Preparation of Ibuprofen-loaded Eudragit S100 nanoparticles by Solvent evaporation technique.

VINEELA CH*1, KRISHNA SAILAJA K 2.

[1]Research scholar, department of pharmaceutics, RBVRR women's college of pharmacy, Barkatpura, Hyderabad, India.
[2]Associate professor, department of pharmaceutics, RBVRR women's college of pharmacy, Barkatpura, Hyderabad, India.
chandavathvineela@gmail.com

Abstract

Aim

The aim of the present study is to prepare Ibuprofen loaded Eudragit-S100 nanoparticles by means of Solvent evaporation method. Span 80 is used as surfactant. The model drug, Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the relief of symptoms of arthritis, primary dysmenorrheal, alleviating fever and reducing inflammation. It also has an analgesic effect, anti-platelet effect and vasodilation effect. Ibuprofen is available in the form of extended release tablets, chewable tablets, sustained release capsules, liquid filled capsules, syrup and suspension.

Methodology Solvent evaporation technique was adapted for the preparation of Ibuprofen loaded Eudragit S100 nanoparticles. Preformed polymeric and drug solution was used as internal phase and mineral oil with 1% span 80 is used as external phase and allowed for stirring resulting in the formation of nanoparticles. Parameters like stirring rate, polymer to drug concentration and organic solvent quantity were optimized.

Results and Conclusion

In order to optimize the concentration of drug, polymer and organic solvent, three formulations were prepared by varying the concentration of polymer and solvents. The results obtained were compared. On comparision formulation 3(1:2) was showing particles in nanorange (345nm), higher stability (-26.9mV) and better entrapment efficiency (96.47). Invitro drug release studies were performed for a period of 10hrs and 46.02% of the drug has been released from the formulation.

Conclusion

It was observed that as the polymer ratio increases the release rate is sustained and encapsulation efficiency also increased.

Keyword

Solvent evaporation**,** Ibuprofen, Eudragit S-100, drug content, encapsulation efficiency, invitro drug release.

1. Introduction:

The outstanding contribution of polymeric nanoparticles as a physical approach to alter and improve the pharmacodynamic and pharmacokinetic properties of various types of drug entities has been studied. In addition to their advantages, various polymers were extensively employed for the formulation of nanoparticles for the delivery of drug to increase the therapeutic benefits, while minimizing side effects.

Nanoparticles are defined as drug loaded nano carriers in which drug is either encapsulated into the polymeric matrix or else adsorbed on the surface[1]. Nanoparticles are a collective term used for nanocapsules, nanospheres and/ or nanocrystals ranging from 1 to 1000nm[2]. Compared to microspheres and liposomes nanoparticles bear numerous therapeutic advantages[3, 4]. Such as;

- Sustained drug release to the targeted organs
- Ease of surface property manipulation for desires drug release mechanism.
- Protecting drug from degradation by modulating the choice of matrix constituents
- Site specificity and targeting can be achieved by attaching targeting ligand to the surface.
- They can be used for various routes of administration including oral, nasal, parentral, intra-ocular etc.

In order to optimize the size and surface morphology and properties of nanoparticles, selection of appropriate fabrication method plays a vital role. Numbers of methods are available for the preparation of nanoparticles, such as amphiphillic macromolecular cross linking, polymerization and polymer precipitation methods[5].

Because of the narrow size distribution and ease of process scale-up, solvent evaporation method is generally considered to be the best method for the preparation of nanoprarticles[6, 7].

The popular method for the encapsulation of drugs within water-insoluble polymers is the emulsion solvent evaporation method[8, 9]. This technique offers several advantages and is preferable to other preparation methods such as spray drying, sonication and homogenization because it requires only mild conditions such as ambient temperature and constant stirring[10, 11]. Thus, a stable emulsion can be formed without compromising the activity of the drugs. This method is partially useful for the drugs that are slightly soluble in water[12].

Polymeric nanoparticles systems by far the most studied organic particles in the literature. Majority of the contribution towards the field of site specificity is by polymeric nanoparticles. Wide classes of biocompatible and bio-degradable polymers are available for the fabrication of drug loaded nanoparticles. The nature, surface charge and properties of the polymers controls important parameters of the formulation i.e. drug release, stability and forth[13, 14, 15]. List of synthetic and natural polymers that can be used are;

Synthetic polymers: Poly(lactide), Poly(lactide-co-glycolide), Poly(epsilon-caprolactone), Poly(isobutylcyanoacrylate), Poly(isohexylcyanoacrylate), Poly(n-butylcyanoacrylate), Poly(acrylate) and Poly(methacrylate) (Eudragit), Poly(ethylene glycol),

Natural polymers: chitosan, Alginate, Gelatin, Albumin, Fibroin, Lectins, Legumin, Vicillin, Pullulan

Conjugated polymers: Polypyrrole, Polyaniline, Polyacetylene, Poly (dialkyl fluorene), Poly(p-phenyleneethynylene), Poly(p-phenylenevinynylene).

2. Materials and methods:

2.1. Materials: Ibuprofen (gift sample), Eudragit S100, Light liquid paraffin, Acetone, petroleum ether from SD Fine Chemical Limited, (Mumbai).

2.2. Methodology: Solvent evaporation method was adapted for the preparation of Eudragit nanoparticles. Eudragit and Ibuprofen were accurately weighed and dissolved in acetone. At 15^0c the preformed drug polymer solution was added drop wise to liquid paraffin containing 1%w/w of span-80[16] and kept for magnetic stirring at 1000rpm for 2hrs. The formed particles were separated from solvent and washed twice with petroleum ether. Three trails were performed by considering different drug to polymer ratios and varying solvent volume. Throughout the trails polymer to solvent concentration was kept constant i.e. 36.5mg/ml[17].

Trail no.& ratio	Drug (in mg)	Polymer (in mg)	Solvent (in ml)
F1 (1:1)	365	365	10
F2 (1:1.5)	182.5	273.7	10
F3 (1:2)	110	220	6

3. Characterization of nanoparticles: The obtained nanoparticles were characterized for following parameters[18, 19, 20;]

3.1. Drug content: 50 mg of the prepared particles from three formulations were dissolved in 50ml methanol and kept for stirring at 600 rpm for 3hrs separately. The resultant samples were observed under UV spectrophotometer for concentrations.

3.2. Encapsulation efficiency: Ideally the nanoparticles should have high encapsulation efficiency in order to reduce the quantity of matrix materials for administration. Encapsulation efficiency is conducted by taking 50mg of prepared particles in 50ml 7.2 pH phosphate buffer. The nanoparticles suspension is ultra centrifuged at 17000rpm and temperature of -4 ^{o}c for 40 mins. The encapsulation efficiency can be expressed as follow;

$$\text{Entrapment Efficiency} = \frac{\text{Total amount of the drug entrapped}}{\text{Total amount of the drug initially taken}} \times 100$$

$$\text{Loading Capacity} = \frac{\text{Total amount of the drug entrapped}}{\text{Total weight of the nanoparticles taken}} \times 100$$

3.3. Determining the particle size: The mean size and polydispersity index (P.I.) of prepared nanoparticles were measured using Zetasizer (Horiba Instruments Ltd. The nanoparticles were dispersed in deionized water.

3.4. Determination of zeta potential: The zeta potential is commonly used to characterize the surface charge property of nanoparticles. It reflects the electrical potential of the particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents particle aggregation.

3.5. In vitro drug release studies: For the nanoparticles both the drug release and polymer degradation are two important considerations. In vitro drug release studies were conducted by means of Arbitary shaker in 7.2 pH buffer at a temperature of 37 (+/-) 0.5^{o}c and rotation speed of 100 rpm. 5ml of sample was withdrawn at regular

time interval and replaced with equal quantity of buffer solution. Then the withdrawn samples were centrifuged at 3000 rpm for 15 mins after which the supernatant was collected. The drug concentration in the supernatant was observed under UV spectrophotometer at a wavelength of 221nm.

4. RESULTS AND DISCUSSION:

4.1. Drug content: The prepared nanoparticles were evaluated for drug content and it was found that the nanoparticles prepared by formula 2 (F2) showed higher drug content i.e. 96.6% than that of F1 and F3 i.e. 81.9 % and 90.3% respectively (see figure 1).

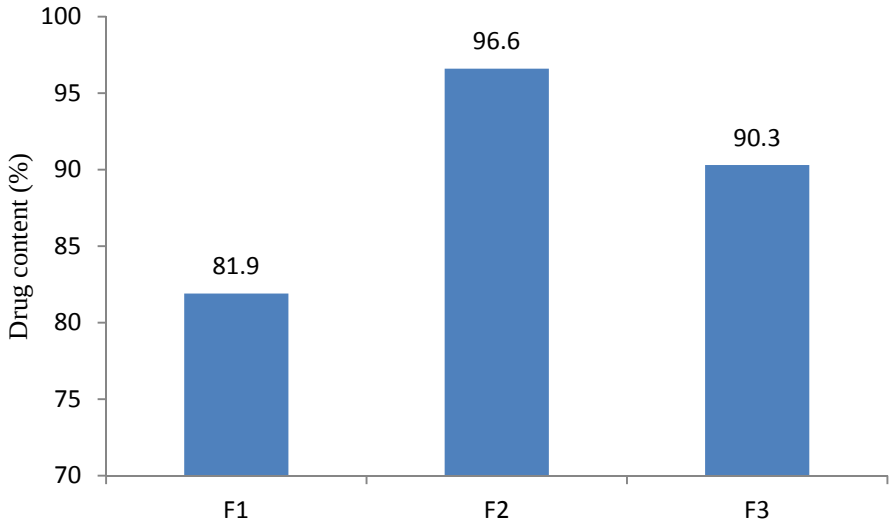

Figure 1: Comparative drug content of prepared formulations.

4.2. Encapsulation efficiency: The prepared nanoparticles were evaluated for Encapsulation efficiency and it was found that nanoparticles prepared by formula 3 (F3) showed higher encapsulation efficiency i.e. 96.47% than that of F1 and F2 i.e. 74.09 % and 65.5% respectively and for the three formulations F1, F2 and F3 the loading capacity were found to be 41.12%, 26.87% and 30.14% respectively (see figure 2 & 3).

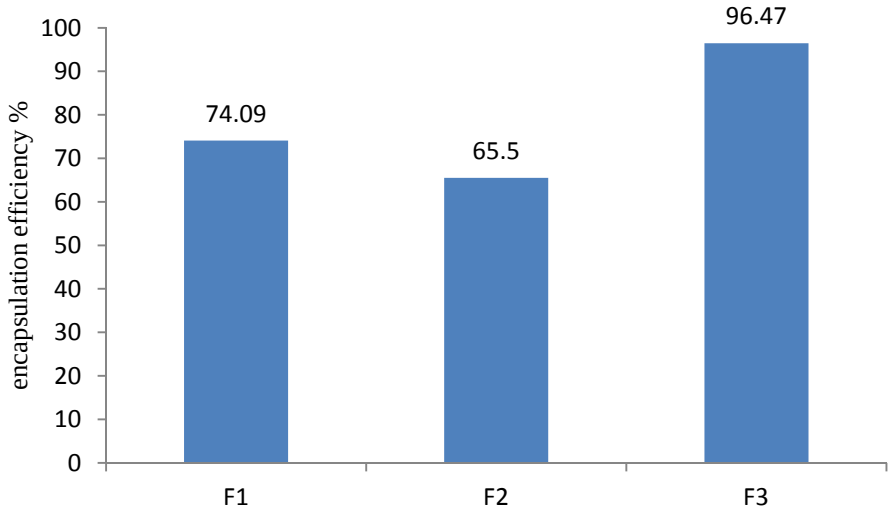

Figure 2: Comparative encapsulation efficiency of prepared formulations.

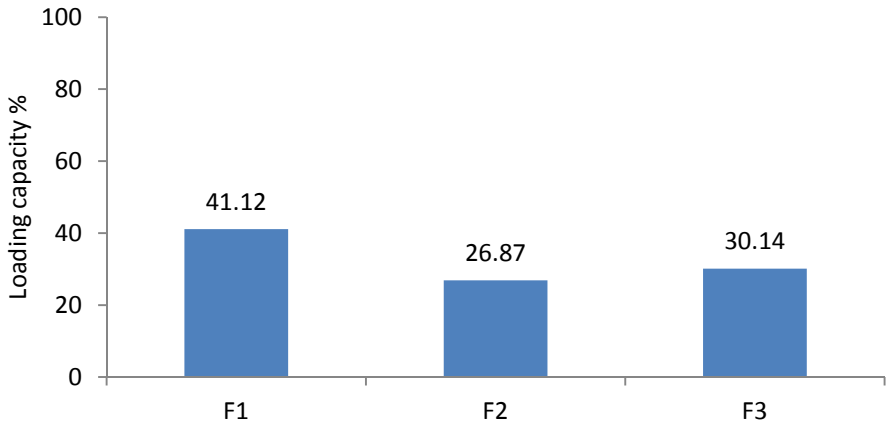

Figure 3: Comparative loading capacity of prepared formulations.

4.3. Determining the particle size: The size distribution of the prepared nanoparticles and the mean diameter were measured by using particle size analyzer. The average particle size of the prepared nanoparticles formulations F1 and F3 were observed as 354.7 nm and 345 nm respectively (see figure 4 and 5).

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Measurement Results

Date	:	14 May 2014 12:50:40
Measurement Type	:	Particle Size
Sample Name	:	F1-1:1
Scattering Angle	:	90
Temperature of the holder	:	25.0 deg. C
T% before meas.	:	34233
Viscosity of the dispersion medium	:	0.895 mPa.s
Form Of Distribution	:	|Standard|
Representation of result	:	Scattering Light Intensity
Count rate	:	211 kCPS

Calculation Results

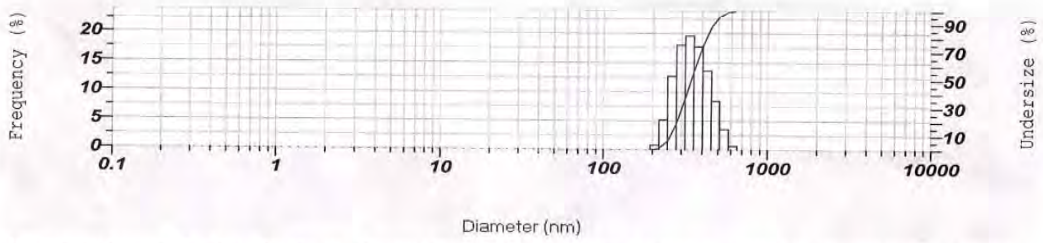
Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	354.7 nm	81.6 nm	334.8 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	354.7 nm	81.6 nm	334.8 nm

Histogram Operations

% Cumulative (1)	:	10.0 (%) - 256.8 (nm)
% Cumulative (2)	:	50.0 (%) - 342.8 (nm)
% Cumulative (3)	:	90.0 (%) - 472.1 (nm)
Mean	:	354.7 nm

Cumulant Operations

Z-Average	:	258.8 nm



No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation	No.	Diameter	Frequency	Cumulation
1	0.34	0.000	0.000	28	9.15	0.000	0.000	55	246.98	5.175	5.942	82	6667.10	0.000	100.000
2	0.38	0.000	0.000	29	10.34	0.000	0.000	56	279.04	12.669	18.611	83	7532.65	0.000	100.000
3	0.43	0.000	0.000	30	11.68	0.000	0.000	57	315.27	17.973	36.584	84	8510.56	0.000	100.000
4	0.49	0.000	0.000	31	13.20	0.000	0.000	58	356.20	19.530	56.114				
5	0.55	0.000	0.000	32	14.91	0.000	0.000	59	402.44	17.720	73.834				
6	0.62	0.000	0.000	33	16.84	0.000	0.000	60	454.69	13.590	87.424				
7	0.70	0.000	0.000	34	19.03	0.000	0.000	61	513.71	8.388	95.811				
8	0.80	0.000	0.000	35	21.50	0.000	0.000	62	580.41	3.530	99.341				
9	0.90	0.000	0.000	36	24.29	0.000	0.000	63	655.76	0.659	100.000				
10	1.02	0.000	0.000	37	27.45	0.000	0.000	64	740.89	0.000	100.000				
11	1.15	0.000	0.000	38	31.01	0.000	0.000	65	837.07	0.000	100.000				
12	1.30	0.000	0.000	39	35.03	0.000	0.000	66	945.74	0.000	100.000				
13	1.47	0.000	0.000	40	39.58	0.000	0.000	67	1068.52	0.000	100.000				
14	1.66	0.000	0.000	41	44.72	0.000	0.000	68	1207.24	0.000	100.000				
15	1.87	0.000	0.000	42	50.53	0.000	0.000	69	1363.97	0.000	100.000				
16	2.11	0.000	0.000	43	57.09	0.000	0.000	70	1541.04	0.000	100.000				
17	2.39	0.000	0.000	44	64.50	0.000	0.000	71	1741.10	0.000	100.000				
18	2.70	0.000	0.000	45	72.87	0.000	0.000	72	1967.14	0.000	100.000				
19	3.05	0.000	0.000	46	82.33	0.000	0.000	73	2222.51	0.000	100.000				
20	3.45	0.000	0.000	47	93.02	0.000	0.000	74	2511.05	0.000	100.000				
21	3.89	0.000	0.000	48	105.10	0.000	0.000	75	2837.04	0.000	100.000				
22	4.40	0.000	0.000	49	118.74	0.000	0.000	76	3205.35	0.000	100.000				
23	4.97	0.000	0.000	50	134.16	0.000	0.000	77	3621.48	0.000	100.000				
24	5.61	0.000	0.000	51	151.57	0.000	0.000	78	4091.63	0.000	100.000				
25	6.34	0.000	0.000	52	171.25	0.000	0.000	79	4622.81	0.000	100.000				
26	7.17	0.000	0.000	53	193.48	0.000	0.000	80	5222.96	0.000	100.000				
27	8.10	0.000	0.000	54	218.60	0.766	0.766	81	5901.02	0.000	100.000				

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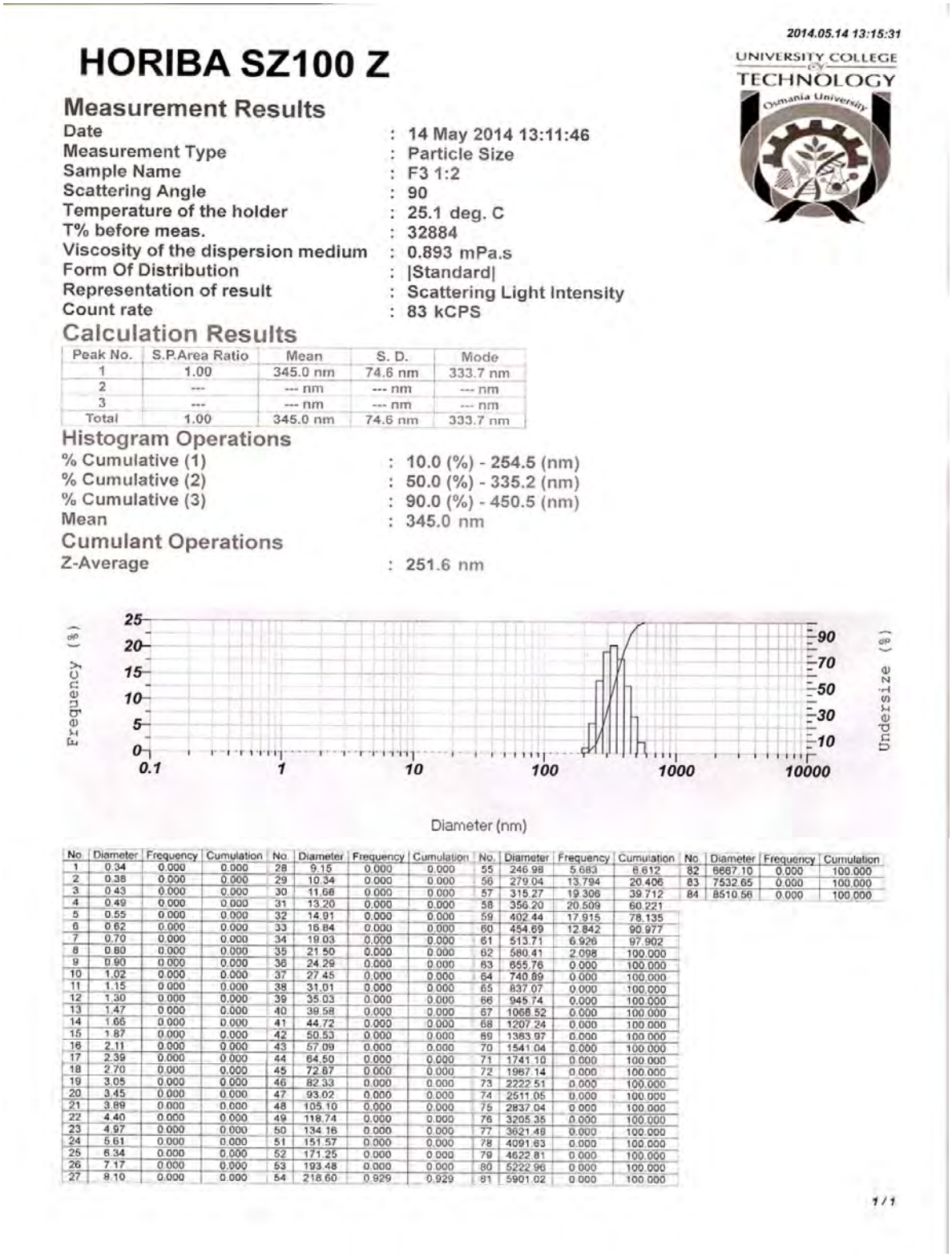
Figure 4: Mean particle diameter of Nanoparticles prepared by F1 formulation.



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Measurement Results

Date	:	14 May 2014 13:11:46
Measurement Type	:	Particle Size
Sample Name	:	F3 1:2
Scattering Angle	:	90
Temperature of the holder	:	25.1 deg. C
T% before meas.	:	32884
Viscosity of the dispersion medium	:	0.893 mPa.s
Form Of Distribution	:	|Standard|
Representation of result	:	Scattering Light Intensity
Count rate	:	83 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	345.0 nm	74.6 nm	333.7 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	345.0 nm	74.6 nm	333.7 nm

Histogram Operations

% Cumulative (1)	:	10.0 (%) - 254.5 (nm)
% Cumulative (2)	:	50.0 (%) - 335.2 (nm)
% Cumulative (3)	:	90.0 (%) - 450.5 (nm)
Mean	:	345.0 nm

Cumulant Operations

Z-Average	:	251.6 nm

No	Diameter	Frequency	Cumulation	No	Diameter	Frequency	Cumulation	No	Diameter	Frequency	Cumulation	No	Diameter	Frequency	Cumulation
1	0.34	0.000	0.000	28	9.15	0.000	0.000	55	246.98	5.683	6.612	82	6667.10	0.000	100.000
2	0.38	0.000	0.000	29	10.34	0.000	0.000	56	279.04	13.794	20.406	83	7532.65	0.000	100.000
3	0.43	0.000	0.000	30	11.66	0.000	0.000	57	315.27	19.306	39.712	84	8510.56	0.000	100.000
4	0.49	0.000	0.000	31	13.20	0.000	0.000	58	356.20	20.509	60.221				
5	0.55	0.000	0.000	32	14.91	0.000	0.000	59	402.44	17.915	78.135				
6	0.62	0.000	0.000	33	16.84	0.000	0.000	60	454.69	12.842	90.977				
7	0.70	0.000	0.000	34	19.03	0.000	0.000	61	513.71	6.926	97.902				
8	0.80	0.000	0.000	35	21.50	0.000	0.000	62	580.41	2.098	100.000				
9	0.90	0.000	0.000	36	24.29	0.000	0.000	63	655.76	0.000	100.000				
10	1.02	0.000	0.000	37	27.45	0.000	0.000	64	740.89	0.000	100.000				
11	1.15	0.000	0.000	38	31.01	0.000	0.000	65	837.07	0.000	100.000				
12	1.30	0.000	0.000	39	35.03	0.000	0.000	66	945.74	0.000	100.000				
13	1.47	0.000	0.000	40	39.58	0.000	0.000	67	1068.52	0.000	100.000				
14	1.66	0.000	0.000	41	44.72	0.000	0.000	68	1207.24	0.000	100.000				
15	1.87	0.000	0.000	42	50.53	0.000	0.000	69	1363.97	0.000	100.000				
16	2.11	0.000	0.000	43	57.09	0.000	0.000	70	1541.04	0.000	100.000				
17	2.39	0.000	0.000	44	64.50	0.000	0.000	71	1741.10	0.000	100.000				
18	2.70	0.000	0.000	45	72.87	0.000	0.000	72	1967.14	0.000	100.000				
19	3.05	0.000	0.000	46	82.33	0.000	0.000	73	2222.51	0.000	100.000				
20	3.45	0.000	0.000	47	93.02	0.000	0.000	74	2511.05	0.000	100.000				
21	3.89	0.000	0.000	48	105.10	0.000	0.000	75	2837.04	0.000	100.000				
22	4.40	0.000	0.000	49	118.74	0.000	0.000	76	3205.35	0.000	100.000				
23	4.97	0.000	0.000	50	134.16	0.000	0.000	77	3621.48	0.000	100.000				
24	5.61	0.000	0.000	51	151.57	0.000	0.000	78	4091.63	0.000	100.000				
25	6.34	0.000	0.000	52	171.25	0.000	0.000	79	4622.81	0.000	100.000				
26	7.17	0.000	0.000	53	193.48	0.000	0.000	80	5222.96	0.000	100.000				
27	8.10	0.000	0.000	54	218.60	0.929	0.929	81	5901.02	0.000	100.000				

1 / 1

Figure 5: Mean particle diameter of Nanoparticles prepared by F3 formulation.

4.4. Determination of zeta potential: The zeta potential of the prepared nanoparticles was determined by means of zeta meter indicator and it was found that formulation F3 showed better stability compared to formulation F1 and F2 i.e. -26.9Mv (see figure 6)

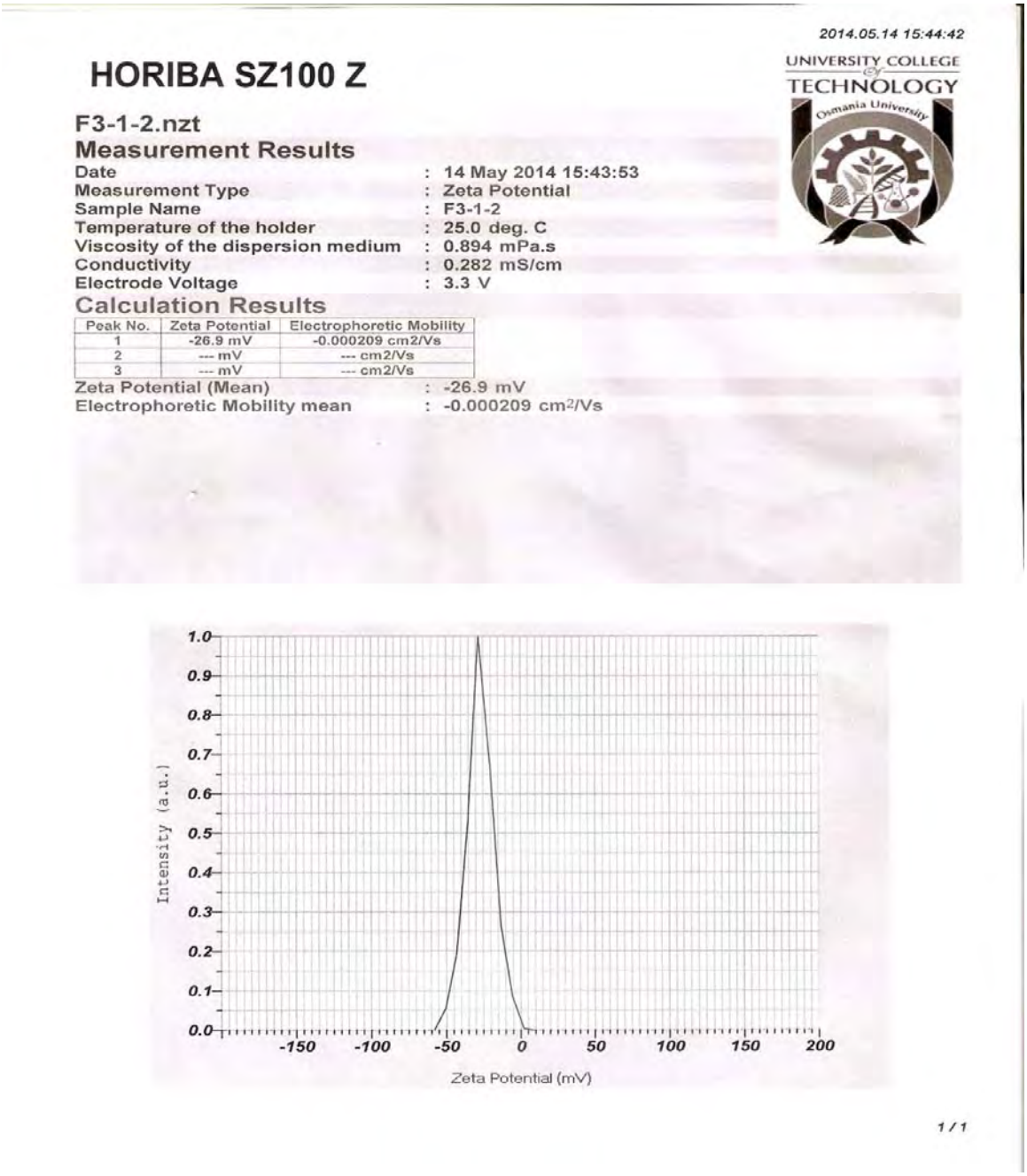

Figure 6: Zeta potential (mean) of Nanoparticles prepared by F3 formulation.

4.5. In vitro drug release studies: The Invitro drug release studies shows that the drug release from the particles prepared by F1, F2 and F3 were sustained for 10hrs with percentage drug release of 49.05%, 46.83 and 46.02% respectively (see figure 7, 8, 9, 10 &11 and Table 1).

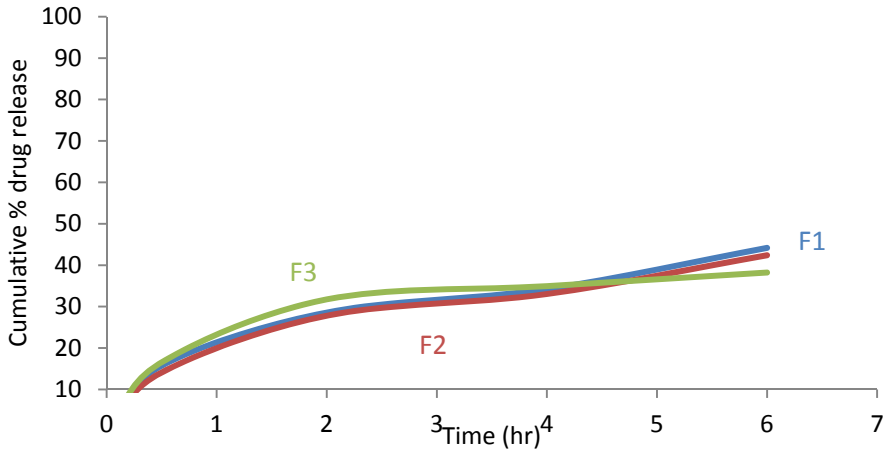

Figure 7: Comparative cumulative drug release from prepared formulations.

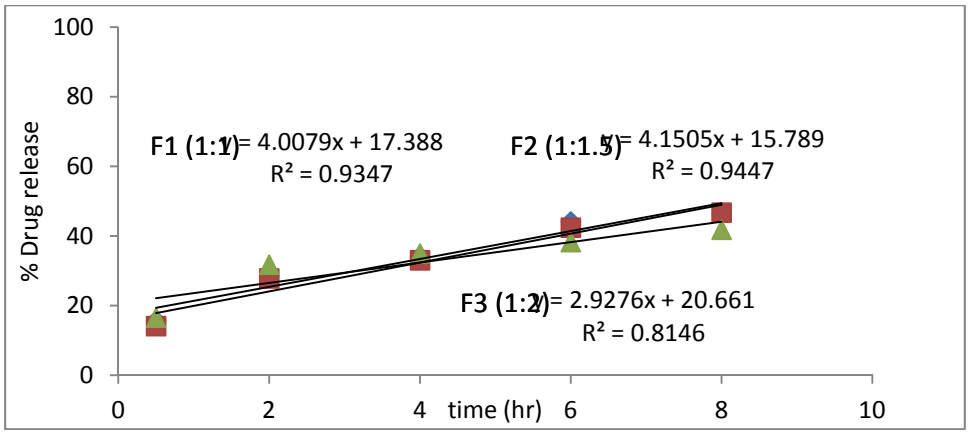

Figure 8: Comparative zero order plot of prepared formulations

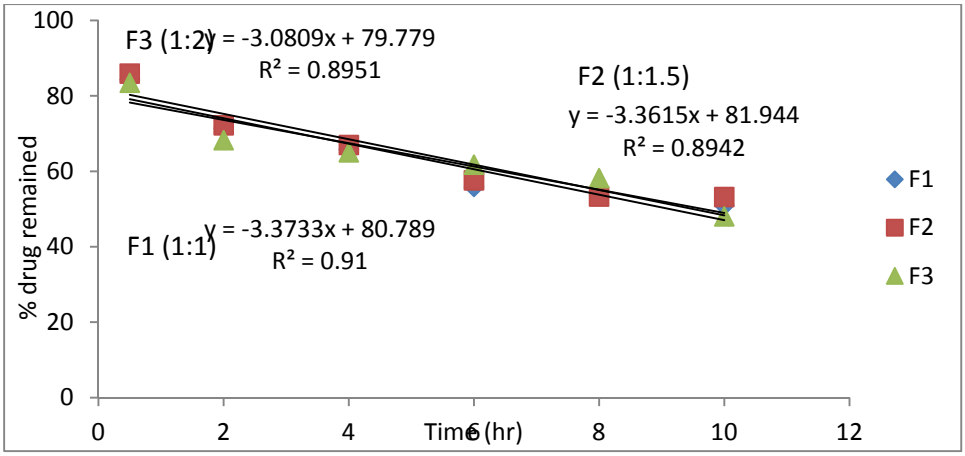

Figure 9: Comparative first order plot of prepared formulations

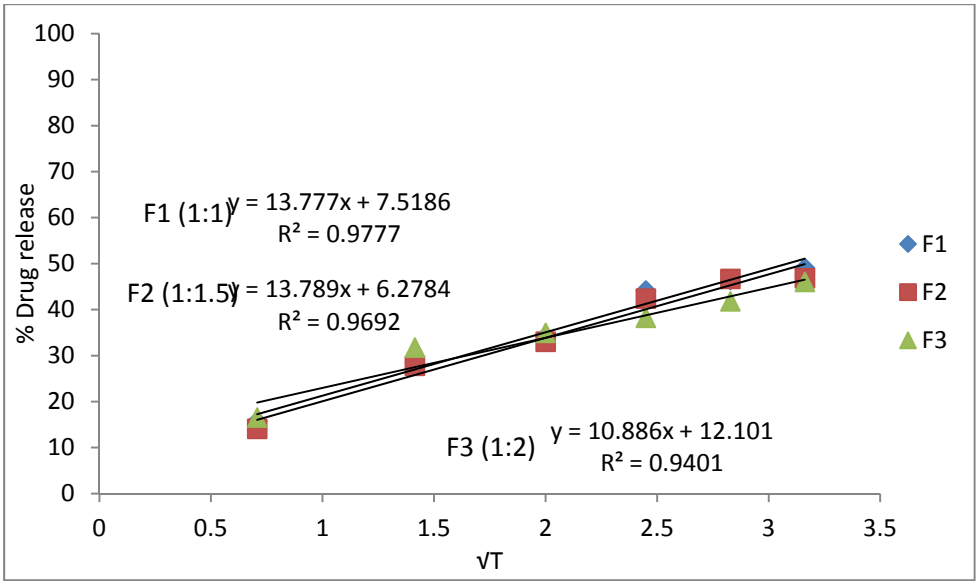

Figure 10: Comparative higuchi plot of prepared formulations

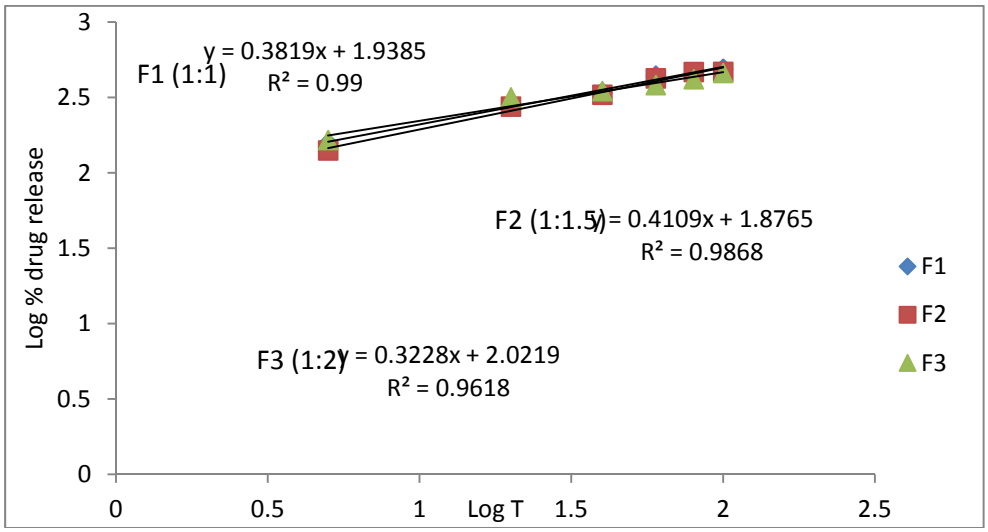

Figure 11: Comparative peppas plot of prepared formulations

Table 1: Parameters determined from the Invitro Release Studies performed on prepared nanoparticle formulations*:*

Formulation	**Zero Order Plot (R^2)**	**First order Plot (R^2)**	**Peppas Plot (n)**	**Higuch Plot(R^2)**
F1 (1:1)	0.934	0.91	0.381	0.977
F2 (1:1.5)	0.944	0.894	0.410	0.969
F3 (1:2)	0.814	0.895	0.322	0.940

5. Discussion

In this study attempts have been made to prepare ibuprofen loaded Eudragit S-100 nanoparticles by solvent evaporation technique. In order to obtain best formulation, three formulations were prepared by varying the concentration of drug and polymer. In formulations 1, 2and 3 the concentration of drug and polymer were maintained 1:1, 1:1.5 and 1:2 respectively. The effect of polymer concentration on nanoparticle size, shape, stability, encapsulation efficiency, loading capacity and drug release was studied and compared. The obtained particles are found to be in nanoscale in all three formulations. On comparison mean particle diameter of formulation 3 was showing particles in nanorange (345nm) and good stability (-26.9mV).The encapsulation efficiency was also found to be more in Formulation 3 (96.47%).This was mainly because of the higher

polymer concentration. Increased polymer concentration is supporting maximum entrapment of the drug.Invitro drug release studies were performed for all the three formulations. In all the three formulations the drug release was sustained upto 10 hrs. The percentage of drug release within a period of 10 hrs was found to be 49.05%, 46.83 and 46.02% respectively. In formulation 1 the drug and polymer were taken at equal concentration.So 49% of drug has been released.When the polymer concentration was increased from F1 to F2 the percentage of drug release was decreased. By furthur increasing the concentration of drug from F2 to F3 the drug release was slightly decreased. From the results it was observed that by increasing the polymer concentration the drug release was decreasing.

6. Conclusions:

On comparison Formulation 3 can be considered as the best formulation for the preparation of ibuprofen loaded Eudragit S100 nanoparticles because of small particle size, good stability and maximum entapment efficiency. The drug release was also sustained upto 10 hrsThe drug release followed zero order kinetics following fickian diffusion mechanism. Furthur studies can be performed to improve the percentage of drug release from the formulation.

7. Acknowledgements

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8. References:

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