FORMULATION AND EVALUATION OF FLURBIPROFEN NANOPARTICLES

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Abstract: Flurbiprofen nanoparticles were prepared by emulsion -droplet coalescence method and the polymer concentrations were optimized by various trials In the present study Chitosan nanoparticles containing Flurbiprofen was prepared. The effect of increase in Chitosan concentration on various parameters like particle size and invitro release profile were studied. The Flurbiprofen nanoparticles were formulated and evaluated for its invitro drug release profile. The results showed that the in vitro drug release for FNP1, FNP2, FNP3, FNP4 and FNP5 were found to be 99.45± 0.31, 99.41± 0.17, 99.45± 0.19, 73.65± 0.15 and 69.76± 0.23 respectively at the end of 24hr. Based on the drug content,entrapment efficiency,particle size,zeta potential and in vitro drug release profile of Flurbiprofen nanoparticles formulations (FNP1-FNP5) formulation FNP3 was selected as the best formulation in which the particle size was 271.4nm. The in vitro % drug release of FNP3 formulation was 99.45± 0.19 at the end of 24 hr and it was found to be suitable formulation to manage the condition of rheumatoid arthritis. Hence it can be concluded that the newly formulated controlled release nanoparticulate drug delivery systems of Flurbiprofen may be ideal and effective in the management of pain due to arthritis by allowing the drug to release continuously for 24 hr.

Keywords: Formulation, Evaluation, Flurbiprofen, Nanoparticles

1. INTRODUCTION

Over the years, nanoparticles (NPs) made of both organic and inorganic materials have been engineered to circumvent the biological barriers and deliver drugs for a variety of indications.[1], [2] Water-insoluble or hydrophobic drugs, pose a challenge in terms of achieving optimal bioavailability and thereby, adequate efficacy.[3] As reported in 2015, 40% of drugs on the market and 90% of drugs within the discovery pipeline face solubility issues.[4] Other statistics, cite 40% of all potential drug candidates were shelved as a result of intrinsic aqueous solubility issues.[5] Thus, a number of hydrophobic drugs, which could potentially be useful for treatments are in need of clinically acceptable carriers.[6]

For the purpose of this review article, drug nanocrystals may be defined as pure solid particles with a mean diameter <1 μm and a crystalline character. The platform offers an exceptional opportunity to deliver hydrophobic drugs. Its uniqueness originates from the fact that nanocrystals are composed entirely of 100% drug or the payload thereby eliminating the ancillary role of a carrier.[7] In addition, surfactants or stabilizers are commonly used to stabilize the crystalline dispersions in liquid media.

Nanocrystalline drug technology improves the solubility of hydrophobic drugs due to an increased surface area to volume ratio and improved dissolution rates (i.e., dissolution velocity) associated with nanosizing.[8] The drug crystals are singularly well-suited for the rehabilitation of previously unsuccessful Biopharmaceutics Classification System (BCS) Class II and IV drugs (low solubility drugs).[9] The BCS classification system is an experimental model that measures permeability and solubility under prescribed conditions. The system divides the drugs into four classes. While Class I drugs have high solubility and high permeability, Class II molecules have low solubility and high permeability, Class III identifies with high solubility and low permeability, and drugs in Class IV have low solubility and low permeability.[4]

Nanocrystal drug formulations have also been shown to be stable in suspensions and are often referred to as nanocrystal colloidal dispersions (NCD's). The dispersions provide a platform for easy scale-up and manufacturing of highly stable and marketable products. Their synthesis and scale-up considerations have been described at length elsewhere.[10], [11] Commonly used synthesis techniques include the use of microfluidic based platforms or the milling method, which, among others, is both flexible and tunable.[7], [12], [13], [14], [15], [16], [17] Taken together, the nanocrystal drug technology has been studied extensively and is well positioned for further exploration in the field of drug delivery.

Several hydrophobic drugs have been salvaged via the nanocrystal formulation method. The drugs were successfully developed, and approved by the FDA to treat a variety of indications ranging from dental disorders to cancer in the

clinic.[14], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28] Depending on the disease, the approved formulations can be administered via different routes including oral, dermal, and parenteral. This highlights the versatility of a nanocrystal drug platform. Pharmacokinetic, biodistribution, and bioavailability data for organs involved in delivery routes tested using nanocrystal technology have been addressed at length previously.[10], [13], [18], [24], [25], [29], [30], [31], [32], [33], [34] Specifically, the reviews of Lu et al. 2016 and 2017 delve into the biodistribution pattern of nanocrystal drugs in the blood, heart, liver, spleen, lung, kidney, tumor, and thymus (i.e., the organs involved in clearance/circulation and host immune responses).[24], [35]

The main aim of present study is to prepare and characterize polymeric nanoparticlesfor the selected drug Flurbiprofen is a member of the phenylalkanoic acid derivative family of nonsteroidal anti- inflammatory drugs (NSAIDs). It is primarily indicated as a pre-operative anti-miotic (in an ophthalmic solution) as well as orally for arthritis or dental pain. Side effects are analogous to those of ibuprofen.Flurbiprofen is in a group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Flurbiprofen works by reducing hormones that cause inflammation and pain in the body.Flurbiprofen is used to treat pain or inflammation caused by arthritis.

MATERIALS AND METHODS

List of Materials :

Table 1. Materials used

Materials	Supplier
Flurbiprofen	Sigma aldrich pvt.ltd
Chitosan	Sigma aldrich pvt.ltd
Poloxamer	Sigma aldrich pvt.ltd
Ethanol	Sigma aldrich pvt.ltd
Potassium di hydrogen phosphate	M/S SD Fine Chemicals, Mumbai, India
Ortho phosphoric acid	M/S SD Fine Chemicals, Mumbai, India

METHODS :

Preformulation studies:

Preparation of calibration graph for Flurbiprofen:

Preparation of calibration curve in pH 1.2, pH 7.2 and pH 6.8 buffer solutions:

An accurately weighed amount of Flurbiprofen 100mg was dissolved in small volume of buffer solutions in each of three 100 ml volumetric flask and the volume was adjusted to 100 ml with 1.2 pH buffer in first volumetric flask, 7.2 pH buffer in second volumetric flask and the third one was adjusted to 100 ml with 6.8 pH buffer. A series of standard solution containing in the concentration range from 10 to 50 µg/ml of Flurbiprofen were prepared for 1.2 pH buffer solution, 7.2 pH buffer solution and 6.8 pH buffer solution separately, absorbance was measured at 247 nm and calibration graph was plotted using concentration versus absorbance.

Drug-excipient compatibility study by DSC:

Differential scanning calorimetry (DSC):

Samples of individual components as well as each drug-excipient were weighed (Mettler Electranic balance) directly in pierced aluminum crucible pans (5-10 mg) and scanned in the 50-300°C temperature range under static air, with heating rate of 10 ºC /min, using shimadzu DSC-60 equipment.

METHOD OF PREPARATION:

Table 2. Formula used for the preparation of Flurbiprofen nanoparticles :

S.NO	FORMULATION	DRUG (mg)	CHITOSAN (%W/V)	TWEEN(%V/V)
1.	**FNP-1**	100mg	0.5	5
2.	**FNP -2**	100mg	1	5
3.	**FNP -3**	**100mg**	**1.5**	**5**
4.	**FNP -4**	100mg	2	5
5.	**FNP -5**	100mg	2.5	5

METHOD:

PREPARATION OF FLURBIPROFEN NANOPARTICLES BY EMULSION -DROPLET COALESCENCE METHOD

- Chitosan was dissolved in 1% acetic acid and 100 mg of Flurbiprofen in phosphate buffered saline. This solution was added to 10 ml of liquid paraffin containing 5% v/v tween 20. This mixture was stirred using a homogenizer 3 minutes to form water in oil (w/o) emulsion.
- The resultant Flurbiprofen nanoparticles were centrifuged at 3000 rpm for 60 mts and washed using ethanol and water, consecutively to remove the remaining surfactant andliquid paraffin.
- Later they were dried in air for 3 hour followed by hot air oven at 50° for 4 hour and stored in a dessicator
- Several batches namely **(FNP1, FNP2, FNP3, FNP4 and FNP5)** were formulated by changing the drug and polymeric ratio and the effect of polymer concentration on the encapsulation efficiency and the drug loading capacity was studied.

CHARACTERIZATION STUDIES

- Particle size and zeta potential
- Drug content
- Encapsulation efficiency
- In vitro drug release

Particle size and Surface charge :

Surface charge is important in adhesion and interaction of particle with cells. The zeta- potential is used to measure the cell surface charge density. It can be measured using Malvern-Zeta sizer. The prepared nanoparticles were evaluated for their particle size and surface charge by photon correlation spectroscopy (PCS) using zeta sizer. The formulations were diluted to 1:1000 with the aqueous phase of the formulation to get a suitable kilo counts per second (kcps). Analysis was carried out at 25°C with an angle of detection of 90°. In this experiment six replicates were taken for the measurement. The results were given in results and discussion section.

Drug content:

1gm of Flurbiprofen nanoparticles were accurately weighed and transferred into a 25ml volumetric standard flask. The sample was dissolved with methanol .1ml of this solution was diluted to 25ml with the purified water. The standard Flurbiprofen was dissolved and diluted with same methanol and water respectively.
Then the standard and sample absorbance was measured at 247 nm using UV-Visible spectrophotometer. The percentage of drug content was calculated. The results were given in results and discussion section.

Entrapment efficiency :

The drug loaded nanoparticles in buffer solutions were subjected to centrifugation at 15000 rpm for 30 min.The supernatant liquid was separated and 1ml of this solution was diluted withbuffer solution and the absorbance was

measured at 247 nm. The amount of Flurbiprofen unentrapped in the supernatant was calculated. The amount of Flurbiprofen entrapped was determined by subtracting amount of free unentrapped Flurbiprofen from the total amount of Flurbiprofen taken for the preparation.
The formula used to calculate entrapment efficiency was given below

$$\text{Drug entrapment}(\%) = \frac{\text{mass of drug in nanoparticles x100}}{\text{mass of drug used in formulation}}$$

The results were given in results and discussion section.

In vitro drug release:

The release of Flubiprofen nanoparticles were carried out using USP Type II dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. The drug release studies were carried out in 7.2 pH phosphate buffer. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered, by filtering through 0.45 µm membrane filters and analyzed spectrophotometrically at247 nm. From the absorbance values the cumulative percentage drug release was calculated. The results were given in results and discussion section.

RESULTS AND DISCUSSION

Preformulation studies :

Preparation of calibration graph for Flurbiprofen :

Standard calibration data of Flurbiprofen in pH 1.2, 7.2 and 6.8 buffers at 247 nm

Table 3. Absorbance of Flurbiprofen in buffer solutions :

S.No	Concentration (µg / ml)	Absorbance		
		pH 1.2	pH 7.2	pH 6.8
1	10	0.050	0.102	0.070
2	20	0.102	0.203	0.142
3	30	0.152	0.305	0.210
4	40	0.201	0.402	0.285
5	50	0.253	0.507	0.351

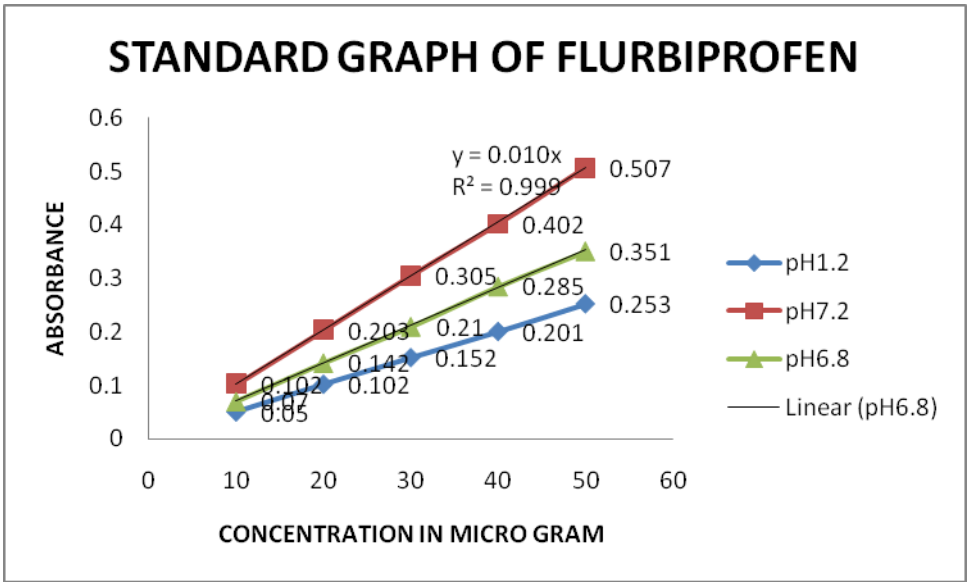

Fig. 1.Calibration curve of Flurbiprofen in pH 1.2,7.2 and 6.8 buffers

Standard calibration curve of Flurbiprofen was carried out in 1.2 pH, 7.2 pH and 6.8 pH bufferat 247 nm. The r^2 value in the entire medium shows nearly 1, which signifies linearity.

DSC analysis

DSC of Flurbiprofen showed a sharp endothermic peak at about 117^0C (melting point). The physical mixture of Flurbiprofen with other excipients also showed the same thermal behavior(120.01^0C) as the individual component. DSC results also revealed that the physical mixture of Flurbiprofen with excipients showed superimposition of the thermogram. There was no significant change observed in melting endotherm of physical mixture of Flurbiprofen and excipients.

Hence from the DSC study, it was found that there was no interaction between Flurbiprofen and other excipients used in the formulation.

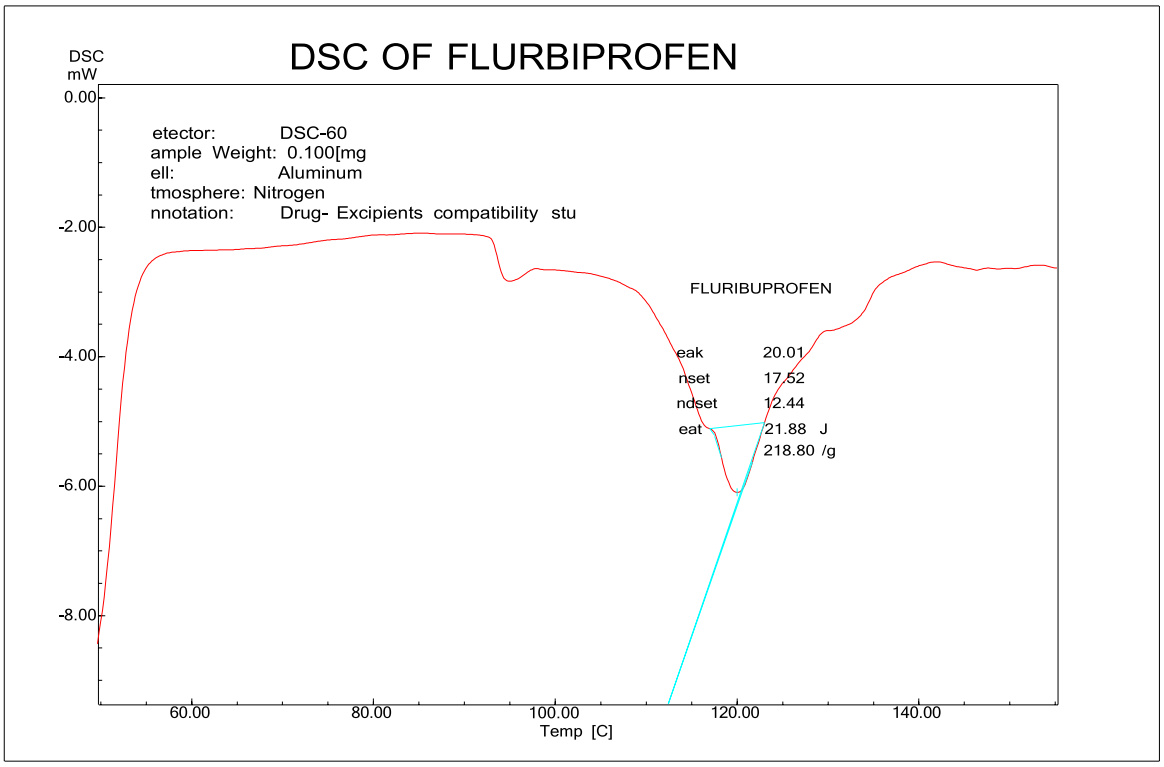

Fig.2

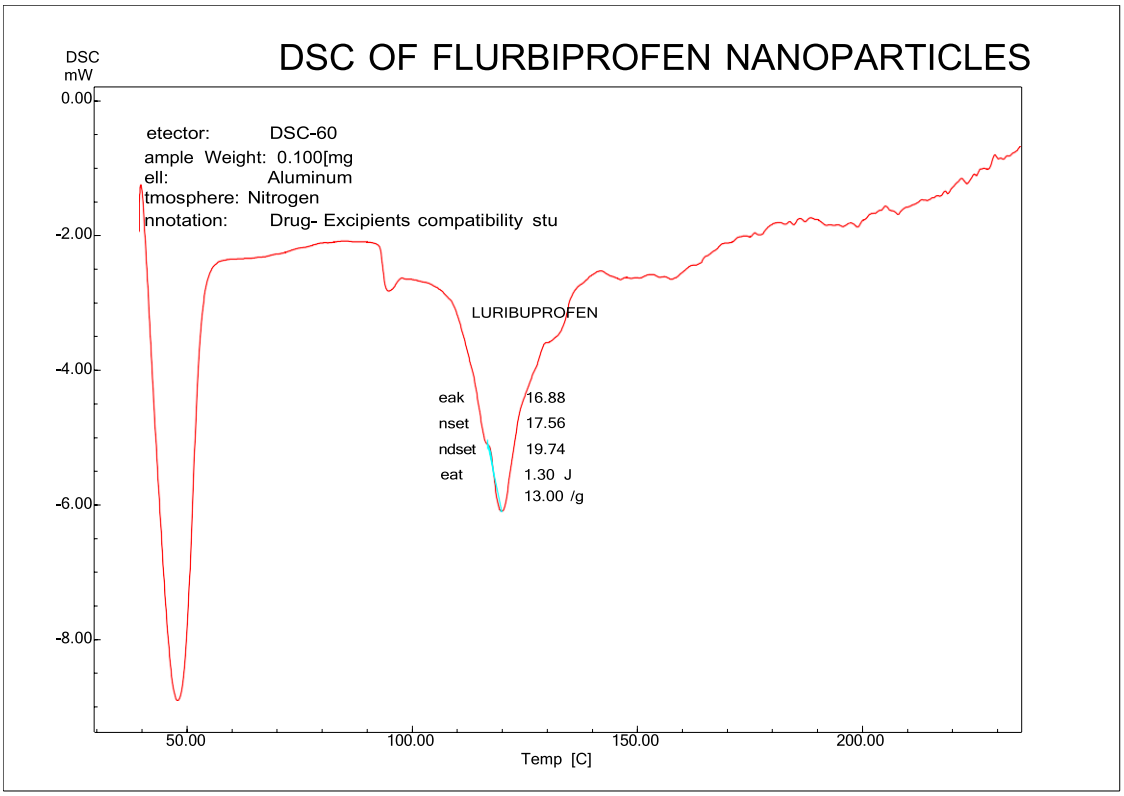

Fig.3

DSC Thermogram of Flurbiprofen and Flurbiprofen nanoparticlesDrug –Excipients accelerated compatibility study - Physical observation and assay

Upon analysis of the drug excipient mixture for their physical characteristics no colour changewas observed. Based on the chemical evaluation it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients. The results of this study were given in Table 7.2

Table 4. Physical characteristics of Flurbiprofen :

S.No	Physical parameters	Results
1	Description	White crystalline powder
2	Melting point	117°C
3	Loss on drying	0.04%
4	Assay	99.47%

Table 5. Physical characteristics of individual drug and excipients

S.No	Sample ID	Initial Description	Final Description
1.	Flurbiprofen	White crystalline powder	No change
2.	Chitosan	off-white powder	No change

Table 6. Physical characteristics of drug-excipient mixture

S.No	Sample ID	Initial Description	Final Description
1	Flurbiprofen	White crystalline powder	No change
2	Flurbiprofen+ Chitosan	Off White powder	No change

Table 7. Chemical characteristics of drug-excipient mixture

S.No	Sample ID	Initial Assay (%)	Final Assay (%)
1.	Flurbiprofen	99.47%±0.13	99.46%±0.14
2.	Flurbiprofen+ Chitosan	99.48%±0.04	99.41%±0.12

n = 3; Mean ± S.E.M.

Table.8. Drug content and entrapment efficiency Particle size and zeta potential ofFlurbiprofen nanoparticles.

Trials	Zeta potential (mV)	Particle size (nm)	Entrapment Efficiency (%)	Drug Content (%)
FNP1	18.5	385.5	51.75	99.38
FNP 2	15.2	355.7	67.83	99.41
FNP 3	**14.7**	**271.4**	**85.73**	**99.46**
FNP 4	12.3	267.8	85.50	99.37
FNP 5	11.9	260.4	85.13	99.35

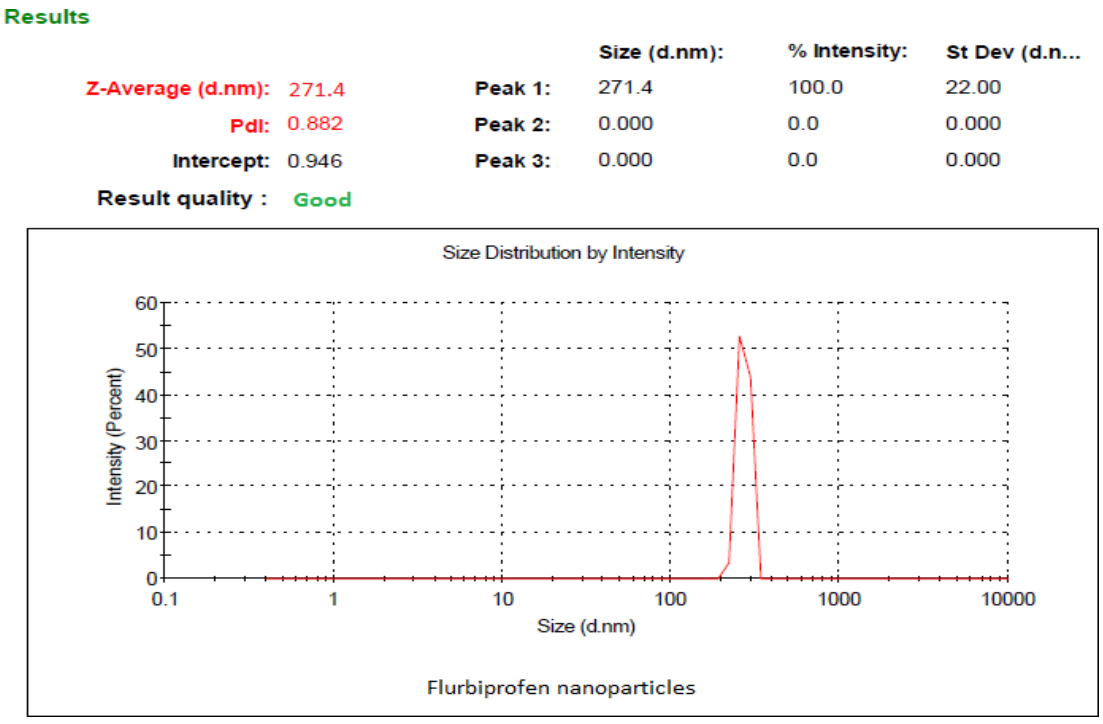

Fig.4.Particle size of optimized Flurbiprofen nanoparticles (FNP3)

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): 14.7	Peak 1:	14.7	100.0	4.53
Zeta Deviation (mV): 4.53	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.0720	Peak 3:	0.00	0.0	0.00
Result quality : Good				

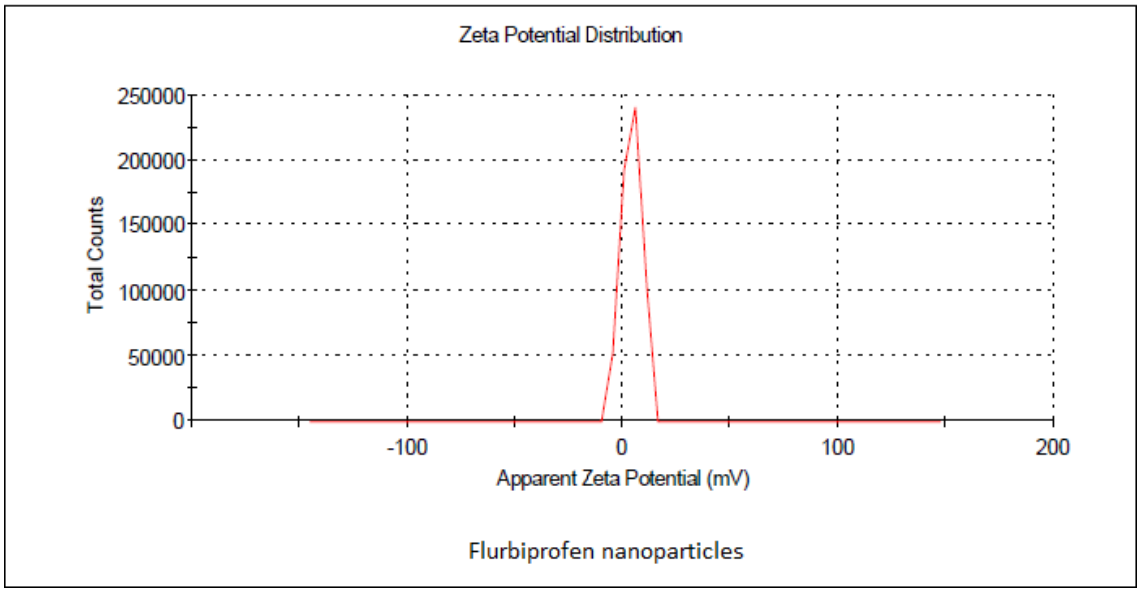

Fig.5. Zeta potential of optimized Flurbiprofen nanoparticles (FNP3)

- Particle size and entrapment efficiency of the **Flurbiprofen nanoparticles** (**FNP1-FNP3**) were increased with increasing Chitosan concentration.
- This may be due to high amount of availability of Chitosan to encapsulate the drug, upon increasing the Chitosan concentration, number of layers coated the drug was increased, this resulted in increased particle size and entrapment efficiency.
- Further increase in the Chitosan concentration (FNP4-FNP5), there is no much increase in the entrapment efficiency due to the availability of the drug to be incorporated is low which is not enough for further encapsulation of drug by Chitosan.

In- vitro drug release :

Table 9. In vitro release studies of Flurbiprofen nanoparticles :

S.NO	Time(Hrs)	%CUMULATIVE DRUG RELEASE				
		FNP1	FNP 2	FNP 3	FNP 4	FNP 5
1	0.5	68.43± 0.12	60.84± 0.21	**35.72± 0.22**	20.16± 0.21	15.83± 0.34
2	1	76.46± 0.26	70.73± 0.67	**43.86± 0.13**	31.78± 0.14	23.65± 0.96
3	6	89.76± 0.09	85.12± 0.62	**52.37± 0.26**	39.82± 0.47	33.46± 0.57
4	12	**99.43± 0.07**	90.16± 0.76	**62.35± 0.57**	48.76± 0.78	45.82± 0.68
5	16	99.41± 0.12	94.82± 0.21	**73.86± 0.78**	55.81± 0.65	51.39± 0.76
6	20	99.43± 0.11	**99.42± 0.07**	**85.56± 0.21**	65.65± 0.56	60.92± 0.38
7	24	99.45± 0.31	99.41± 0.17	**99.45± 0.19**	**73.65± 0.15**	**69.76± 0.23**

mean±S.D, n=3

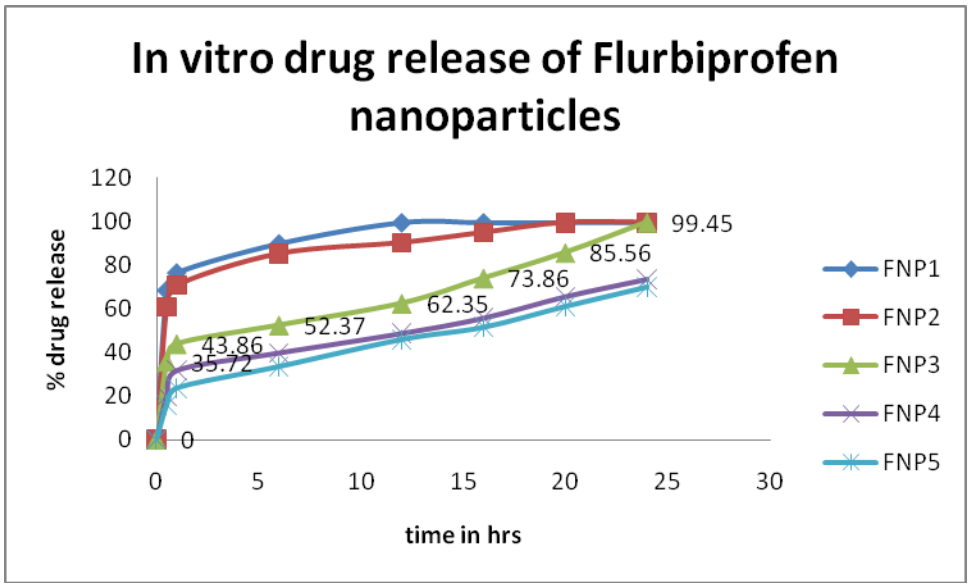

FIG.6.

Effect of Chitosan concentration on Invitro drug release of Flurbiprofen nanoparticles : From the in vitro drug release study results, the maximum percentage drug release (**99.45±0.19**) at the end of 24hwas observed with trial **FNP3** which contains **100mg of drug** and **1.5%w/v of Chitosan**.
Below**1.5% w/v of Chitosan** concentration as in the case of trials **FNP1** and **FNP2** the maximum percentage drug release **99.43± 0.07** and **99.42± 0.07** were obtained at the end of 12 and 20 respectively which was not desirable.
Above **1.5% w/v of Chitosan** concentration, reduction in drug release was observed as in the case of trial **FNP4** and **FNP5**. The maximum percentage drug release for **FNP4** and **FNP5** were found to be **73.65± 0.15** and **69.76± 0.23** respectively at the end of 24h was obtained.
From the in vitro drug release data for **FNP1- FNP5,** it was observed that increase in Chitosanconcentration delays the drug release due to increased particle size and reduced surface area ofthe prepared nanoparticles.
From all the formulations, **FNP3** was selected as best formulation due to its ideal particle size(271.4 nm), high entrapment efficiency (**85.73%**) and desirable drug release (**99.45± 0.19**% atthe end of 24 h).

SUMMARY AND CONCLUSIONS

The active pharmaceutical ingredient Flurbiprofen was evaluated for its Organoleptic properties and solubility. The results obtained were satisfactory.

Flurbiprofen nanoparticles were prepared by emulsion -droplet coalescence method and the polymer concentrations were optimized by various trials

In the present study Chitosan nanoparticles containing Flurbiprofen was prepared. The effect of increase in Chitosan concentration on various parameters like particle size and invitro release profile were studied.

The Flurbiprofen nanoparticles were formulated and evaluated for its invitro drug release profile. The results showed that the in vitro drug release for **FNP1, FNP2, FNP3, FNP4** and **FNP5** were found to be **99.45± 0.31, 99.41± 0.17**, **99.45± 0.19**, **73.65± 0.15** and **69.76± 0.23**
respectively at the end of 24hr.

Based on the drug content,entrapment efficiency,particle size,zeta potential and in vitro drug release profile of Flurbiprofen nanoparticles formulations **(FNP1-FNP5)** formulation **FNP3** was selected as the best formulation in which the particle size was **271.4nm**.

The in vitro % drug release of **FNP3** formulation was **99.45± 0.19** at the end of 24 hr and it was found to be suitable formulation to manage the condition of rheumatoid arthritis. Hence itcan be concluded that the newly formulated controlled release nanoparticulate drug delivery systems of Flurbiprofen may be ideal and effective in the management of pain due to arthritis by allowing the drug to release continuously for 24 hr.

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