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Original Article

PREPARATION AND CHARACTERISATION OF IBUPROFEN LOADED POLYMERIC NANOPARTICLES BY SOLVENT EVAPORATION TECHNIQUE

VUTPALA SREELOLA[*1], ABBARAJU KRISHNA SAILAJA[2]

[1]M.Pharmacy Student, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, [2]Associate Professor, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad.
Email: vutpalasreelola@gmail.com

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ABSTRACT

Objective: In the present study Ibuprofen loaded nanoparticles were prepared by solvent evaporation technique. Comparative study was done among the formulations to know the best stabilizer and the polymer for ibuprofen loaded nanoparticles.

Methods: Four formulations F1, F2, F3 and F4 were prepared by solvent evaporation technique by changing the polymers and the stabilizers. The polymers used were Ethyl cellulose and Eudragit S-100 and the stabilizers were tween 80 and 0.4% PVA.The drug and the polymers was dissolved in solvent mixture of DCM and methanol in 1:1 ratio and added to the aqueous stabilizers. Comparative study was done to know the better formulation for EC with 0.4% PVA and tween 80, and also for Eudragit S-100 with Tween 80 and 0.4%PVA.Further Comparative study was performed between the best formulation of EC (F2) and Eudragit S-100 (F3).The effect of stabilizer and the polymer on nanoparticle size, stability, loading capacity, encapsulation efficiency and *In vitro* drug release was studied.

Results: Ibuprofen nanoparticles.F1,F2,F3 and F4 were prepared by using EC with tween 80 and 0.4% PVA and Eudragit with the same stabilzers. The particle size and stability of the formulations was determined by Horiba SZ 100 series particle size analyzer. Encapsulation efficiency and loading capacity were determined by ELTEK NP 400 Ultracentrifuge. The drug content was found to be 87%,88.72%,81.05% and 80.6%,encapsulation efficiency was found to be 56.25%,88.36%,71.7% and 55.9 %,loading capacity was found to be 28.8%,39.2%,33% and 28.4% respectively for F1,F2,F3 and F4. The average particle size was found to be 320.9 nm for F2 and 694.8 nm for F3.The zeta potential was found to be optimum for both the formulations.

Conclusions: On comparison F2 was considered to be the best formulation for the preparation of Ibuprofen loaded nanoparticles because of the smaller particle size and greater stability, greater loading capacity and encapsulation efficiency. The drug release was sustained till 8 hrs for nanoparticles in F2.

Keywords: Nanoparticles, Ethyl cellulose, Eudragit, Solvent evaporation, Drug release.

INTRODUCTION

Now-a-days nanotechnology is gaining prominence as one of the novel methods of drug delivery system. It is used to improve the bioavailability of the drugs and minimize the side effects of drugs. Pharmaceutical nanotechnology focuses on formulating therapeutically active agents in different nanoforms such as nanoparticles, nanocapsules. These systems offer many advantages in drug delivery, mainly focusing on improved safety and efficacy of the drugs, e.g. providing targeted delivery of drugs, improving bioavailability, extending drug or gene effect in target tissue, and improving the stability of therapeutic agents against chemical/enzymatic degradation. Nanoparticle formulations provide the feasibility to use a wide range of polymers like synthetic, natural, biodegradable or non-biodegradable are used for short term therapy and non-biodegradable polymers are used for long term therapy to administered vaccines and hormones. As the size range of the nanoparticles is 1-1000 nm, a wide choice for selection of route of administration is also possible [1].

Over the past decades, nanotechnology has gained great attention in the field of drug delivery system. Many attempts have made to fabricate the nanoparticles as effective nano-carriers to overcome the limitation of drug administration; to surpass the physiological barrier, to deliver to the targeted tissue or organ, to extend the desired residence time, to enhance the therapeutic activity and to minimize the undesirable side effects. Many methods have employed to prepare nanoparticles [2].Polymers play an important role in enhancing the quality of dosage form design and thus improving patient compliance. Polymeric nanoparticles constitute a versatile drug delivery system, which can potentially overcome physiological barriers, and guide the drugs to specific cells or intracellular compartments. They are mostly vesicular or spherical systems in which drug molecules are physically and uniformly dispersed within polymeric matrix systems [3].The polymers used for the preparation of nanoparticles are classified into natural and synthetic. Natural polymers are again classified into proteins and polysaccharides. Proteins like gelatin, albumin, lectin, vicilin legumin and polysaccharides like chitosan, alginate, dextran, agarose, pullulan [4].Synthetic polymers are differentiated into pre-polymerized and polymerized polymers. Examples for prepolymerized polymers are polylactic acid, poly lactide co-glycolide, polycaprolactone and for polymerized polymers are Polyisobutyl cyanoacrylates, Polybutyl cyanoacrylate, and Polymethyl methacrylate [5].The method employed for the fabrication of nanostructures depends on the type and the desired properties of the nanostructure to be produced. Methods for preparing of polymeric nanoparticles have been reviewed and they include ionic gelation, Co-acervation, solvent evaporation, spontaneous emulsification or solvent diffusion, salting out/emulsification-diffusion, supercritical fluid technology and polymerization [6]. Ibuprofen (IB) is a weak acid non-steroidal anti-inflammatory drug (NSAIDs) available in the market. Typically, this drug is orally effective in medical treatment of osteoarthritis, rheumatoid arthritis, inflammations, and a variety of pains. Prostaglandins have an important role in the production of pain, inflammation, and fever. So, this drug will act on prostaglandins [7]. The major side effect of this drug is known to irritate the GI tract.

Eudragit S100 is the co-polymer of poly(ethylacrylate, methyl-methacrylate and chlorotrimethyl-ammoniumethyl methacrylate) containing quaternary ammonium group. Eudragit® RS100 is commonly used for the formulation of controlled and sustained release dosage forms [8].

The rationale behind the selection of the work was to prepare the best formulation of Ibuprofen nanoparticles with less particle size,

uniform size distribution and good stability. Two polymers (Ethyl cellulose, Eudragit S-100) and two stabilizers (tween 80 and 0.4% PVA) were used. Comparative study was done among them to know the best stabilizer and the polymer for the preparation of Ibuprofen nanoparticles. In order to produce small particle size, often a high-speed homogenization or ultrasonicator may be employed [9].

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from Dr. Reddy Labs.Ltd, Hyderabad. EC and Eudragit S-100 was supplied from S.D Fine Chemicals Ltd, Mumbai.

METHODOLOGY

Preparation of nanoparticles:

Ibuprofen loaded polymeric nanoparticles were formulated by solvent evaporation technique. Four formulations were prepared. For F1, the drug and polymer (EC) were dissolved in a mixture of methanol and DCM in (1:1) ratio, each of 5 ml and added drop wise into the aqueous 0.4% PVA solution (100 ml). For F2 the drug and polymer (EC) were dissolved in a mixture of methanol and DCM in (1:1) ratio, each of 5 ml and added drop wise into the aqueous tween 80 solution (100 ml) under stirring at 1200 rpm. The stirring was continued until the organic solvent mixture was evaporated and then filtered. The same procedure was followed for Ibuprofen loaded Eudragit S-100 nanoparticles. F3 was prepared by using 0.4% PVA and F4 by tween 80 using same solvent mixture.

Comparative study was done for four formulations in order to know the best formulation for the preparation of Ibuprofen nanoparticles. The prepared nanoparticles were evaluated for percentage yield, drug content, encapsulation efficiency, loading capacity and drug release and characterized for particle size and surface charge.

Percentage yield

It was calculated using the formula

$$\% \text{ yield} = \frac{\text{Amount of nanoparticles}}{\text{Amount of drug and polymer}} \times 100$$

Drug content

50mg of the drug was accurately weighed and added 50 ml of methanol to it. The resulting mixture was agitated for 3 hrs on a mechanical stirrer. The solution was decanted and the drug content was estimated at 221 nm by U.V spectroscopy with suitable dilutions. The same procedure was done for four of the formulations.

Table 1: Polymers and stabilizers used for the formulations

Formulation	Polymer	Stabilizer
F1	EC	Tween 80
F2	EC	0.4% PVA
F3	Eudragit S-100	0.4% PVA
F4	Eudragit S-100	Tween 80

Encapsulation efficiency

The nanoparticle dispersion was transferred into centrifuge tube and centrifuged at 17640 rpm for 40 min at -4 °C. The entrapment efficiency was calculated by using the formula.

$$\text{Encapsulation efficiency} = \frac{\text{Amount of drug present in the nanoparticles}}{\text{Total amount of drug present in the collected nanoparticles}} \times 100$$

Loading capacity

The loading capacity (L.C) refers to polymer carrying capacity of the drug. It was determined by ultra centrifugation of the samples for 40 min at -4°C at 17640rpm.The amount of free Ibuprofen was determined in the clear supernatant solution by using U.V spectrophotometer at 221 nm.

$$\% \text{ Loading capacity} = \frac{\text{Total amount of drug} - \text{Amount of unbound drug}}{\text{Weight of nanoparticles}} \times 100$$

In vitro drug release studies:

In vitro drug dissolution studies were performed for F1, F2, F3 and F4 in an orbital shaker.50mg of all the formulations was taken in conical flasks with 50 ml 7.2 pH phosphate buffer. They were kept in orbital shaker at 100rpm at 37 C for 24 hrs.5 ml aliquots were withdrawn at 30 min, 2hr, 4hr,6hr.8hr,10hr,12hr and 24hr and replaced by buffer each time. These samples were analyzed in U.V spectrophotometer at 221 nm with necessary dilutions.

Nanoparticles Characterization

Particle Size Distribution (PSD)

The size of drug nanoparticles was measured immediately after precipitation by dynamic laser light scattering (Nanoparticles size analyzer, Horiba Sz-100). Before analysis, the drug suspension was diluted by purified water.

Zeta potential

It is a physical property in suspension. It is defined as the difference between the bulk solution (dispersing medium) and the surface of the hydrodynamic shear (slipping plane).It can be used to optimize the nanoparticle formulation for long time stability. It was measured by (Nanoparticles size analyzer, Horiba Sz-100).

RESULTS

The percentage yield of F1, F2, F3 and F4 were found to be 80%, 96%, 91%, 76% respectively and illustrated below in Fig.1.

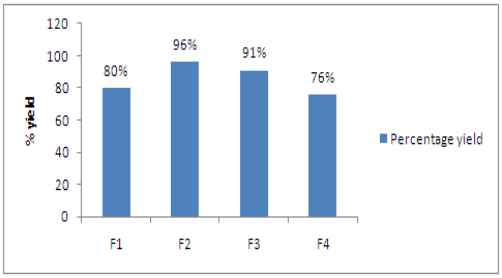


Fig. 1: Percentage yield of Ibuprofen loaded nanoparticles in F1, F2, F3 and F4.

The drug content of F1, F2, F3 and F4 were found to be 85%, 88.72%, 87.05% and 80.6% respectively and are illustrated below in Fig.2.

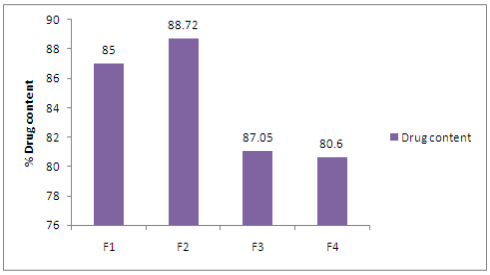


Fig. 2: Drug content of Ibuprofen loaded nanoparticles in F1, F2, F3 and F4.

The encapsulation efficiency of F1, F2, F3 and F4 was found to be 56.25%, 88.36%, 71.7% and 55.9% respectively and are illustrated below in Fig.3.

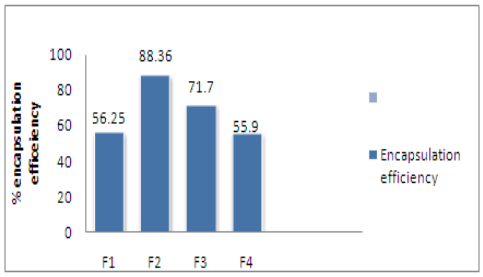


Fig. 3: Encapsulation efficiency of Ibuprofen loaded nanoparticles in F1, F2, F3 and F4.

The loading capacity of F1, F2, F3 and F4 were found to be 28.8%, 39.2%, 33% and 28.4% respectively and illustrated in Fig.4.

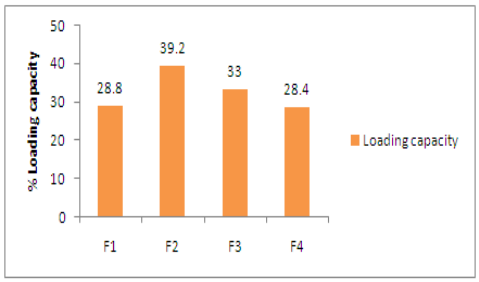


Fig. 4: Loading capacity of Ibuprofen loaded nanoparticles in F1, F2, F3 and F4.

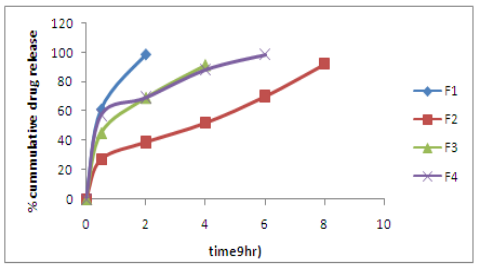


Fig. 5: Comparative drug release studies of F1, F2, F3 and F4 in pH 7.4 buffer.

The Invitro drug release of F1, F2, F3 and F4 was found to be 99.2%, 92.1%, 91.3% and 98.4% at the end of 2 hrs, 8hr, 4hr and 6hr respectively and illustrated in Fig.5.

Kinetic study

In Higuchi plot, % drug release was plotted against√t to know whether the release followed controlled fashion.

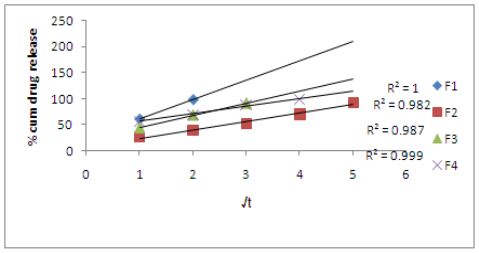


Fig. 6: Higuchi plot of Ibuprofen loaded nanoparticles in F1, F2, F3 and F4.

In Peppas plot, log % drug release was plotted against log t to know whether the release followed fickian or non fickian diffusion.

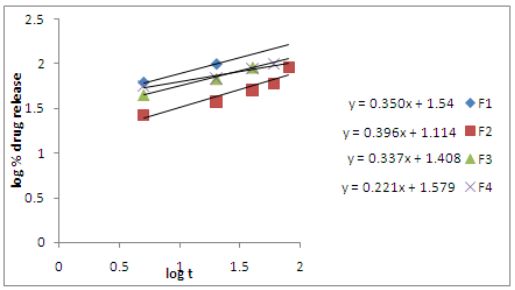


Fig. 7: Peppas plot of Ibuprofen loaded nanoparticles of F1, F2, F3 and F4.

In first order plot, a graph is drawn between log% remaining and time in hours.

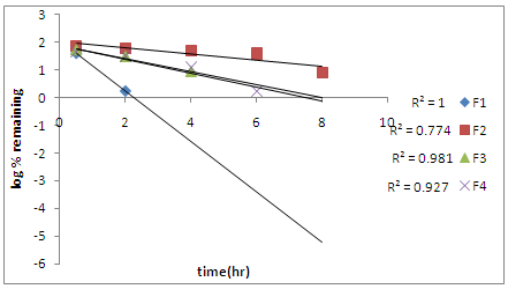


Fig. 8: First order plot of Ibuprofen loaded nanoparticles for F1, F2, F3 and F4.

The kinetic study was done to know release profile of the formulations. The Higuchi, first order and Peppas plots were drawn.

The correlation coefficients of the F1, F2, F3 and F4 are listed below:

Table 2: Correlation coefficients of kinetic plots of F1, F2, F3 and F4

Formulation	First order	Higuchi	Peppas(n Value)
F1	1	1	0.35
F2	0.774	0.982	0.39
F3	0.981	0.987	0.337
F4	0.927	0.99	0.221

The percentage yield, drug content, encapsulation efficiency, loading capacity and Invitro drug release studies of all four formulations were compared and found that F2 and F3 were more than the other two. On comparison the F2 and F3 showed controlled release. So F2 and F3 were characterized for average particle size and zeta potential.

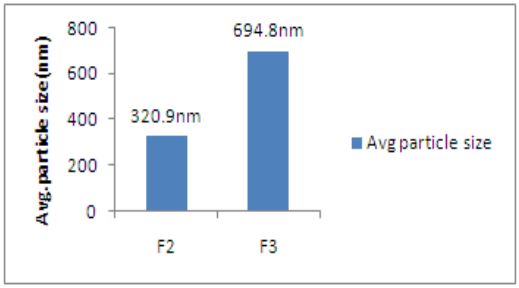
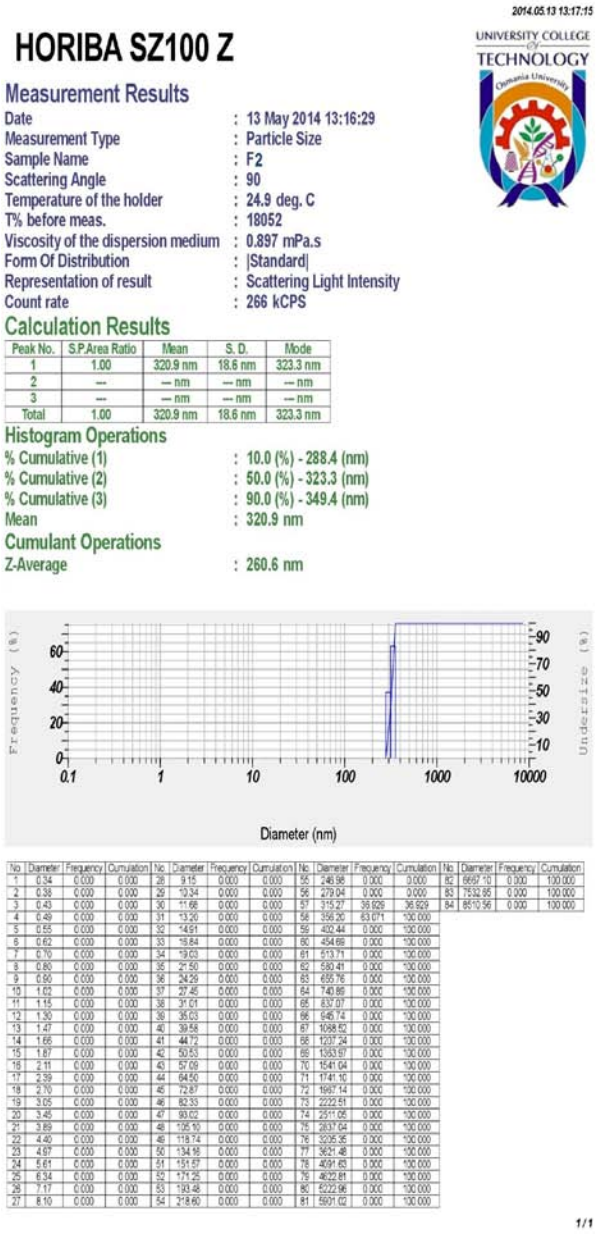


Fig. 9: Average particle size of Ibuprofen loaded nanoparticles for F2 and F3.



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Measurement Results

Date	: 13 May 2014 13:16:29
Measurement Type	: Particle Size
Sample Name	: F2
Scattering Angle	: 90
Temperature of the holder	: 24.9 deg. C
T% before meas.	: 18052
Viscosity of the dispersion medium	: 0.897 mPa.s
Form Of Distribution	: |Standard|
Representation of result	: Scattering Light Intensity
Count rate	: 266 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	320.9 nm	18.6 nm	323.3 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	320.9 nm	18.6 nm	323.3 nm

Histogram Operations

% Cumulative (1)	: 10.0 (%) - 288.4 (nm)
% Cumulative (2)	: 50.0 (%) - 323.3 (nm)
% Cumulative (3)	: 90.0 (%) - 349.4 (nm)
Mean	: 320.9 nm

Cumulant Operations

Z-Average	: 260.6 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	0.000	0.000	82	6697.10	0.000	100.000
2	0.38	0.000	0.000	29	10.34	0.000	0.000	56	279.04	0.000	0.000	83	7532.65	0.000	100.000
3	0.43	0.000	0.000	30	11.68	0.000	0.000	57	315.27	36.929	36.929	84	8510.56	0.000	100.000
4	0.49	0.000	0.000	31	13.20	0.000	0.000	58	356.20	63.071	100.000				
5	0.55	0.000	0.000	32	14.91	0.000	0.000	59	402.44	0.000	100.000				
6	0.62	0.000	0.000	33	16.84	0.000	0.000	60	454.69	0.000	100.000				
7	0.70	0.000	0.000	34	19.03	0.000	0.000	61	513.71	0.000	100.000				
8	0.80	0.000	0.000	35	21.50	0.000	0.000	62	580.41	0.000	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	1363.67	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	2837.64	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	0.000	0.000	81	5901.02	0.000	100.000				

1/1

Fig. 10: Average particle size of Ibuprofen loaded polymeric nanoparticles for F2 formulation

DISCUSSION

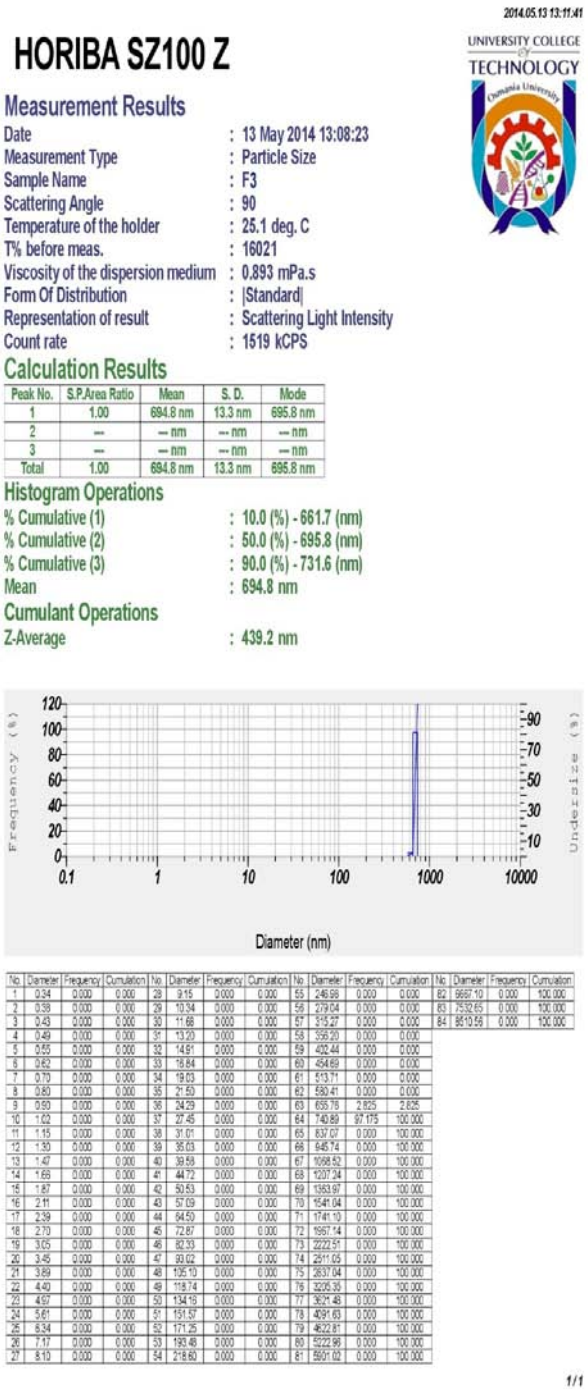
In this present study Ibuprofen loaded nanoparticles were prepared by solvent evaporation technique by using two polymers (EC and Eudragit S-100) and stabilizers(0.4% PVA and tween 80), DCM and methanol as the solvent mixture.

Ibuprofen is a non-steroidal non inflammatory drug used to treat osteo arthritis,rheumatoid arthritis and other inflammatory disorders. Ibuprofen is available in the form of tablets,capsules,gels and microspheres.In order to avoid systemic side effects and to achieve targetted drug delivery,attempts have made to prepare Ibuprofen nanoparticles.F1,F2,F3 and F4 were prepared by using EC with tween 80 and 0.4% PVA and Eudragit with the same stabilzers.

The effect of these two polymers and stabilizers on production yield,drug content,encapsulation efficiency,loading capacity and drug release were studied.The percentage yield was 80%,96%,91% and 76% drug content was 85%,88.72%.87.05% and 80.6%,encapsulation efficiency was 56.25%,88.36%,71.7% and 55.9%,loading capacity was 28.8%,39.2%,33% and 28.4% and Invitro drug release was 99.2%,92.1%,91.3% and 98.4% at the end of 2 hrs,8hr,4hr and 6hr for F1,F2,F3 and F4 respectively. By the kinetic study of the formulations, F2 and F3 showed controlled release. Among them F2 was considered better.

On comparision F2 was found to be better with EC polymer and F3 was better with Eudragit S-100.So, these both formulations were characterized for average particle size and zeta potential. Comparitive study was performed to determine the best formulation for Ibuprofen loaded nanoparticles The average particle size was found to be 320.9 nm for F2 and 694.8 nm for F3.

The zeta potential was found to be optimum for both the formulations.Based on the particle size,F2 was found to be the best formulation for Ibuprofen loaded polymeric nanoparticles.



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Measurement Results

Date	: 13 May 2014 13:08:23
Measurement Type	: Particle Size
Sample Name	: F3
Scattering Angle	: 90
Temperature of the holder	: 25.1 deg. C
T% before meas.	: 16021
Viscosity of the dispersion medium	: 0.893 mPa.s
Form Of Distribution	: |Standard|
Representation of result	: Scattering Light Intensity
Count rate	: 1519 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	694.8 nm	13.3 nm	695.8 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	694.8 nm	13.3 nm	695.8 nm

Histogram Operations

% Cumulative (1)	: 10.0 (%) - 661.7 (nm)
% Cumulative (2)	: 50.0 (%) - 695.8 (nm)
% Cumulative (3)	: 90.0 (%) - 731.6 (nm)
Mean	: 694.8 nm

Cumulant Operations

Z-Average	: 439.2 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	0.000	0.000	82	6697.10	0.000	100.000
2	0.38	0.000	0.000	29	10.34	0.000	0.000	56	279.04	0.000	0.000	83	7532.65	0.000	100.000
3	0.43	0.000	0.000	30	11.68	0.000	0.000	57	315.27	0.000	0.000	84	8510.56	0.000	100.000
4	0.49	0.000	0.000	31	13.20	0.000	0.000	58	356.20	0.000	0.000				
5	0.55	0.000	0.000	32	14.91	0.000	0.000	59	402.44	0.000	0.000				
6	0.62	0.000	0.000	33	16.84	0.000	0.000	60	454.69	0.000	0.000				
7	0.70	0.000	0.000	34	19.03	0.000	0.000	61	513.71	0.000	0.000				
8	0.80	0.000	0.000	35	21.50	0.000	0.000	62	580.41	0.000	0.000				
9	0.90	0.000	0.000	36	24.29	0.000	0.000	63	655.76	2.825	2.825				
10	1.02	0.000	0.000	37	27.45	0.000	0.000	64	740.89	97.175	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	1363.67	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	2837.64	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	0.000	0.000	81	5901.02	0.000	100.000				

1/1

Fig. 11: Average particle size of Ibuprofen loaded polymeric nanoparticles for F3 formulation

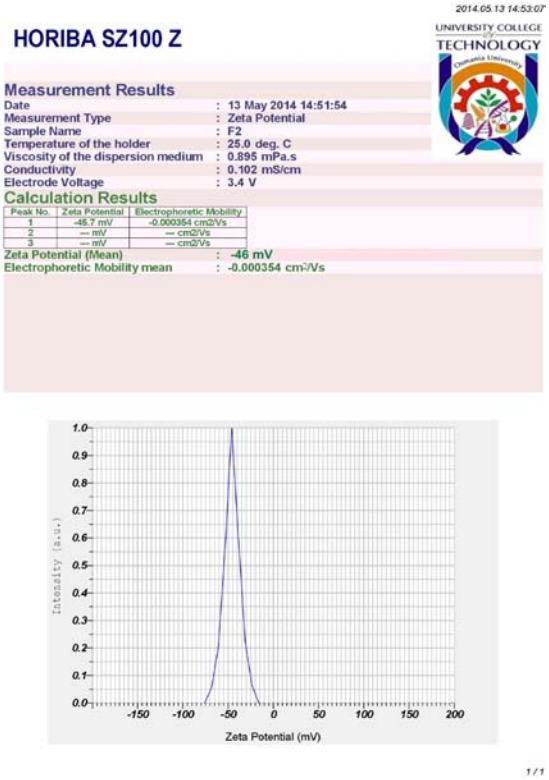

Fig. 12: Zeta potential of Ibuprofen loaded polymeric nanoparticles of F2 formulation

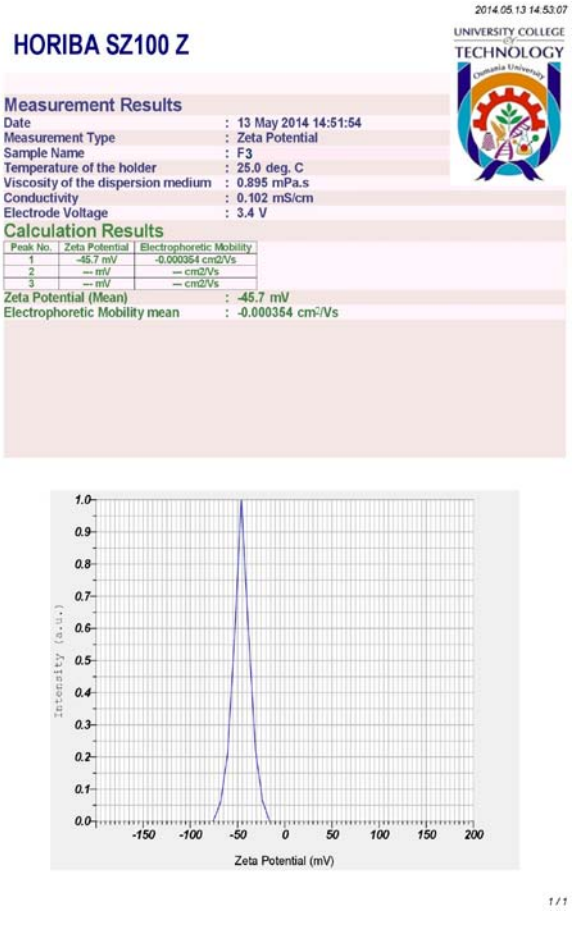

Fig. 13: Zeta potential of Ibuprofen loaded polymeric nanoparticles of F3 formulation

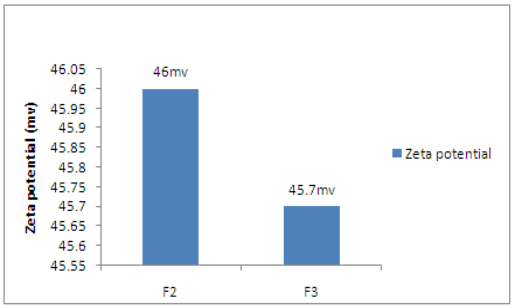

Fig. 14: Zeta potential of F2 and F3 formulations.

CONCLUSION

Ibuprofen loaded ploymeric nanoparticles were prepared by solvent evaporation technique using DCM and methanol as the solvent mixture,EC and Eudragit S-100 as polymers. The drug content, loading capacity and encapsulation efficiency were found to be more for the formulation prepared by EC with 0.4% PVA (F2) The *In vitro* drug release studies revealed that the nanoparticles prepared by EC with 0.4% PVA(F2) could be able to control drug release for extended period of time (8 hrs) than F3.

CONFLICT OF INTERESTS

Declared None

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