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Development And Characterization Of Solid Lipid Nanoparticles Of Anti-Inflammatory Drug For Ocular Drug Delivery System

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ABSTRACT

By creating and testing flurbiprofen-solid lipid nanoparticle (SLN) loaded to enhance its therapeutic activity and lower dosage frequency to aid patient compliance, this study sought to create a novel topical ocular system of flurbiprofen. Lipids and Tween 80 or Poloxamer 180 as stabilisers were used to create SLNs utilising ultrasonic and modified high shear homogenisation methods. Particle size (PS), zeta potential (ZP), polydispersity index (PI), entrapment efficiency percentage (EE %), percentage of drug content, and in-vitro drug release were all measured and recorded for the manufactured SLNs. A transmission electron microscope (TEM) was used to do the morphological analysis of the selected SLNs. An FTIR compatibility investigation was conducted. According to the in-vitro drug release data, it was evident that the rate of drug release from SLN lasted for 10 hours when compared to plain medication. This suggested that the flurbiprofen-SLN loaded was able to regulate the flurbiprofen release rate. The results showed that, in contrast to the ocular drug delivery system, FF5 offered an efficient pharmaceutical system with a regulated release.

Keywords: *Flurbiprofen, Anti-inflammatory drug, Solid lipid nanoparticle, In vitro study*

1. INTRODUCTION

Prior to reaching their target site, where they exert their pharmacological action, drugs must overcome a number of challenges. The capacity to penetrate the tissue epithelium while remaining stable is the primary challenge. Solid lipid nanoparticles (SLNs), a novel medication delivery vehicle, can aid in mitigating these issues. SLNs are significant since it was discovered that, in addition to being lipophilic, a particle must be submicron in size in order to pass through the ocular mucosa (1,2). A good ocular drug delivery system must have a narrow size range, tiny particle size (less than 10 µm) (3), be non-irritating, sufficiently bioavailable, compatible with ocular tissue, and not induce blurred vision (4, 5). Because of the intricate structure and nature of the eye, pharmaceutical experts face difficulties when it comes to ocular drug delivery.

Drug access into the eye is restricted by barriers such the blood–aqueous barrier, blood–retinal barrier, aqueous–vitreous barrier, and epithelial barrier. To treat glaucoma or uveitis and combat viral infections that have spread throughout the eye, deep medication penetration into the posterior chamber is typically required (6).

Because of the eye's distinct physiological and anatomical obstacles, such as the corneal epithelium's impermeability, blinking reflex, and tear drainage, effective ocular drug administration continues to be a significant issue in pharmaceutical sciences. (7) The ocular bioavailability of medications applied topically is severely restricted by these barriers; frequently, less than 5% of the applied dose reaches the intraocular tissues. As a result, frequent dosing is necessary, which raises the possibility of systemic side effects and may decrease patient compliance. Non-steroidal anti-inflammatory drugs (NSAIDs), such as flurbiprofen, are frequently used to treat ocular inflammation, including anterior uveitis, photophobia, and postoperative discomfort. (8) However, when administered using traditional eye drops, its short precorneal residence time, restricted corneal permeability, and poor aqueous solubility limit its therapeutic efficiency.

Solid Lipid Nanoparticles (SLNs) have become a viable nanocarrier method for ocular medication delivery in order to get over these restrictions. SLNs are physiological lipid-based submicron colloidal carriers that stay solid at room temperature and body temperature. (9) Improved corneal penetration, prolonged medication release, protection of labile medicines from degradation, and increased patient compliance because of fewer doses are just a few benefits they provide. (10, 11) By improving drug retention at the site of action, decreasing systemic absorption, and offering regulated release, the addition of flurbiprofen to SLNs is anticipated to increase its ocular bioavailability. (12, 13) Additionally, to maximise the therapeutic effect, SLNs might be made with biocompatible and mucoadhesive surfactants to lengthen their residence time in the precorneal region. (14) In order to improve the drug's solubility, corneal penetration, and therapeutic efficacy while maintaining patient safety and comfort, this study focusses on the development and characterisation of flurbiprofen-loaded solid lipid nanoparticles for ocular delivery.

2. MATERIALS AND METHODS

Materials: Flurbiprofen was purchased from Sigma Chemical Co. St. Louis, MO, USA. Tween 80 was purchased from Yarrow Chem Pvt. Ltd, Mumbai, India. Methanol, sodium chloride, sodium bicarbonate, dimethyl sulfoxide, and calcium chloride.2H2O were purchased from S.D. Fine Chemicals, India

Methods

Formulation of flurbiprofen-solid lipid nanoparticles (flurbiprofen-SLNs): Tween 80 or Poloxamer 180a was used as a surfactant, while oleic and stearic acids were used as lipids in the ultrasound and modified high shear homogenisation process to create flurbiprofen-SLNs. The temperature at which the lipid-drug mixture was heated and kept above the lipid melting point was 80 °C. The weighted surfactant was dissolved in distilled water and heated to the same temperature as the lipid phase to create an aqueous phase. After adding this heated aqueous phase to the lipid phase, it was homogenised for ten minutes at 21,000 rpm using a homogeniser. To create hot SLN, a hot coarse oil in water emulsion was prepared and ultrasonically sonicated for 10 minutes using a probe sonicator (ultrasonic processor, GE130, probe CV18, USA). Finally, the heated SLNs were allowed to cool to ambient temperature (15, 16). The composition of twelve SLNs made with various lipid and surfactant types is displayed in Table 1.

Pharmaceutical evaluation of flurbiprofen-SLNs

Particle size (PS), zeta potential (ZP) and polydispersity index (PI) determination: The Zetasizer Nano ZS (Software Ver 6,20. Malvern instruments; Worcestershire, UK) was used to assess the mean vesicle diameter and PI of flurbiprofen-SLNs using Dynamic Light Scattering (DLS) technology. (17) To obtain an appropriate scattering intensity at 90° for the incident beam, each SLN was diluted 100 times with deionised water before the tests were conducted. The ZP (ζ) values of the prepared systems were estimated using the Laser Doppler Anemometer in conjunction with the same apparatus. (18) After suitable dilution with a considerable amount of bidistilled water, this technique examined the electrophoretic mobility of vesicles under an electric field (19, 20). For this test, independent samples were measured three times in succession.

Determination of flurbiprofen entrapment efficiency percentages (EE %): The dialysis method was used to calculate the flurbiprofen entrapment efficiency percentages (EE%) in various SLNs. Using a paddle, a dialysis bag containing 1 ml of SLN was agitated at 37±0.5 ◦C while being submerged in 30 ml of 1% tween aqueous solution (dialysis medium). Dialysis lasted for one hour. (21) After that, aliquots of the dialysis medium were taken out of the dissolution cup and passed through a filter membrane with a pore size of 0.45 µm. Using UV spectroscopy (Shimadzu-1800, Japan), the drug-free percentages were measured spectrophotometrically at a particular λmax (274 nm). (22) The following formula was used to determine the EE% values:

EE%= Dt – Dd / Dd x 100

Where: Dt: the total amount of flurbiprofen in the SLN

Dd: the amount of flurbiprofen that diffused into the receiver medium

The results were shown as an average of three independent experiments for each formula.

Determination of drug content: To guarantee full dissolution, 1g of each SLN was shaken with 100 ml of an appropriate solvent for one hour in an incubator shaker. After being extracted, the samples were diluted and filtered. With the aid of UV spectroscopy (Shimadzu-1800, Japan), flurbiprofen was measured spectrophotometrically at λmax 274 nm. (23) The mean of three recordings ± SD was used to determine the percentage of flurbiprofen.

Transmission electron microscopy (TEM): A transmission electron microscope (TEM) (Jeol JEM 1230, Tokyo, Japan) operating at 70 kV was used to analyse the morphology of flurbiprofen-SLN following a 50-fold dilution of SLN with distilled water. Using this method, a drop of each diluted SLN was applied to a copper grid coated with carbon mesh (300 mesh) and allowed to settle for three to five minutes. A filter paper was used to separate the extra fluid, and it was let to dry at ambient temperature for ten minutes before being examined under a 70kV transmission electron microscope. (24, 25)

Infrared Spectroscopy using the Fourier Transform (FTIR): Evaluations have been done on drug interactions with formulation excipients. The FTIR spectra of the FF5 and F11 samples were examined using the Bruker Alpha FTIR. After placing a little portion of the samples on the sample holder, the IR spectra were obtained using the attenuated total reflection technique. In the 400–4000 cm-1 range of the IR spectra, a resolution of 1 cm-1 was achieved. (26, 27)

Study of flurbiprofen release profile from SLN: A modified version of the USP dissolving equipment II was used for this investigation. By easily eliminating the entire diameter close to the nozzle, a syringe with a 10 ml capacity was made to function as a tube (28). A piece of fabric held up by a wire mesh was then securely placed over the syringe's bottom. After detaching the pump and attaching it to the revolving paddle, one gramme of each SLN formula was weighed and inserted into the syringe from the top. With a paddle speed of 50 rpm, the syringe tube was submerged in a tank filled with 100 ml of artificial tear fluid buffer pH=7.4 at 37 °C±0.5. Over the course of 12 hours, a 2 ml sample was obtained at predetermined intervals and immediately replaced with a new release medium. (29–31) The amount of released medicine in the withdrew samples was measured using spectrophotometry at λmax (274 nm) in comparison to the commercially available product MP (flurbiprofen ophthalmic solution). For each formula, the mean of three runs (n=3) was used to report the findings.

3. RESULTS AND DISCUSSION

Formulation of Flurbiprofen-SLN: The ultrasound approach and modified high shear homogenisation are the best methods for preparing flurbiprofen-SLNs. For ocular distribution, this technique uses water-based technology to create safe, organic solvent-free nanoparticles. Additionally, it is repeatable, simple to use, and produced positive outcomes that demonstrated the effectiveness of this preparatory technique.

Table 1: Composition of prepared Flurbiprofen Solid Lipid Nanoparticles

Code	Drug	Surfactant (gm%)		Lipids (gm%)	
		Tween 80	Poloxamer 180	Oleic acid	Stearic acid
FF1	10	5	-	5	5
FF2	10	-	5	5	5
FF3	10	7.5	-	2.5	5
FF4	10	5	7.5	2.5	-
FF5	10	-	5	5	5
FF6	10	7.5	-	2.5	5
FF7	10	5	7.5	2.5	-
FF8	10	-	5	5	5
FF9	10	7.5	-	2.5	5
FF10	10	5	7.5	2.5	-
FF11	10	-	5	5	5
FF12	10	7.5	-	2.5	5

Pharmaceutical evaluation of NAT-SLN

Particle size (PS), zeta potential (ZP) and polydispersity index (PI) measurements: Table 2 displays the developed SLNs' mean PS, ZP, and PI values. SLNs' mean PS ranged from 371.53 nm (FF3) to 123.64 nm (FF7). Remarkably, when compared to mixed lipids or stearic acid, oleic acid was observed to raise the PS. This may be explained by the fact that oleic acid has a greater melting point (69–74 °C) than stearic acid (55 °C). It was claimed that higher melting lipids resulted in higher PS of SLNs. However, the current findings demonstrated that, in contrast to Tween 80, Poloxamer 180 enhanced PS. The prepared SLNs' PI values were found to be less than 1, indicating that the fine vesicle size distributions were homogenousAll prepared SLNs have negatively charged ZP values. The slightly ionised fatty acids from the glycerides utilised (stearic acid and oleic acid) most likely increased this negative charge. According to the data, FF1, which was made with 5% Tween 80 and 5% Oleic acid, had the greatest ZP value (27.21 mV), whereas FF7, which was made with 5% Tween 80 and 2:.1 Oleic acid and Stearic acid, had the lowest ZP value (15.75 mV). Tween 80 and Poloxamer 180 are the steric stabilisers that are recommended for creating a stable dispersion of nanoparticles. All prepared SLNs had negative ZP values above |8-9| mV as a result of the presence of this stabiliser, indicating the stability of the SLNs.

Table 2: The PS, ZP, PI and EE % values of NAT-SLN formulae

Code	PS (nm)	ZP (mV)	PDI
FF1	289.43±3.65	-27.21±4.3	0.632±0.03
FF2	311.53±4.64	-21.53±2.64	0.753±0.02
FF3	371.53±4.22	-23.32±2.63	0.589±0.01
FF4	312.53±6.32	-20.11±1.21	0.654±0.06
FF5	276.53±4.32	-21.6±2.64	0.312±0.01
FF6	189.32±4.75	-16.21±4.53	0.501±0.02
FF7	123.64±1.76	-15.74±1.27	0.264±0.02
FF8	156.43±3.44	-17.11±1.75	0.462±0.02
FF9	204.62±3.63	-19.53±3.23	0.711±0.03
FF10	345.11±3.62	-20.64±1.43	0.843±0.01
FF11	167.23±2.5	-24.43±1.53	0.635±0.03
FF12	267.54±3.53	-17.11±4.32	0.957±0.02

*All values are (mean ± SD “standard deviation’’, n= 3). Abbreviations: PS, particle size; ZP, zeta potential; PI, polydispersity index;

Entrapment efficiency percentage (EE %) determination: Table 3 displays the flurbiprofen entrapment efficiency percentage (EE%) in the various SLNs that were created. According to the results, SLNs with oleic acid had a higher EE than those with stearic acid and mixed lipids. These formless perfect crystals with numerous imperfections created space to hold the medicine because oleic acid is a mixture of mono-, di-, and triglycerides as well as fatty acids with varying chain lengths. Additionally, increasing the lipophilicity of the utilised lipid raised the EE of the synthesised SLNs. Using the principle that molecules become more lipophilic as their alkyl chain length rises, oleic acid is more lipophilic than stearic acid (C18). Thus, compared to stearic acid, oleic acid has a greater capacity to accommodate lipophilic medications like flurbiprofen. When compared to Tween 80, Poloxamer 180 was found to improve entrapment efficiency.

Determination of drug content: In any pharmaceutical form, the drug content is regarded as a measure of the medicine's consistency. Figure 1 illustrates the findings, which showed that the drug concentration of every created formulation fell within the US Pharmacopeia's recognised range of 92 to 99%. The medication content was reasonably consistent across all formulations. This guarantees that, following the injection of the SLN formulation, the medicine will reach the spot as planned.

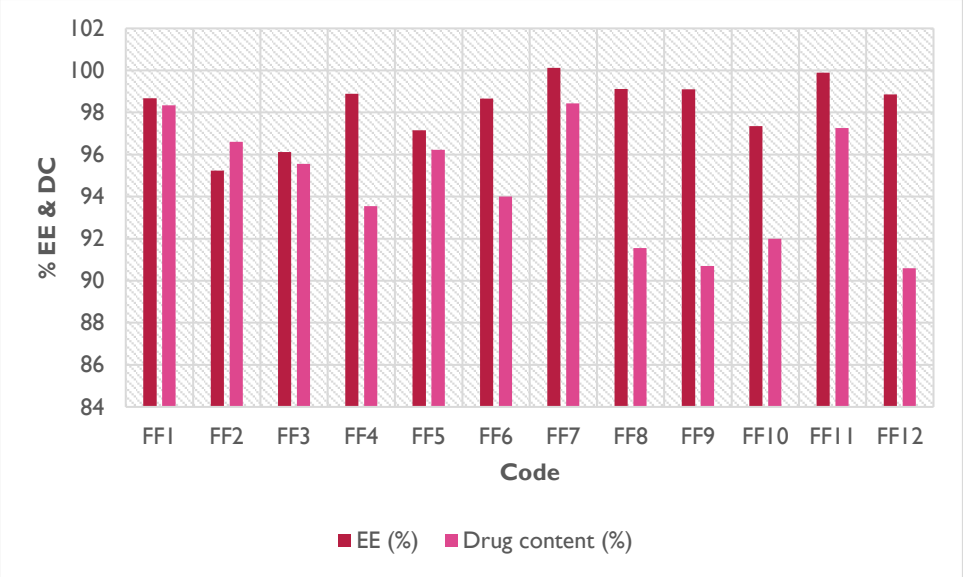
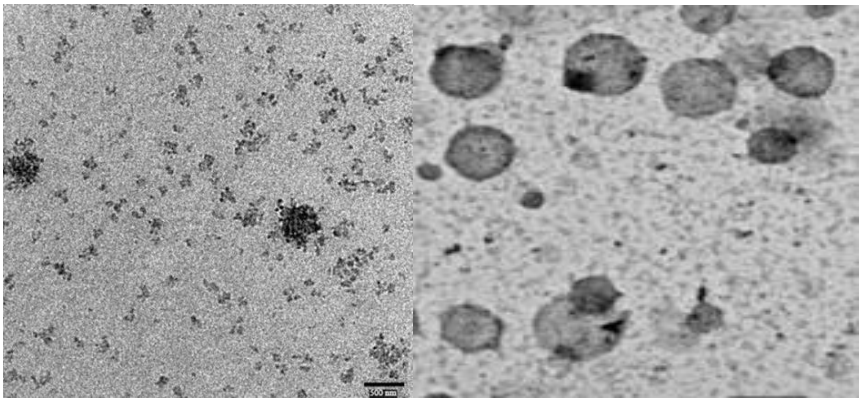


Figure 1: % Entrapment Efficiency and % drug content. All values are (mean ± SD "standard deviation'', n= 3)

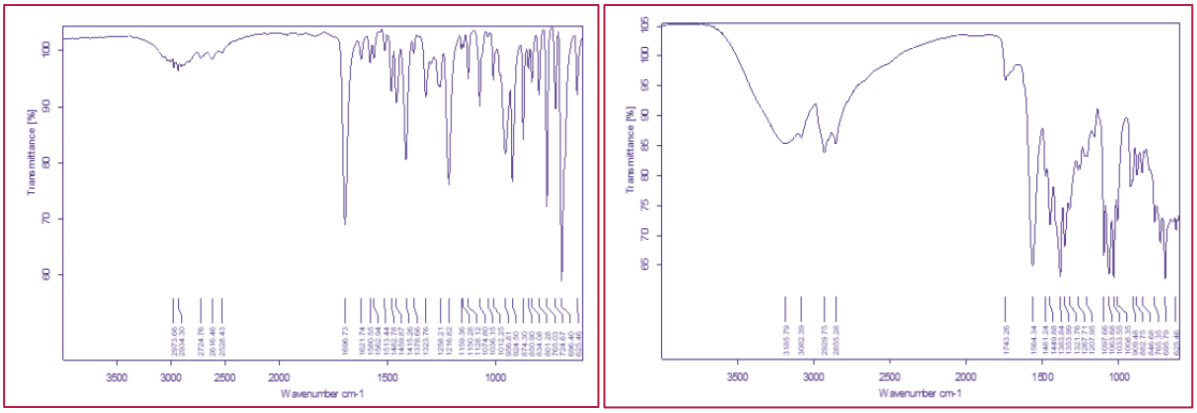
Morphology of prepared SLNs by transmission electron microscopy (TEM): SLNs (FF7, FF11) were chosen for morphological study based on statistical analysis using a design expert (version 11, Stat-Ease, Inc) for PS, ZP, PI, and EE %. According to the PS measurements, Fig. 2 verified the creation of a spherical vesicle containing nanoparticles. The produced dispersions' non-aggregated nature may be explained by the high repulsive forces between the negatively charged surfaces of the SLNs, as demonstrated by the ZP data.



A **B**

Fig. 2: Transmission electron micrographs of SLN A) FF7, B) FF11

Compatibility study: The FTIR spectra showed no discernible difference between the mixture and the pure flurbiprofen peaks. As a result, the medicine and the chemicals that make up SLN did not interact. Flurbiprofen's broad peaks at 1765, 19875, and 3075 cm−1 were seen due to the stretching of the drug's hydroxyl and carbonyl groups. The combination spectrum displayed the drug's peaks from these two fingerprint groups. However, because of the hydrogen bond, the SLN mixture's spectra displays a large peak between 3400 and 1700 cm−1.



A **B**

Fig. 3: FTIR spectra of flurbiprofen formulations FF7 (A) FF11 (B)

In vitro release from prepared SLN: Figure 4 shows a graphic representation of the in vitro release of flurbiprofen from optimised formulations FF7 and F11 in comparison to the plain medication. According to the results, it was evident that the rate of drug release from SLN lasted for 10 hours when compared to plain medication. This suggested that the flurbiprofen-SLN loaded was able to regulate the flurbiprofen release rate. The proportion of flurbiprofen released from the SLN form was inversely proportional to the concentrations of polymers. At high polymer concentrations, the density of the chain structure—which had been seen in SLN nanostructure—increased, limiting the space in which the active material could move and lowering its release.

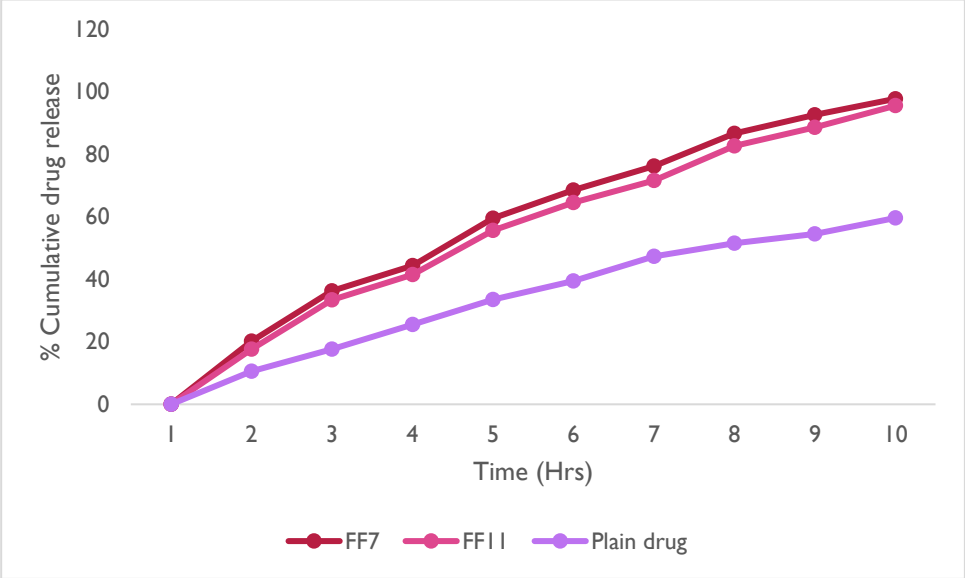


Figure 4: In vitro release from prepared SLN formulation FF7, FF11 and Plain drug (Flurbiprofen)

4. CONCLUSION

An important development in the realm of ocular medication administration for anti-inflammatory therapy is represented by SLNs. Their capacity to improve permeability, extend retention time, and encapsulate lipophilic medications provides a calculated method of getting around obstacles to ocular distribution. SLNs have the potential to take the place of traditional ocular dose forms with further study and clinical validation, which would enhance patient compliance and treatment results.

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