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Formulation and Characterization of Nanoparticle Based Drug Delivery System of Flurbiprofen

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ABSTRACT

In the present study Chitosan nanoparticles containing Flurbiprofen was prepared. The effect of increase in Chitosan concentration on various parameters like particle size and *in-vitro* release profile were studied. The Flurbiprofen nanoparticles were formulated and evaluated for its *in-vitro* 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.

1. INTRODUCTION

Nano Drug Delivery Systems

Nano drug delivery systems represent a promising drug delivery system of controlled and targeted drug release. They are specially designed to release the drug in the vicinity of target tissue. They exist as particulates or globular dispersions with a size in the range of 10-1000nm. In nano drug delivery systems, the drug or active ingredient is dissolved, entrapped, encapsulated, adsorbed or attached to the matrix system.[1,2]

Nano sized materials have more advantages over other dosage forms with larger particle size, as it can provide more surface area and increased solubility. It also provides the facility to control the drug release along with the ability to deliver the entrapped therapeutic agents to the desired site of action. Nano drug delivery systems are widely investigated for the oral delivery of drugs. Oral delivery is the most preferred route of drug administration due to convenience, patient compliance and cost-effectiveness. This system has been also used to increase bioavailability of drugs having poor bioavailability. However, due to the small size, extensive research was carried out on administration of these systems by various parenteral routes like intravenous, intra muscular and subcutaneous routes. The drugs loaded in nano drug delivery system were also reported to exhibit improved shelf life and stability.[3-4]

The wide choice of methods of preparation available to formulate these dosage forms facilitates utility of various polymers, inorganic materials, proteins and even lipids. But the components used for the preparation should be nontoxic, biodegradable, non-immunogenic and non-inflammatory. The nano drug delivery systems has been reported for incorporation of anticancer, anti-Alzhiemeric, Antiparkinson, analgesic, anti-inflammatory, antiviral, anti-infective agents etc.

Merits of Nano Drug Delivery Systems:[5]

1. They can be enabled with site specific delivery of drugs.
2. Site specific delivery of drugs facilitates enhanced therapeutic response and reduction in adverse effects.
3. Drug degradation by enzymatic action can be prevented.

4. Active and passive targeting of drug can be achieved by manipulating the particle size and surface characteristics.

5. Suitable for incorporation of wide range of therapeutic agents ranging from inorganic, organic, synthetic, semi-synthetic compounds, lipids and proteins.

6. They can be used for administration by oral, nasal, parenteral and ocular routes.

7. Controlled release of drug can be achieved.

8. Surface modification using ligands can be made to improve the specificity of drug targeting.

Demerits[6]

1. Aggregation of particles due to their small size and large surface area, however, this problem can be overcome by adjustment of surface charge (zeta potential) of the nanoparticles by addition of suitable surface active agents.

2. Difficult to handle in liquid forms (nanosuspensions). Freeze drying (lyophilization) had facilitated the maintenance of nanoparticles in dry form with enhanced stability.

Types of Nanoparticles[7,8]

Nano drug delivery systems are classified based on the morphological characters, structure, composition as well as the arrangement of drug and polymer in the formulation:

Polymeric Nanoparticles:

The polymeric nanoparticles can be further classified into two types:

1. Nanospheres, which are polymeric matrix systems which consist of the drug that is dispersed physically and uniformly. The polymeric nano sized spherical matrix system provides effective control of the loaded drugs.

2. Nanocapsules are those systems containing vesicles in which the drug is confined to a cavity surrounded by a polymer membrane. In nanocapsules, the polymeric membrane encapsulates the core material, usually a drug.

Drug Loading in Nanoparticles[9]

Nano drug delivery systems are exhibited with high drug loading capacity. This ability reduces the amount of the excipients like polymers, lipids etc. required for drug delivery in the body. The incorporation of the drug into nanoparticles can be carried out by two methods.

a) By incorporating the drug at the time of preparation of nanoparticles

b) After the formation of nanoparticles, the drug is adsorbed which is achieved by incubating nanoparticles in a concentrated drug solution.

Various factors like chemical structure of drugs and polymer and condition of drug loading influences the amount of drug bound to nano drug delivery systems.

Mechanism of Drug Release[10]

Sustained/controlled release of drug depends on release mechanism of the system. The drug release rate depends on various parameters like solubility of drug, desorption of the surface bound adsorbed drug, drug diffusion through matrix system of polymer. To improve the drug release a thorough understanding of the mechanism of drug release is required which includes knowledge of solubility, diffusion and biodegradation of the carrier system. On polymer based nano drug delivery systems such as polymeric nanoparticles the release rate of drug can be modified by varying the concentration of polymer in the matrix system. Larger particles have initially smaller burst release than small particles.

Applications of Nanoparticles: [11,12]

a) Cancer treatment: It can target tumor, sense the pathological changes in tumor cells and delivers the neurotherapeutic agents on tumors. Nanoparticles are nanosized but still these are bigger than many anticancer drugs which makes it difficult to evade many organs. Indeed, recently that researchers have begun to design nanoparticles which involves attaching molecules known as ligands which can actively target tumor cells.

b) Treatment of tuberculosis: Nanoparticles are used for directing antitubercular drugs in to the target cells as the causative microorganisms are found inside the cells. Nanoparticles provide sustained release of antitubercular drugs and increased their efficacy after oral administration.

c) Colon targeting: Colon specific drug delivery to target colon can help to improve bioavailability of drugs and helps in treating colon diseases like ulcerative colitis, chrons disease etc.

d) Brain targeting: The preclinical studies using nanoparticles are reported to cross blood brain barrier and delivers the neurotherapeutic agents to treat several central nervous system ailments like Parkinson's disease, Alzheimer's disease, schizophrenia and other neurodegenerative disorders. They are also being investigated as possible agents in imaging brain disorders.

Arthritis[13]

- Arthritis is very common but is not well understood. Actually, "arthritis" is not a single disease; it is an informal way of referring to joint pain or joint disease. There are more than 100 different types of arthritis and related conditions. People of all ages, sexes and races can and do have arthritis, and it is the leading cause of disability in America. More than 50 million adults and 300,000 children have some type of arthritis. It is most common among women and occurs more frequently as people get older.

- Common arthritis joint symptoms include swelling, pain, stiffness and decreased range of motion. Symptoms may come and go. They can be mild, moderate or severe. They may stay about the same for years, but may progress or get worse over time. Severe arthritis can result in chronic pain, inability to do daily activities and make it difficult to walk or climb stairs. Arthritis can cause permanent joint changes. These changes may be visible, such as knobby finger joints, but often the damage can only be seen on X-ray. Some types of arthritis also affect the heart, eyes, lungs, kidneys and skin as well as the joints.

Flurbiprofen[14]

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.

2. MATERIALS AND METHODS

MATERIALS: Flurbiprofen, chitosan, poloxamer was procured from Sigma Aldrich Pvt. Ltd. All other ingredients used was of analytical grade.

METHODS:

Pre-formulation 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.[15]

Differential scanning calorimetry (DSC)

Samples of individual components as well as each drug-excipient were weighed (Mettler Electronic balance) directly in pierced aluminium 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 Schimadzu DSC-60 equipment.[16]

Method of Preparation[17,18]:

Table 1. Formula used for the preparation of Flurbiprofen nanoparticles:

SR.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 and liquid paraffin.
- Later they were dried in air for 3 hour followed by hot air oven at 50° for 4 hour and stored in a desiccator.
- 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 [19]:

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[20]:

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 with buffer 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[21,22]:**

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 at 247 nm. From the absorbance values the cumulative percentage drug release was calculated. The results were given in results and discussion section.

3. 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 2. Absorbance of Flurbiprofen in buffer solutions:

Sr. 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

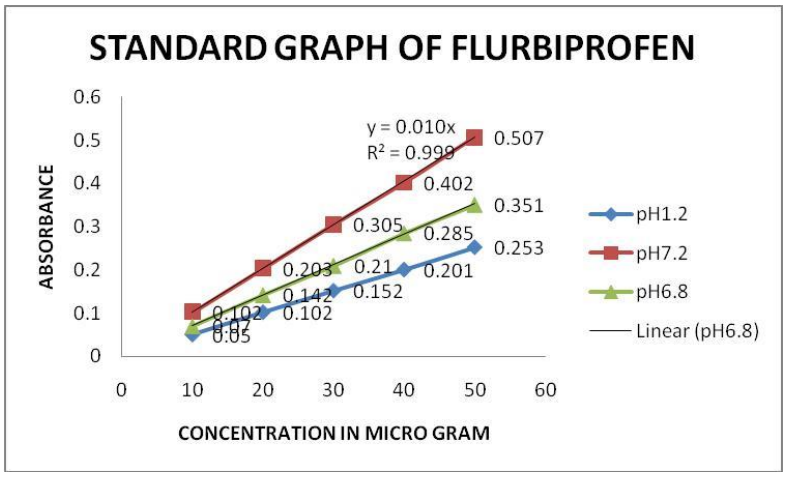

Fig. 1: Calibration curve of Flurbiprofen in pH 1.2,7.2 and 6.8 buffers

Standard calibration curve of Flurbiprofen was carried out in 1.2 pH, 7.2 pH and 6.8 pH buffer at 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 behaviour (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.

The DSC thermogram were given in the **Fig. 2 and 3.**

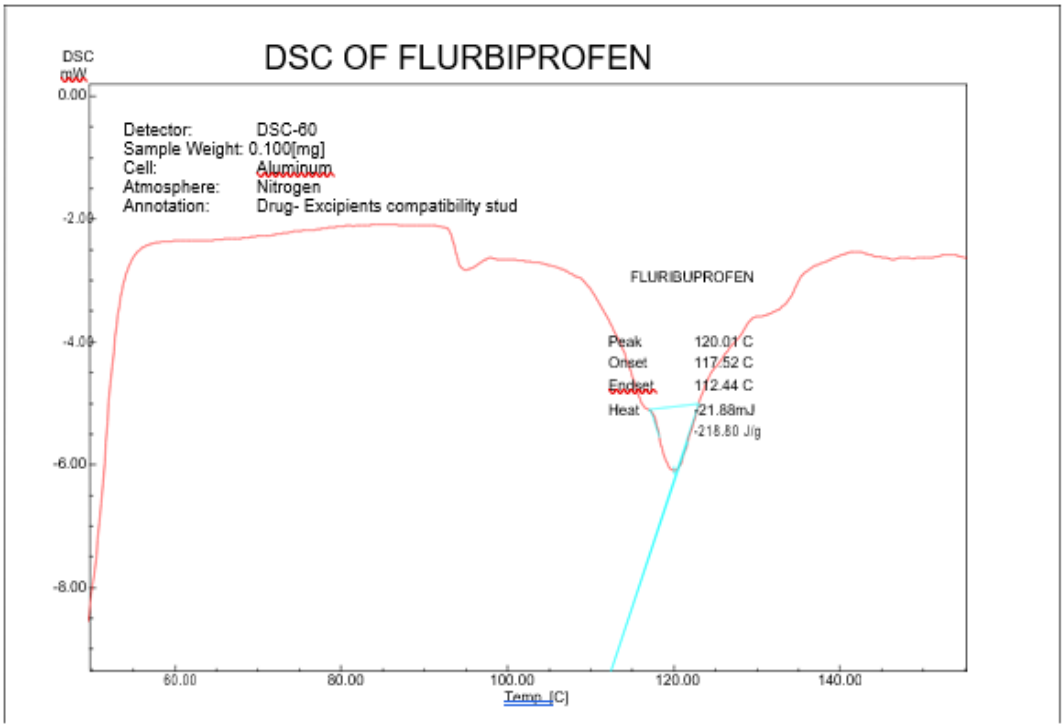

Fig.2

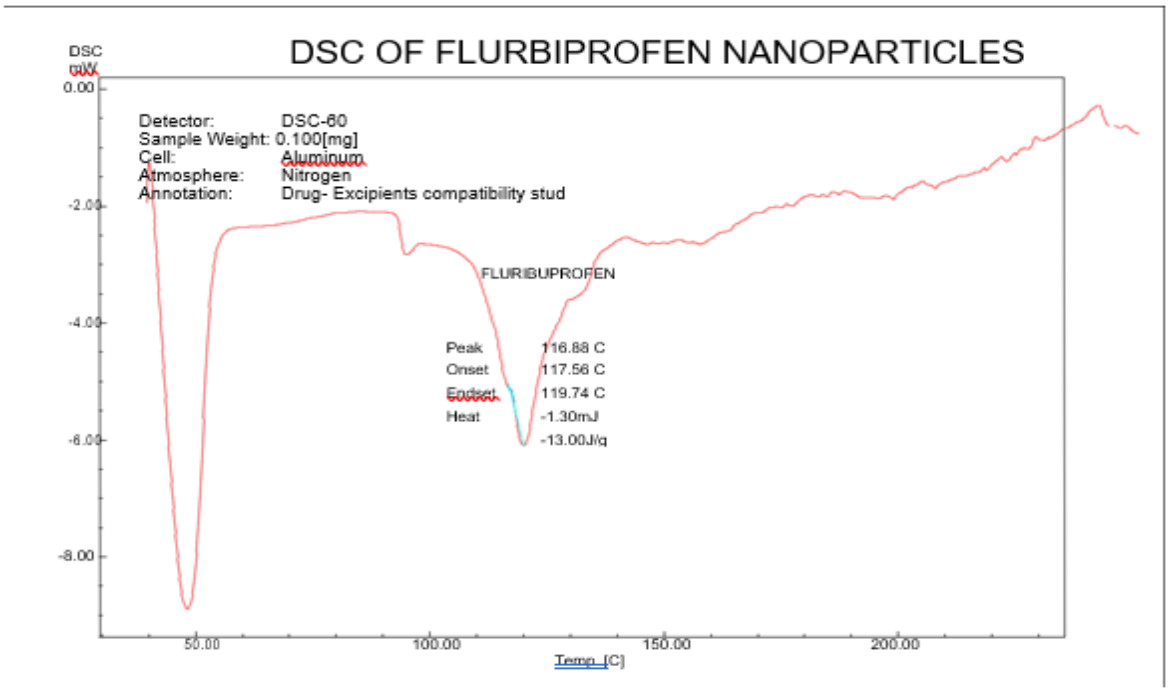

Fig.3

DSC Thermogram of Flurbiprofen and Flurbiprofen nanoparticles

Drug –Excipients accelerated compatibility study - Physical observation and assay

Drug –Excipients accelerated compatibility study - Physical observation and assay

Upon analysis of the drug excipient mixture for their physical characteristics no colour change was 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 3.

Table 3. Physical characteristics of Flurbiprofen:

Sr. 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 4. Physical characteristics of individual drug and excipients

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

Table 5. Physical characteristics of drug-excipient mixture

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

Table 6. Chemical characteristics of drug-excipient mixture

Sr. 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 7. Drug content and entrapment efficiency Particle size and zeta potential of Flurbiprofen 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

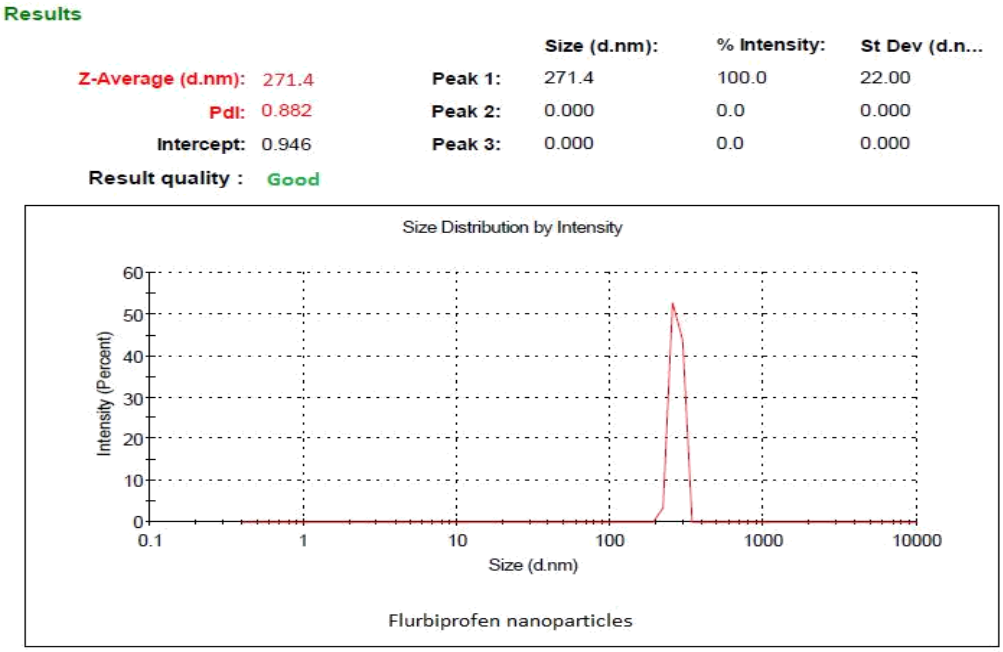

Fig.4. Particle size of optimized Flurbiprofen nanoparticles (FNP3)

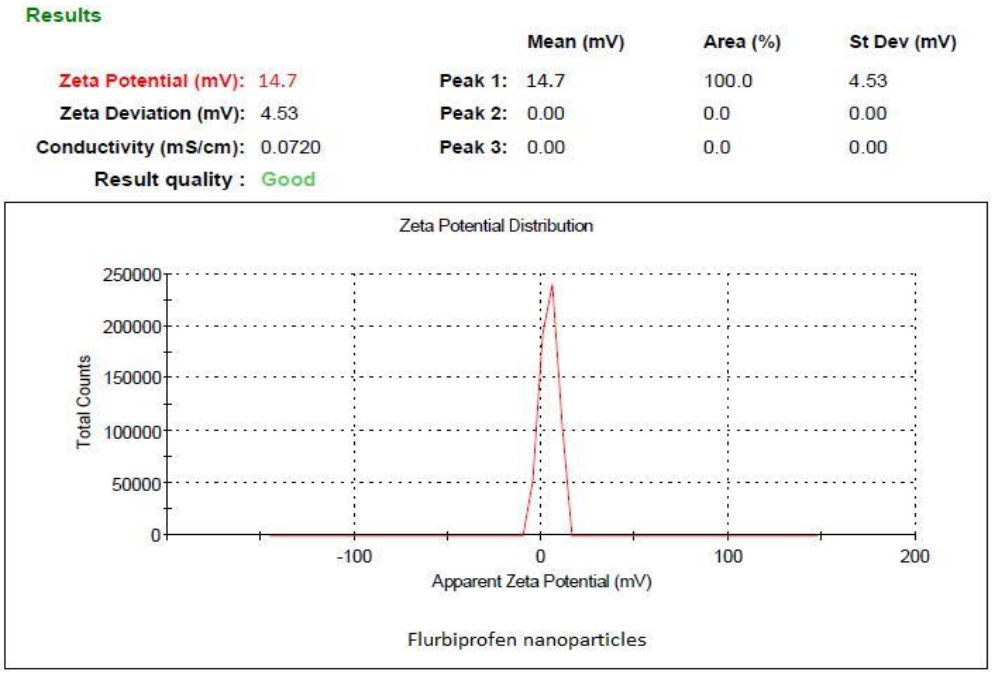

Fig.5. Zeta potential of optimized Flurbiprofen nanoparticles (FNP3)

➢ 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 8. *In vitro* release studies of Flurbiprofen nanoparticles:

Sr. 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

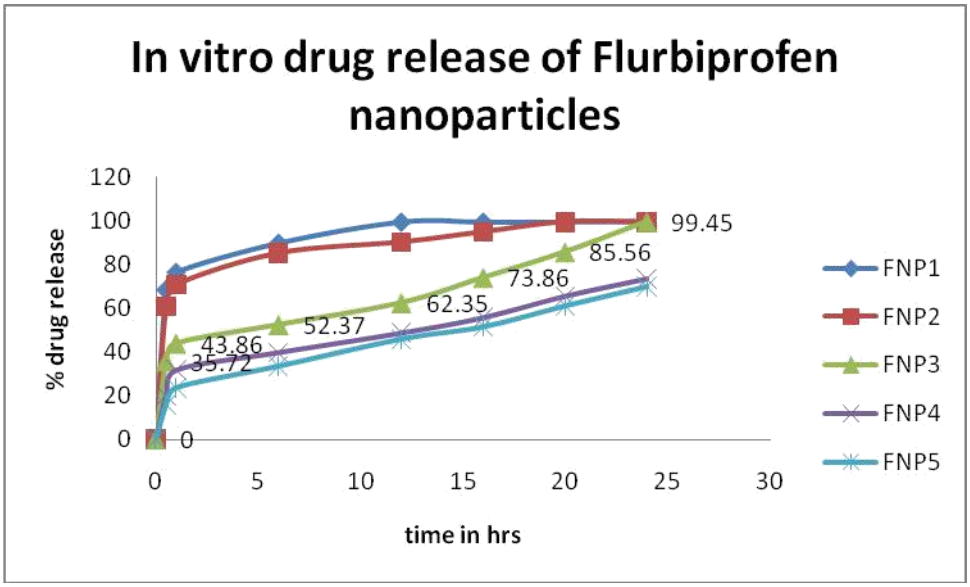

Fig.6. Effect of Chitosan concentration on Invitro drug release of Flurbiprofen nanoparticles

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 Chitosan concentration delays the drug release due to increased particle size and reduced surface area of the 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**% at the end of 24 h).

4. 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 *in-vitro* release profile was 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.

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