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Formulation and Evaluation of Nano Structured Lipid Carrier Delivery of Celecoxib

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A B S T R A C T

Objective: Celecoxib is non steroidal anti inflammatory drug (NSAID) and is considered to be first line drug in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis. Celecoxib undergoes first pass metabolism when taken orally and it also produces some GI problems. The limitations of oral administration have been overcome by topical route. Drug Celecoxib has been loaded with lipid carriers and then formulated in to topical formulation with the objective of prolonging its action and avoiding its most side effects by incorporation of solid lipid carriers which is achieved by Nanostructured lipid carrier (NLC).

Methods: Nanostructured lipid carrier was prepared by Ultra sonication or High Speed Homogenization method.

Results and Discussion: Characterization of nanostructured lipid carrier was performed by measuring particle size, drug entrapment eficiency and *in-vitro* drug release. Spherical uniform particles (size below 500 nm), Drug entrapment eficiency was found to be in the range of about 75-85%. The drug release proile of all the formulations after 8 h study was found to be in the range of 40%- 78 %. Formulation showing sustained release proile at the end of the study was found to be the best formulation. Optimized formulation was converted in to Topical gel with Carbopol as gelling agent was formulated and characterized for its physical appearance, pH, viscosity, spreadability, homogeneity studies.

Conclusion: The result concludes that Celecoxib loaded nanostructured lipid carrier could be a potential drug delivery system for topical applications.

Keywords*:* Celecoxib, Ultra Sonication, High Speed Homogenization, Entrapment Efficiency, In-Vitro Release Studies.

1. Introduction

Nanostructure lipid carriers (NLC) are the novel colloidal carriers in the new genera-tion of lipid nanoparticles which have been gaining attention in recent trends. Solid lipid Nano particles have been administrated through several routes such as parenteral, oral and topical routes by controlled and sustained release formulations. It has to be explored for its delivery in commercial market.[1] Some of the advantages of this drug delivery includes controlled release profile, drug targeting, high stability, good entrapment efficiency, incorporation of both lipophilic and hydrophilic drug, non biotoxicity of the carrier, avoidance of organic solvents, good scalability and also this system is attractive for their potential to improve performance of pharmaceuticals, nutraceuticals and other materials. There are different techniques employed for prep-aration of SLN particles like modified high shear homogenization, ultrasound techniques, emulsification diffusion, solvent injection, solvent diffusion, micro emulsion, hot homogenization and currently membrane contractor technique was employed.

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the first line treatment of rheuma- toid arthritis, osteo arthritis and ankylosing spondyli- tis. Celecoxib is partially water insoluble drug which undergoes first pass metabolism when taken orally also it produces some GI problems.

Hence better alternate route of administration of Celecoxib is transdermal route. Encapsulation of aceclofenac in to nano struc-tured lipid carrier with the objective of prolonging its action and avoiding its most side effect.[3] As this dos-age forms would reduce the frequency of dosing result-ing in better therapeutic effect and hence better patient compliance could be achieved. The present research work was aimed to formulate and evaluate the site spe-cific

delivery of Celecoxib as nano structured lipid carriers for topical delivery by using ultra sonication technique. Six formulations with varying lipid concen-trations were studied to optimize the formulation for its maximum entrapment efficiency (EE), drug release and particle size. The optimized formulation showing sustained release with good entrapment efficiency was converted in to topical gel and its characteristic studies were performed.[4]

2. Materials and Method

MATERIALS

Celecoxib was obtained from as a gift sample from Fourtt's India Limited, Chennai. Stearic acid, Oleic acid, Phospholipon 90 H, Carbopol 940 P was purchased from Himedia and other reagents used were of analytical grade.

Method for preparation of Nanostructured lipid carrier (NLC)

Preparation of Celecoxib loaded NLC's[5,6]

Ultrasonication method or High speed homogenizer method

Celecoxib and Phospholipon 90 H were dissolved in methanol and mixed with an acetone solution containing a blend of stearic acid and oleic acid. The mixture was then added drop wise to Tween 80 at 70℃ a pre emulsion was obtained by homogenization at 15000 rpm and ultrasonicate for 10 min at 70℃. Further, this pre emulsion was ultra sonicated for 15 min to prevent the crystallization of lipids. The o/w emulsion obtained was subsequently cooled down to room temperature with continuous stirring and the lipid was recrystallized to form Nanostructured lipid carrier (NLC). The obtained NLC dispersions were lyophilized and used for further characterization studies. The formulation of different ingredients with the composition was listed in the Table1.

Characterization of Prepared Nanostructured lipid carrier (NLC'S)[7,8,9]

Fourier Transforms-Infra Red (FT-IR) studies

Fr- IR spectrum studies helps to confirm the identity of the drug and to detect the interaction of the drug with polymers. FT - IR spectral measurement for pure Celecoxib drug, lipids, phospholipon H, physical mixture and drug loaded NLC dispersion were carried out in order to find out the incompatibility study.

Drug Entrapment Efficiency

A volume of 2 ml of each drug loaded sample was centrifuged at 12500 rpm for 45 min to separate the lipid and aqueous phase. The supernatant was then diluted with methanol filtered through 40 µm filter paper and the drug content was determined by the UV- VIS spec-trophotometer. rhe entrapment efficiency of NLC was calculated as

$$\text{Percent drug content (\%)} = \frac{\text{Actual Drug Content (mg)}}{\text{Theoretical Drug Content (mg)}} \times 100$$

$$\text{Percent drug entrapment (\%)} = \frac{\text{Total Drug Content (mg)} - \text{Free Drug (mg)}}{\text{Total Drug Content (mg)}} \times 100$$

In vitro release study of Nanostructured lipid carrier (NLC)

The in vitro release studies were performed using Franz diffusion cell (FDC) to evaluate the Celecoxib release profile from each formulation. Dialysis membrane was mounted on the Franz diffusion cell. Phosphate buffer of saline (PBS) pH 7.4 was used as the receptor medium (12 ml) being stirred at 700 rpm. NLC dispersion (equivalent to 1 mg of Celecoxib) was placed in the donor compartment. The samples were analyzed by the UV spectrophotometer at 273 nm.

Preparation and evaluation of Celecoxib loaded NLC gel.[10,11]

The suitable NLC formulation for the topical delivery of Celecoxib was selected based on the evaluation characteristics like: particle size, entrapment efficiency and *in vitro* release. It was found that the formulation F 1 is more suitable among the other formulations. Carbopol was used as gelling

Table 1. Composition of Nano structured Lipid Carrier dispersion:.

Composition	NF 1 mg	NF 2 mg	NF 3 mg	NF 4 mg	NF 5 mg	NF 6 mg
Celecoxib	40	40	40	40	40	40
Oleic acid	50	75	100	50	75	100
Stearic acid	200	200	200	150	150	150
Phospho lipon G	0.030	0.030	0.030	0.030	0.030	0.030
Tween 80	2	2	2	2	2	2

agent and it was dispersed in the NLC dispersion using a mechanical stirrer at a speed of 1200 rpm. The dispersion was neutralized using triethanolamine. The gel was allowed to stand overnight to remove entrapped air.

Scanning Electron Microscope (SEM)

The particle sizes of the Nano lipid carrier formulations NF1 were viewed and photographed using scanning electron microscope (HITACHI S- 3000 H, SEM operated at 20kv).The sample preparation for SEM is follow as. The sample was transferred to a glass slide which was cut in the dimension of 20×20mm, which is then were mounted on an aluminum stub using double sided carbon tape. The solution was added a drop on the glass slide and slowly evaporated at room temperature. The com- pletely dried sample was coated with gold by sputter coating unit at 10 Pascal vacuum for 10 sec to a thick- ness of 100 Å using HITACHI evaporator. The image was captured on SEM mode at desired magnification.

Stability Studies

The conditions affecting the physical and chemical stability of lipid nanoparticles were evaluated. rhe first condition was performed at 25ºC± 2ºC/ 60ºC± 5 % RH for 6 months as per ICH guidelines. The pH, viscosity and drug release was determined periodically every month.

Evaluation parameters of Nanostructured Lipid carrier topical gel:[12,13]

Consistency and clarity

After preparation, the gel formulations were visually inspected by naked eyes. The consistency and clarity of the gel formulations were observed.

pH determination

The pH of the gel formulation was measured using digital pH meter. The gel formulations were diluted in ratio 1:25 using distilled water. Standard buffer solution of pH 4, 7 and 10 were used for calibration of pH meter. The gel formulation was tested in triplicate to obtain mean pH value.

Drug content uniformity[14,15]

Fixed quantity (40 mg) of the gel samples were accurately weighed into a 10 ml volumetric flask .After suitable dilution with the phosphate buffered saline of pH 7.4, the sample was then subjected to sonication for about
10 min to effect complete extraction of the drug. Volumes were made then to 10 ml and then these stock solutions were filtered and further diluted. Absorbance of the solutions was measured at 273 nm in U.V visible spectrophotometer.

Rheology

Viscosity was determined by Brook field LDV prime I viscometer model. The gel sample was taken in a beaker and the dial reading was noted at 100 rpm for 60 sec with spindle no CP 52 at the temperature of 30ºC. Viscosity of the gel was measured and was tabulated.

Spreadability

Spread ability is one of the important characteristic for topical formulation as far as patient compliance is concerned. It was determined by placing one gm of gel between the two glasses slides on to which weights were allowed to rest. rhe top slide was subjected to pull of 100 gm weight. The time in seconds required for the top slide to travel 100 cm distance gives relationship of spread ability of gel. The result was tabulated in the Table 3.

3. Results and Discussion

The Celecoxib loaded NLCs were formulated using different concentrations of solid lipid and liquid lipid by the melt dispersion ultrasonication technique as shown in Table 1. Out of six formulations (NF1) seems to exhibit good physical stability indicated by high entrap-ment efficiency value as shown in the Figure 1 and Table 2.

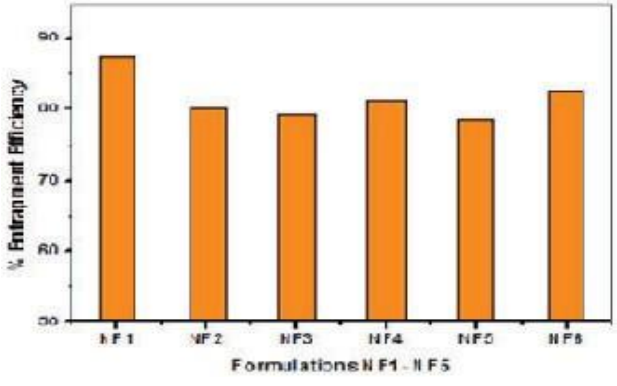

Figure 1: Entrapment Eficiency of all the formulations NF1-NF5

Table 2: Shows the Mean particle Size Drug content% Entrapment Eficiency:			
NF1	360.36 ± 1.20	13.56± 1.65	87.59
NF2	275.5 ± 10.15	18.22± 1.23	80.11
NF3	170.65± 5.70	19.45± 1.89	79.25
NF4	185.55± 10.25	17.52± 1.74	81.19
NF5	140.23± 3.26	19.56 ± 1.78	78.35
NF6	440.56± 6.08	18.11± 1.45	82.56

The drug release profile from the NF1 displayed a biphasic drug release pattern with burst release at the initial stage followed by sustained release as shown in the Figure 2.These results indicated that the NF1 is a suitable carrier of Celecoxib with improved drug loading capacity and sustained drug release properties. The Scanning Electron microscope (SEM) shows the particles of the NF1 formulations were round and spherical in shape as shown in Figure 3.

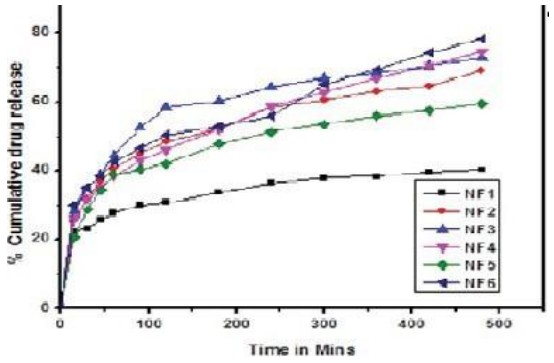

Figure 2: % Cumulative drug release studies of all formula- tions NF1-NF5.

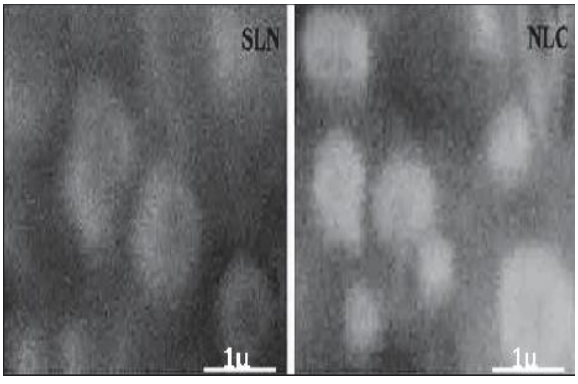

Figure 3: SEM images of SLN and NLC formulations. Shows the spherical in shape and discrete.

Therefore, NF1 was selected and the nanostructured based gel containing Celecoxib was formulated by using the gelling agent Carbopol 934. The drug content of the gel was clearly shown the Figure 4.

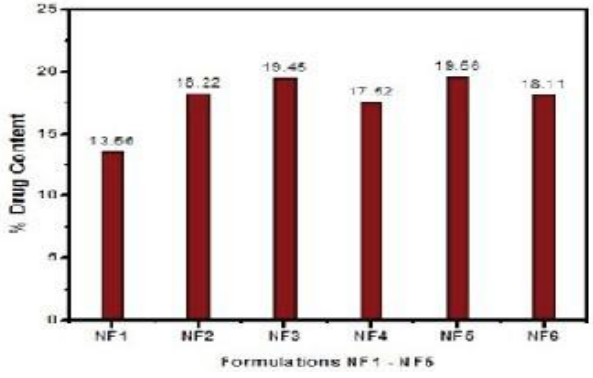

Figure 4: Drug content of the formulations NF1-NF5

It has been observed that NLC gel produces the gel with good consistency, homogeneity, spreadability and rheological behavior as shown the Table 3. It was found that NLC gel showed a biphasic release pattern, and provided a fast release initially for skin saturation followed by a slow and prolonged release profile to maintain the skin concentration.

Table 3: shows the parameters of gel and Observa- tionsi

Parameters	Observation
Homogeneity	Good
pH	5.5 6± 0.57
Drug content	96.42±0.60
Viscosity (cPs)	8370
Spread ability	22.72 gm cm/sec

The present study concluded that the NLC-based gel containing Celecoxib dissolved in a mixture of solid lipid and liquid lipid in the nanoparticulate form helped us to attain the objective of faster onset yet prolonged action as evident from in vitro release profile.

4. Conclusion

Nanostructured lipid carriers were prepared by ultra sonication method by using stearic acid, oleic acid, phospholipon H and Tween 80. FTIR studies proved no interaction between drug, polymer and between the formulations. The particle size of the prepared NLC was suitable for topical application. The mean diameter of the particle and entrapment efficiency increased with increase in the lipid concentration also Celecoxib release studies were dependent upon the size of the nanoparticles. Hence drug loaded topical gel was prepared which would be a promising drug delivery for transdermal application.

ABBREVIATIONS

NLC: Nanostructured Lipid Carriers; **SLN:** Solid Lipid Nanoparticles; **NSAID:** Non-Steroidal Anti Inflamma- tory Drug; **GI:** Gastro intestinal; **EE:** Entrapment Effi-ciency; **FT-IR:** Fourier Transforms-Infra Red; **UV-Vis:** Ultra Violet – Visible; DL: Drug Loading; FDC: Franz Diffusion Cell; PBS: phosphate Buffer Solution; SEM: Scanning Electron Microscope; ICH: International Conference on Harmonization.

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