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FORMULATION AND CHARACTERIZATION OF FLURBIPROFEN LIPOSOMES

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Abstract:
Flurbiprofen liposomes were prepared by thin film hydration technique and the phospolipid concentrations were optimized by various trials In the present study liposomes containing Flurbiprofen was prepared. The effect of increase in phospolipid concentration in various parameters like particle size and invitro release profile were studied. The Flurbiprofen liposomes were formulated and evaluated for its drug content,entrapment efficiency, particle size analysis,zeta potential and invitro drug release profile. Based on the results of Flurbiprofen liposomes formulations (FLF 1- FLF 5) formulation FLF4 was selected as the best formulation in which the particle size was 271.1nm and the entrapment was 85.72%. The in vitro % drug release of FLF4 formulation was 99.47± 0.72% at 24 hrs 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 liposomal 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 hrs.

Key words: *Formulation, Characterizations, Flurbiprofen, Liposomes*

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INTRODUCTION:

Liposome is a microparticulate colloidal vesicle, in which aqueous medium is surrounded by single or multiple concentric layers of phospholipids. Due to their size, both hydrophilic and hydrophobic drugs (besides biocompatibility) can be incorporated, water-soluble drug being entrapped in aqueous core and fat-soluble drug in phospholipids [1,2]. It offers controlled release, targeted drug delivery, thus enhancing therapeutic efficacy, and reduced dosing frequency. Therapeutically, these are used as a carrier for drugs, viruses, bacteria, antigen, peptides, antibiotics, vaccines, genes, and diagnostic agents [3,4]. Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids. Liposome properties differ considerably with lipid composition, surface charge, size, and the method of preparation. Furthermore, the choice of bilayer components determines the "rigidity" or "fluidity" and the charge of the bilayer. For instance, unsaturated phosphatidylcholine (PC) species from natural sources (egg or soybean PC) give much more permeable and less stable bilayers, whereas the saturated phospholipids with long acyl chains (e.g., dipalmitoyl PC) form a rigid, rather impermeable bilayer structure [2]. In general, liposomes are definite as spherical vesicles with particle sizes ranging from 30 nm to several micrometers. They consist of one or more lipid bilayers surrounding aqueous units, where the polar head groups are oriented in the pathway of the interior and exterior aqueous phases. On the other hand, self-aggregation of polar lipids is not limited to conventional bilayer structures which rely on molecular shape, temperature, and environmental and preparation conditions but may self-assemble into various types of colloidal particles [5]. Liposomes are prepared using sonication, thin-film hydration, solvent dispersion method, and detergent removal methods. Drug loading can be attained either passively (i.e., the drug is encapsulated during liposome formation) or actively (i.e., after liposome formation) [6]. The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes. Liposomes can also be classified into one of two categories: (1) Multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) Large unilamellar vesicles and (2) small unilamellar vesicles. In unilamellar liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. In multilamellar liposomes, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water [7-9]. Liposomes are found to be suitable for localization of topically applied drugs at or near the site of application because they may act as slowreleasing vehicles. Topical drug delivery is a pleasing route for local and systemic treatment. The delivery of drug through topical route is the most effective treatment for the skin diseases [10]. Finally, liposomal drugs exhibit reduced toxicities and retain enhanced efficacy compared with free complements. However, based on the pharmaceutical applications and available products, liposomes have definitely established their position in modern delivery systems [6]. Fluconazole (FLZ) is a first-generation water-soluble triazole antifungal medication that is administered orally or intravenously. It is used to treat a variety of fungal infections, especially Candida infections of the vagina, mouth, throat, bloodstream, fungal keratitis, tinea infection, and coccidioidal meningitis. It is now available as tablet, capsule, injection, and eye drop formulations. The dosage forms have well-known side effects including nausea, vomiting, diarrhea, headache, and abdominal pain. To reduce the disadvantages, the topical gel formulation has been proposed [11]. A gel is a two-component, crosslinked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure, which immobilizes the liquid continuous phase within [12]. Both hydrophilic and lipophilic drugs can be easily encapsulated in liposomal formulation, and dispensing in the form of carbopol gel was found to be well suited and sound approach to obtain stable liposomal formulation [13].

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.

The main aim of present study is to prepare and evaluate the liposomes for the selected drug Flurbiprofen.

MATERIALS AND METHODS:

List of Materials

Table 1. Materials used

Materials	Supplier
Flurbiprofen	Sigma aldrich pvt.ltd
Phospolipid	Lipoid, Germany
Cholesterol	Sigma aldrich pvt.ltd

METHODS

Preformulation studies:

Preparation of calibration graph for Flurbiprofen:

Preparation of calibration curve in pH 1.2, pH 7.4 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 100ml with 1.2 pH buffer in first volumetric flask, 7.4 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, 7.4 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 Electronic balance) directly in pierced aluminum crucible pans (5-10 mg) and scannedin 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 Dexibuprofen Liposomes:

S.NO	FORMULATION	DRUG (mg)	Phospolipid(mg)	Cholesterol(mg)
1.	**FLF-1**	100mg	100	100
2.	**FLF -2**	100mg	150	100
3.	**FLF -3**	100mg	200	100
4.	**FLF -4**	100mg	250	100

METHOD:

PREPARATION OF LIPOSOMES BY THIN FILM HYDRATION TECHNIQUE (TFH) :

- Liposomes of Flurbiprofen were prepared by TFH technique. Briefly, the selected lipids, drug and cholesterol were dissolved in a mixture of chloroform and methanol (ratio 2:1 v/v) in a 250ml round bottom flask.
- The solvent was evaporated in the rotary flash evaporator. The thin dry lipid film thus formed was hydrated using aqueous hydrating medium distilled water at 65°C.
- The same procedure was repeated for the preparation of Flurbiprofen liposomes using various concentrations of phospholipids **(FLF1-FLF5).**
- The formed liposomal dispersion was sonicated in probe sonicator using ice bath to prevent temperature induced distortion of liposomes.

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 liposomes 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 liposomes 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 247nm 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 liposomes in buffer solutions were subjected to centrifugation at 15000rpm 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 results were given in results and discussion section.

In vitro drug release :

In vitro release studies were performed for 24 h using dialysis membrane by using the Franz diffusion cell. The prepared Flurbiprofen liposomes formulations were placed inside a dialysis membrane and immersed in buffer pH 6.8. At predetermined time intervals the sample was withdrawn and the amount of Flurbiprofen released was determined by measuring the absorbance at 247 nm using a UV-Visible spectrophotometer. 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, 7.4 and 6.8 buffers at 247 nm

Table 3. Absorbance of Flurbiprofen in buffer solutions

s.no	Concentration	Absorbance		
		pH 1.2	pH 7.4	pH 6.8
1	**10**	0.051	0.105	0.080
2	**20**	0.104	0.211	0.161
3	**30**	0.153	0.317	0.242
4	**40**	0.203	0.403	0.321
5	**50**	0.252	0.507	0.402

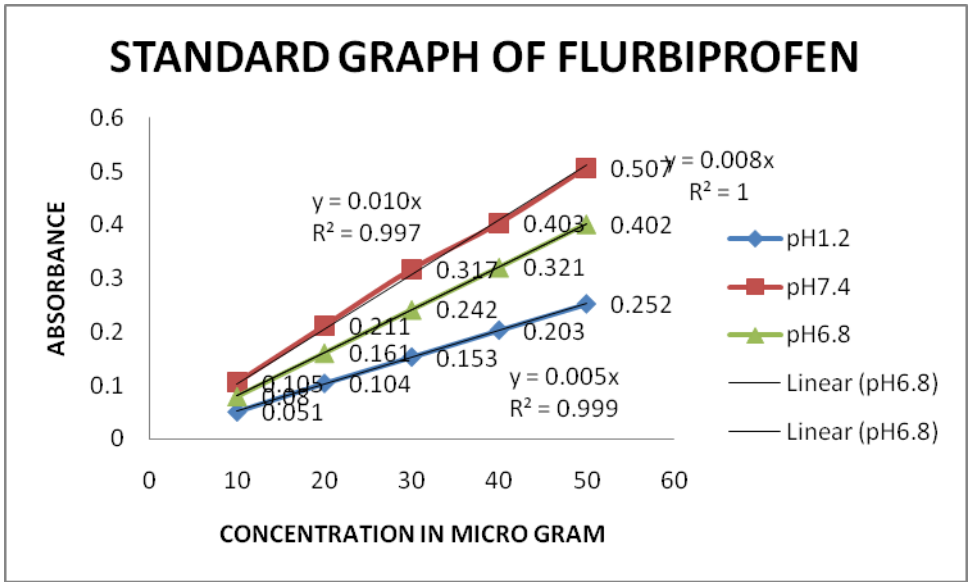

Fig. 1. Calibration curve of Flurbiprofen in pH 1.2,7.4 and 6.8 buffers

Standard calibration curve of Flurbiprofen was carried out in 1.2 pH, 7.4 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 120.01^{0}C (melting point). The physical mixture of Flurbiprofen with other excipients also showed the same thermal behavior (120.01^{0}C) 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.

DSC Thermogram of Flurbiprofen and Flurbiprofen Liposomes

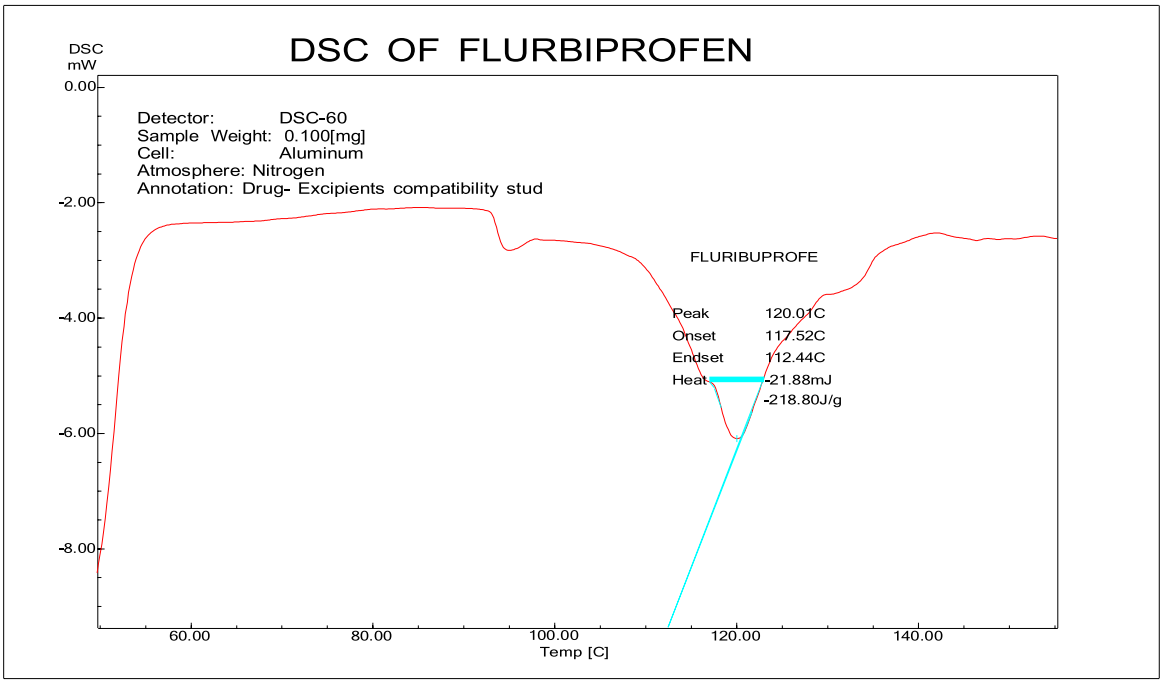

Fig.2

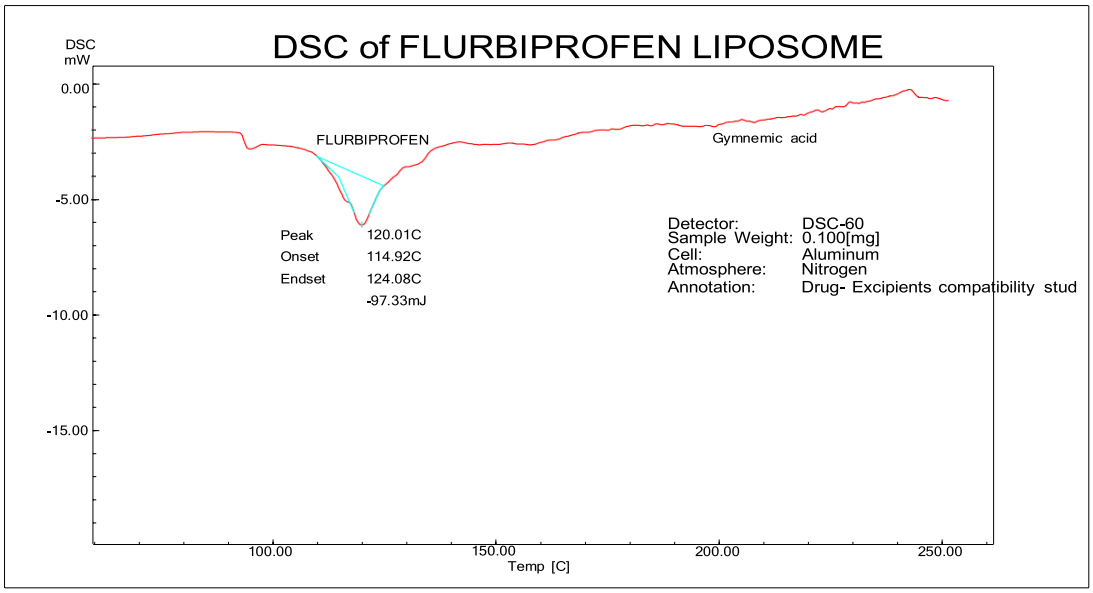

Fig.3

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 4

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.	Phospolipid	Yellowish brown solid mass	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 + Phospolipid	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 + Phospolipid	99.45%±0.54	99.43%±0.62

n = 3; Mean ± S.E.M.

Table 8. Drug content and entrapment efficiency Particle size and zeta potential ofDexibuprofen Liposomes.

Trials	Zeta potential (mV)	Particle size(nm)	Entrapment Efficiency (%)	Drug Content (%)
FLF1	-20.5	268.5	43.21	99.41
FLF 2	-21.4	269.3	49.67	99.46
FLF 3	-22.7	270.2	60.56	99.43
FLF 4	**-26.1**	**271.1**	**85.72**	**99.47**
FLF 5	-28.4	272.5	85.81	99.44

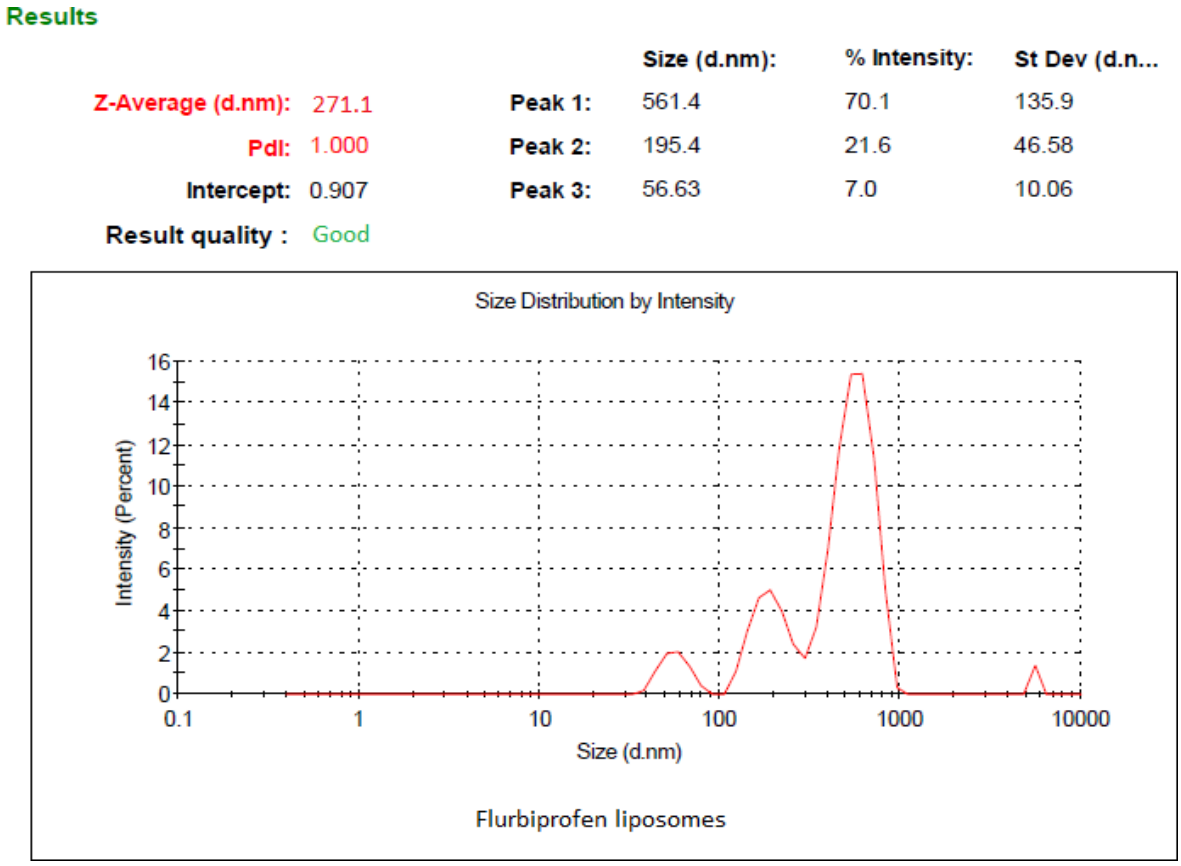

Fig.4. Particle size of optimized Flurbiprofen liposomes (FLF4)

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -26.1	Peak 1:	-28.1	89.9	6.97
Zeta Deviation (mV): 9.87	Peak 2:	-3.17	10.1	4.79
Conductivity (mS/cm): 0.0555	Peak 3:	0.00	0.0	0.00

Result quality : Good

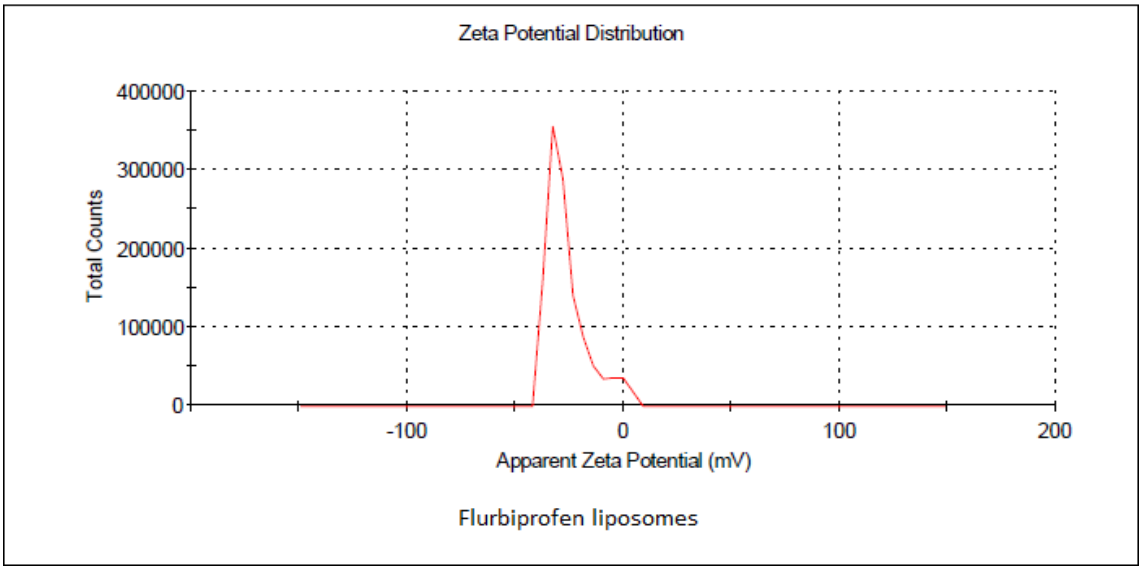

Fig.5. Zeta potential of optimized Flurbiprofen Liposomes (FLF4)

- Particle size and entrapment efficiency of the **Flurbiprofen Liposomes** (**FLF1- FLF4**) were increased with increasing **Phospolipid** concentration.
- This may be due to high amount of availability of Phospolipid to encapsulate the drug, upon increasing the **Phospolipid** concentration, number of layers coated the drug was increased, this resulted in increased particle size and entrapment efficiency.
- Further increase in the **Phospolipid** concentration **(FLF4 and FLF5)**, 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 **Phospolipid**.
- Based on the results of Particle size and entrapment efficiency of the **Flurbiprofen Liposomes** (**FLF1- FLF5**), the trial **FLF4** which contains **250mg of phospolipid** concentration was selected as the best formulation

***In- vitro* drug release :**

Table 9. *In vitro* release studies of Dexibuprofen Liposomes

S.NO	Time(Hrs)	%CUMULATIVE DRUG RELEASE				
		FLF1	FLF 2	FLF 3	FLF 4	FLF 5
1	0.5	80.54± 0.23	74.62± 0.34	68.73± 0.93	50.62± 0.34	35.78± 0.56
2	1	95.43± 0.28	88.39± 0.13	77.82± 0.42	61.46± 0.31	43.76± 0.67
3	6	**99.47± 0.11**	96.52± 0.77	83.71± 0.12	69.82± 0.42	53.78± 0.72
4	12	99.46± 0.34	**99.45± 0.43**	88.91± 0.54	77.89± 0.53	60.83± 0.48
5	16	99.44± 0.67	99.44± 0.31	95.78± 0.52	86.32± 0.17	68.86± 0.81
6	20	99.47± 0.82	99.46± 0.71	**99.46± 0.67**	93.72± 0.82	79.83± 0.42
7	24	99.45± 0.76	99.45± 0.92	99.45± 0.31	**99.47± 0.72**	**87.45± 0.39**

mean±S.D, n=3

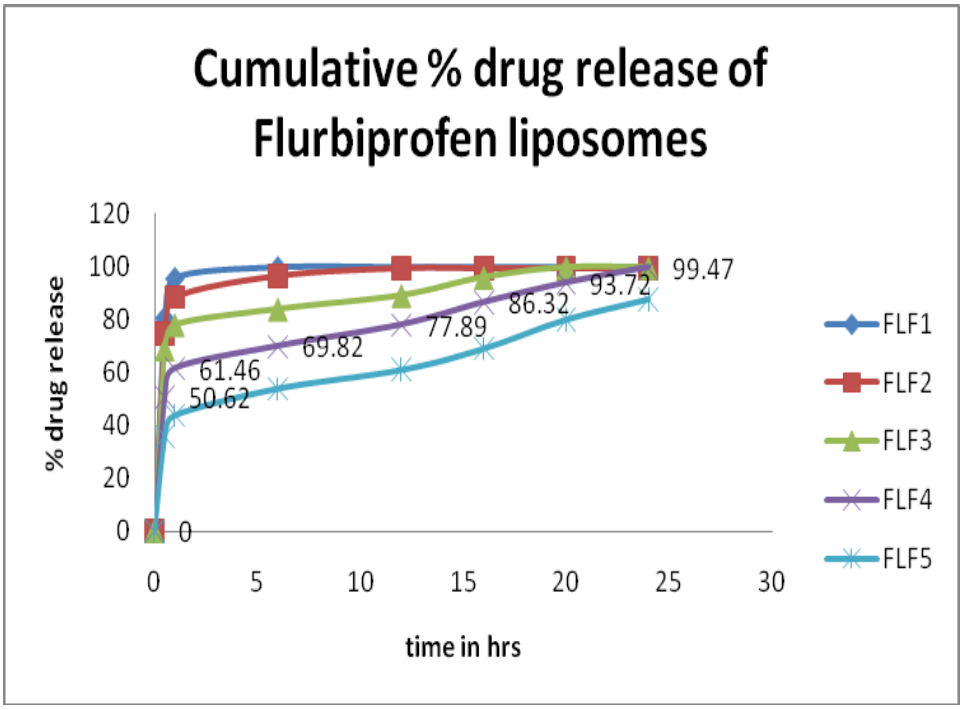

FIG.6.

Effect of Phospholipid concentration on Invitro drug release of Flurbiprofen liposomes

- From the *in vitro* drug release study results, the maximum percentage drug release (**99.47± 0.72%**) at the end of 24hwas observed with trial **FLF4** which contains **250mg of Phospolipid**

- Below **250mg of Phospolipid** concentration as in the case of trials **FLF1,FLF2 and FLF3** the maximum percentage drug release **99.47± 0.11%, 99.45± 0.43%** and **99.46± 0.67%** were obtained at the end of 6h.12h and 20h respectively which was not desirable.

- Above **250mg of Phospolipid** concentration, reduction in drug release was observed asin the case of trial **FLF5**. The maximum percentage drug release for **FLF5** was found to be **87.45± 0.39%** at the end of 24h was obtained.

- From the *in vitro* drug release data for **FLF1-FLF5,** it was observed that increase in Phospolipid concentration delays the drug release due to increased particle size and reduced surface area of the prepared liposomes.

- From all the formulations, **FLF4** was selected as best formulation due to its ideal particle size (**271.1 nm**), high entrapment efficiency (**85.72%**) and desirable drug release (**99.47± 0.72%** at the 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 liposomes were prepared by thin film hydration technique and the phospolipid concentrations were optimized by various trials

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

The **Flurbiprofen** liposomes were formulated and evaluated for its drug content,entrapment efficiency, particle size analysis,zeta potential and *invitro* drug release profile.

Based on the results of **Flurbiprofen** liposomes formulations **(FLF 1- FLF 5)** formulation **FLF4** was selected as the best formulation in which the particle size was **271.1nm** and the entrapment was **85.72%**.

The *in vitro* % drug release of **FLF4** formulation was **99.47± 0.72%** at 24 hrs 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 liposomal 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 hrs

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