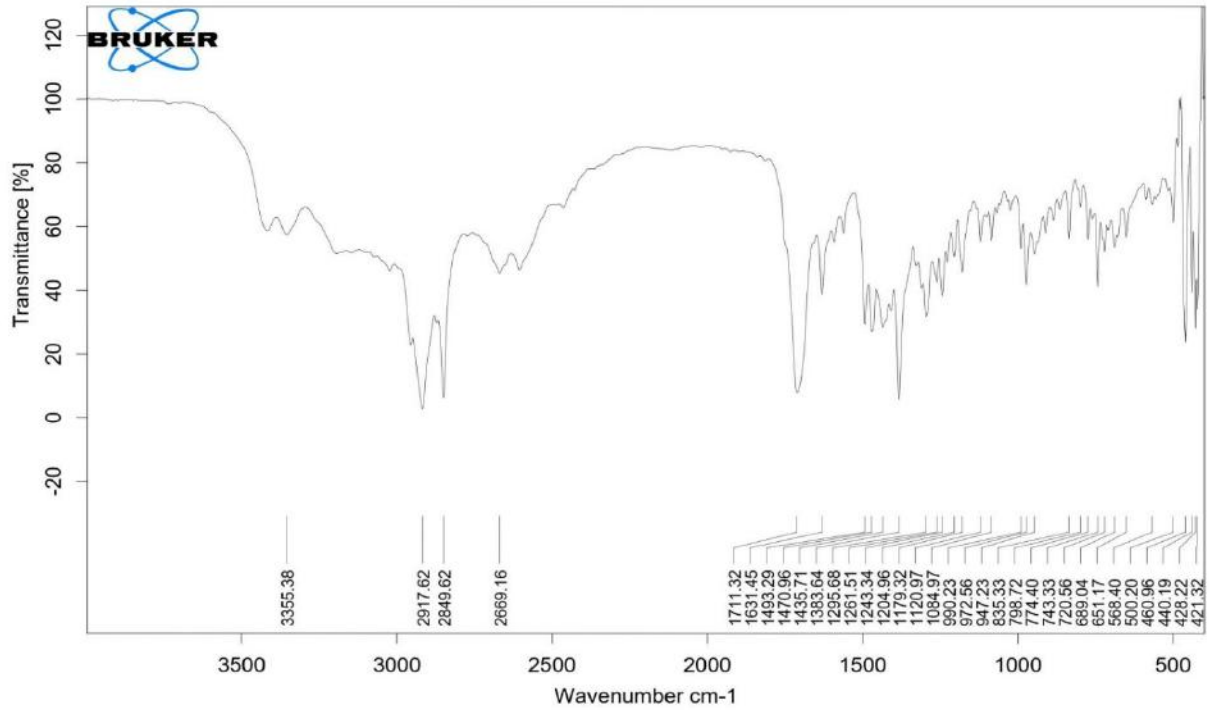


Figure 3.2: Systematic Representation of FTIR of Drug Excipient Compatibility

Sr. No	Reported range (cm^{-1})	Observed range (cm^{-1})	Functional group
1	3550-3200	3355.38	Broad OH stretch (Alcohol)
2	3000-2800	2917.62	Broad N-H Stretch (Amine salt)
3	1725-1705	1711.32	C=O stretch (Aliphatic ketone)
		1631.45	C=C(Alkenyl)
4	1510-1450	1493.29	C=C-C Aromatic ring stretch
5	1480-1375	1435.71	C-H bend alkane (methyl group)
6	1420-1370	1383.64	Organic sulfate
7	1275-1200	1261.51	C-O stretch (Alkyl aryl ether)
8	1250-1020	1243.34	C-N stretch (Amine)
9	1200-1100	1179.32	Sulfonate
10	1085-1050	1084.97	C-OH stretch (1° alcohol)
11	995-985	990.23	C=C bend (Alkene)
12	810-750	774.40	C-H 1,3 Disubstitution(meta)
13	770-735	743.33	C-H 1,2 Disubstitution (ortho)
14	600-500	568.40	C-Cl stretch (Halo compound)

Table 3. 2 : Interpretation of FTIR of Drug Excipient Compatibility

3.2: SLNs EVALUATION

3.2.1.Particle size

	F3	F4	F5
Scattering Angle	90	173	90
Dispersion Medium Viscosity	0.896 mPa.s	0.897 mPa.s	0.897 mPa.s
Distribution Form(Dispersity)	Monodisperse	Monodisperse	Monodisperse
Count Rate	2826 kCPS	1977 kCPS	2132 kCPS
Aspect Ratio	1.00	1.00	1.00
Mean	156.7 nm	167.8 nm	168.9 nm
Standard Deviation (Diameter)	35.3 nm	48.4 nm	39.8 nm
Mode	143.8 nm	160.2 nm	161.0 nm
Z-Average	159.8 nm	418.9 nm	161.3 nm
Polydispersity Index	0.223	0.563	0.233

Table 3.3 : Measurement of particle size

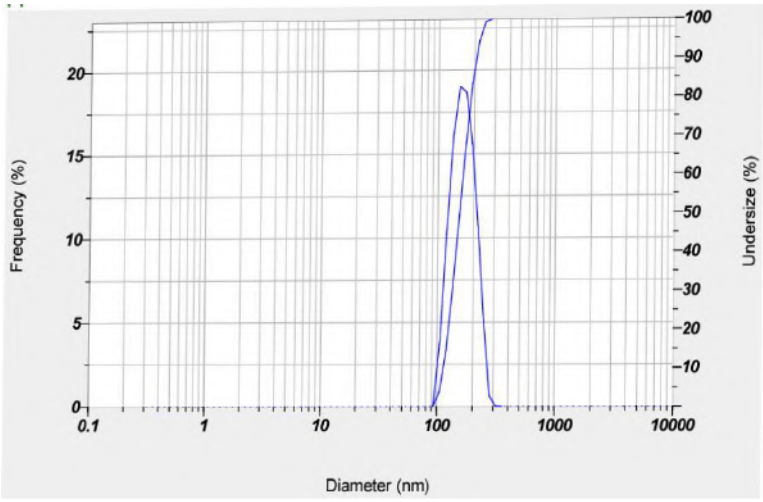


Figure 3.3: particle size of formulation batch 2

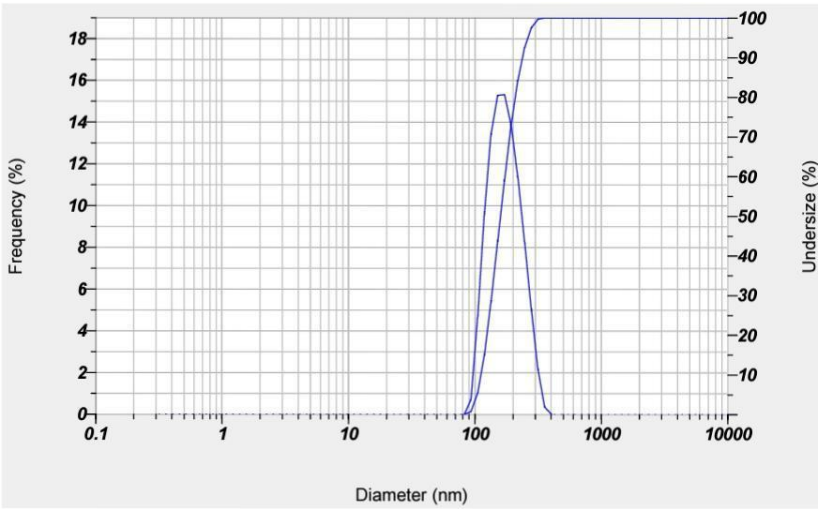


Figure 3.4: particle size of formulation batch 3

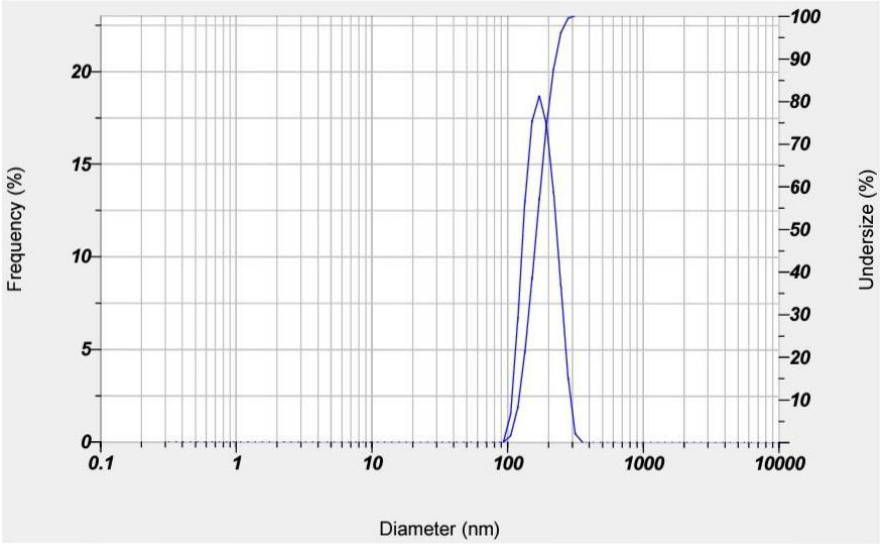


Figure 3.5: particle size of formulation batch 4

3.2.2.Entrapment Efficiency

Batches	% Entrapment of drug
F2	93.81
F3	91.16
F4	95.75

Table 3.4: % entrapment efficiency of formulation

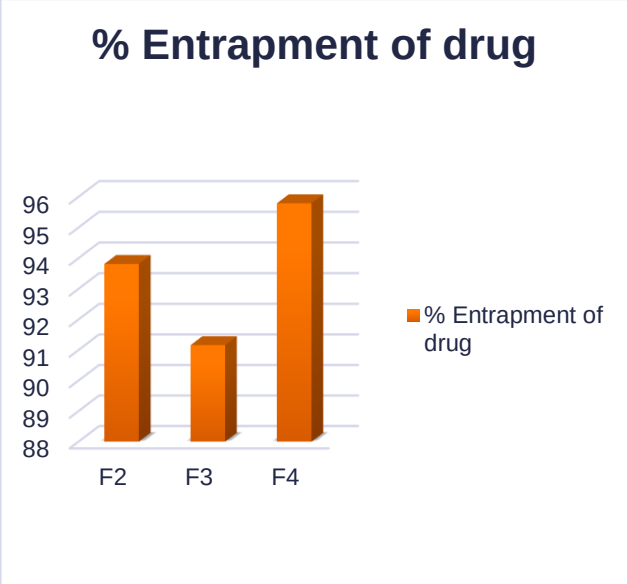


Figure 3.6: systematic representation of % entrapment efficiency of Formulation

3.2.3.Drug Content :

Batches	% Drug Content
F2	96.45
F3	93.48
F5	98.1

Table 3.5: % drug content formulation batches

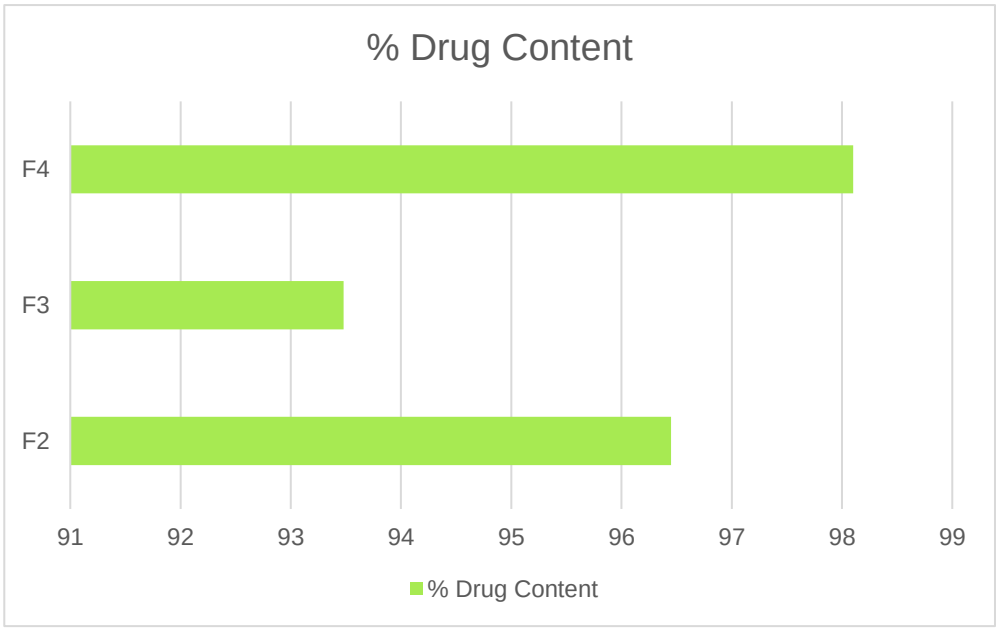
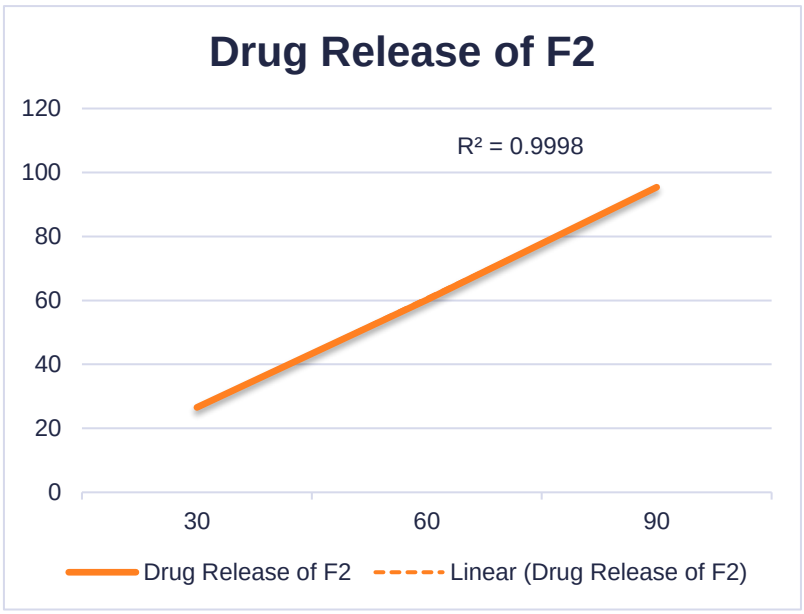


Figure 3.7 :systematic representation of Drug content of Formulation

3.2.4.Drug Release

Time	% Drug Release		
	F2	F3	F4
30	26.55	25.35	25.95
60	60.15	57.60	60
90	95.4	91.95	95.4

Table 3.6: % Drug release of formulation



3.8: systematic representation of % drug release of Formulation batch 2

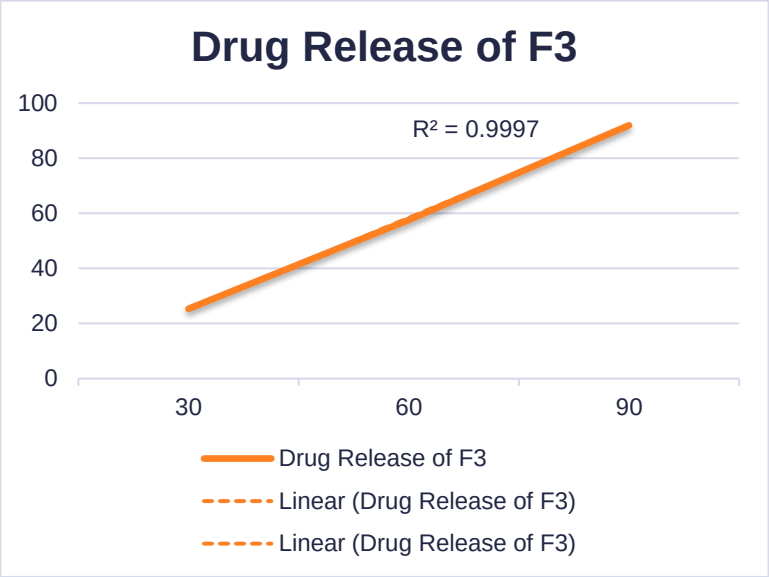


Figure 3.9:systematic representation of % drug release of Formulation batch 3

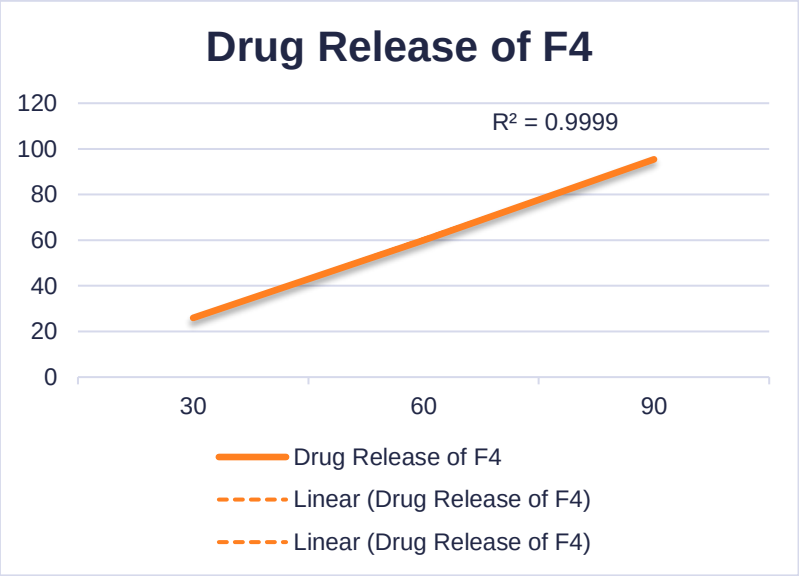


Figure 3.10:Systematic representation of % drug release of Formulation batch 4

4. CONCLUSION:

1. Particle size : The particle size of all formulated batch have size range of nanometer. SO all the batchea pass the test.

2. Entrapment Efficiency: The % entrapment efficiency of formulation batch of 2,3,4 are 93.81 , 91.16 , 95.79 respectively.

3. Drug content:F1 not show the drug content value within a limit, F2, F3, F4 shows the value within a range and these are 96.45 , 93.48 , 98.1 respectively.

4. Drug release : Drug release of formulation shows the steady release of drug with the R^2 value of F2, F3, F4 are 0.9998 , 0.9997 , 0.9999 respectively.

From all above Result & Discussion Formulation batch 4 is optimum batch, and batch 1 is near to optimum and batch 2 is average formulation batch.

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