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RESEARCH ARTICLE

DESIGN AND DEVELOPMENT OF CURCUMIN LOADED NANOSTRUCTURED LIPID CARRIERS FOR SOLUBILITY ENHANCEMENT

***Kabirdas Ghorpade and Sharda Shinde**

School of Pharmacy, SRTMU Nanded, Maharashtra, India

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ABSTRACT

Poor solubility characteristics of curcumin limits its biological application though it possess various activities such as antioxidant, anti inflammatory, antifungal , antibacterial. This study describes the development of the curcumin loaded nano structured lipid carriers for the enhancement of solubility of the curcumin. Particle size is found to be 153.8 nm with a polydispersity index of 0.234 and entrapment efficiency 91.86± 12 and zeta potential 31.1 Mv. Besides the solubility enhancement and increased in vitro dissolution of the nlcs as compaired to drug curcumin is observed. The results of this study promises the curcumin nlcs enhance the drug solubility as well as biloavailability.

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INTRODUCTION

Curcumin is the polyphenolic compound extracted from curcuma longa (such as (turmeric, curcuma zedoary), which posses a series of biological and pharmacological properties such as anticancer, antioxidant and anti-inflammatory activities. Curcumin has a poor bioavailability due to its low solubility and instability which greatly limits its clinical application. The oral absorption rate curcumin is only 25% of the administered dose and little prototype drug is absorbed into blood due to bio transfrmation of curcumin occurring in the course of intestinal absorption. Curcumin has poor bioavalability due to its low solubility and instability which greatly limits its clinical application. In the approach to enhance the bioavailability, the development of NLCs is one of the method. In this study, we increase the solubility and dissolution of poorly water soluble drug by converting into Nanostructured lipid carriers, which ultimately leads to bioavailability enhancement. It has been claimed that NLCs combine the advantages and avoids disadvantage of other colooidal carriers which are: Better drug loading capacity, Higher entrapment efficiency. Smaller size and low polymorphic changes. Possibility of controlled drug release and drug targeting. Increased drug stability. High drug payload. Feasibility in incorporation of lipophilic and hydrophilic drugs. No biotoxicity of the carrier.

Corresponding author: **Kabirdas Ghorpade**
School of Pharmacy, SRTMU Nanded, Maharashtra, India

No problems with large scale production and sterilization. Formulation can be done without the use of organic solvents. The goal of this study was to design and evaluate curcumin loaded nlc. The evaluation includes the particle size, zeta potential. Further objectives was the solubility determination and in vitro dissolution studies of the developed nlcs.

MATERIALS AND METHODS

Materials: Curcumin was obtained from Bhoomi Neutraceuticals Pvt. Ltd. Basma, Nanded. Stearic acid and oleic acid was obtained from Hi Media Lab. Pvt. Ltd, Mumbai. Tween 80 was obtained from Hi Media Lab. Pvt. Ltd, Mumbai. Poloxamer 188 and Mannitol was obtained from S.D. Fine Chemicals, Mumbai. All other reagents used were of analytical grade.

Methods: Stearic acid is used as solid lipid and oleic acid is as liquid lipid which is selected on the basis of lipid screening test. Tween 80 and polaxamer 188 were used as surfactant and stabilizer respectively. Curcumin NLCs were prepared by High Pressure Homogenization (HPH). The Nanostructured Lipid Carriers are prepared by using hot homogenization technique. Accordingly, the weighed amount of drug (curcumin) was added to the mixture of lipids i.e., solid lipid (stearic acid) and liquid lipid (oleic acid) which was heated at 10–150C above the melting point of solid lipid to this mixture co-surfactant (Poloxamer 188) was added and simultaneously, aqueous surfactant (Tween 80) solution was heated at the same

Table 1. The composition of the Curcumin-loaded NLCs

CUR-NLC	Stearic acid (mg)	Oleic acid (mg)	Tween 80 (gm)	Poloxamer188 (Wt %)	Drug-CUR (Wt %)	Water (Wt %)
NLC 1	700	300	2	1.5	5%w/w	96.80
NLC 2	1400	600	2	1.5	5%w/w	94.45
NLC 3	2100	900	2	1.5	5%w/w	93.45

temperature (850C). Then the lipid mixture was poured in the hot aqueous surfactant solution using a magnetic stirrer (Remi instruments Ltd., Mumbai, India) at 12,000 rpm for 30 min, to prepare the primary emulsion. This primary emulsion was converted to the NLC system using high pressure homogenizer (Panda) at 800 bars for 3 cycles. The obtained NLC dispersion was cooled down to room temperature. The NLC dispersion was lyophilized by using lyophilizer (Lark Penguin classic plus) for long term stability. Mannitol (3% w/v was added as cryoprotectant. The 3 different batches are prepared as follows;

Characterization of NLCs

Particle size and polydispersity index: The particle size is important parameter in process control and quality assurance because physical stability of vesicle dispersion depends on particle size and as particle size decreases, surface area characteristics increases as a function of total volume. The mean diameter (z-average diameter) and size distribution were measured by photon correlation spectroscopy (PCS) (Nano ZS Zetasizer, Malvern Instruments Corp, UK) at 25^0c in polystyrene cuvette with path length of 5 mm at an angle of 90^0. Nanostructured lipid carriers were suspended in double distilled water and one drop was placed on clean slide and the particle size was observed.

Zeta potential: Zeta potential is a parameter which is very useful for the assessment of the physical stability of colloidal dispersions. The surfaces of particles develop a charge due to ionization of surface groups or adsorption of ions. This charge depends on both the surface chemistry of the particles and the media around these particles. The surface charge generates a potential around the particle, which is at the highest near the surface and decays with distance into the medium. The zeta potential can be measured by determining the velocity of the particles in an electrical field (electrophoresis measurement). The zeta potential was measured in capillary cells with path lengths of 10 mm, using the Nano ZS Zetasizer. Measurements were performed in distilled water obtained by a MilliQ system.

X-ray Diffraction study: XRD studies of pure drug (CUR) and NLC formulation were done to find out the change in crystallinity when drug was mixed with Stearic acid lipid matrix. XRD pattern were recorded using (Bruker, D8) with Cu-kα radiation. The scanning angle ranged from 3° to 50° of 2θ.

Differential Scanning Colorimetry: DSC is usually used to get information about both the physical and the energetic properties of a compound or formulation. DSC measures the heat loss or gain as a result of physical or chemical changes within a sample as a function of the temperature. The rate of crystallinity using DSC is estimated by comparison of the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion. The DSC thermo grams of the drug and lyophilized NLC was recorded using instrument DSC Q20 V24.11 Build 124 at the scan rate 10^0/min from 30 to 250^0c.

Scanning electron microscopy: The surface morphology of NLC was observed by SEM. NLC loaded with drug were fixed on a stub using double-sided adhesive tape and then made electrically conductive by coating with a thin layer of gold for 30 sec using JEOL fine coat (JFC-1100F ion sputtering device) and scanned using JEOL(JSM-6360) SEM at30.0 KV.

Transmission electron microscopy (TEM): Transmission electron microscope study was performed to confirm size and shape of drug crystal dispersed in the lipid. Before examination the sample were diluted and was placed on a carbon-coated copper grid and then a drop of 2% phosphotungstic acid (negative stain) covered on NLC. The superfluous phosphotungstic acid on NLC was wiped off by filter paper. The TEM images were obtained using instrument (PHILIPS CM 200 with operating voltages: 20-200Kv and resolution: 2.4 Aº).

The entrapment efficiency and drug loading: The entrapment efficiency (%) and drug loading was determined by measuring the concentration of free and entrapped CUR. A known dilution of the NLC dispersion was prepared and 1ml was transferred to the upper chamber of centrifuge tubes of REMI motor centrifuge for 30 min. Centrifuge tubes were centrifuged at 10,000 rpm for 30 min. The filtrate was analyzed for un encapsulated curcumin at 421 nm using a validated UV-Spectrophotometric method after suitable dilution. Entrapment efficiency and drug loading was calculated.

Solubility determination: The solubility of drug and prepared batches of NLCs was determined by taking an excess amount of drug and adding it to 10 ml of solvent (Distilled water), in Teflon-facing screw-capped vials. The samples were kept at equilibrium for a period of 24 h on an orbital shaking incubator (CIS-24; Remi Instruments, Mumbai, India) at 37±0.5°C and 50 rpm. The supernatant liquid were collected and filtered through 0.2µ membrane filter and analyzed by UV visible (Shimadzu, Japan UV-1800) at wavelength 421 nm for Curcumin.

In Vitro dissolution of curcumin and NLCs: In-vitro dissolution studies of curcumin Nanostructured lipid carriers were carried out by USP type rotating basket type dissolution apparatus (Electro lab, Mumbai). Optimization of formulation batches was estimated on the basis of cumulative percentage drug release with respect to time. The dissolution carried out in two different media distilled water and phosphate buffer saline (pH 6.8) each of 900 ml. NLCs were placed in each vessel and the medium was allowed to maintain at 100 ppm at 37^0c ± 0.5^0c. Samples of 10 ml were withdrawn at various time intervals up to 24 hr and sink condition was maintained. The absorbance of sample was measured by UV double beam

spectrophotometer (Shimadzu, Japan UV-1800) at 421 nm and cumulative percentage drug releases were calculated.

RESULTS AND DISCUSSION

Particle size and polydispersity index: The optimized NLCs were in the nanometric size range (153.8 nm) with low polydispersity index 0.234 (fig 9.13). The presence of 30% of oil in the NLC lipid matrix led in to small mean diameter of NLC. Surfactant also greatly influences the particle size of formulation by causing stabilization. The nano size may be the reason for enhanced solubility of drug.

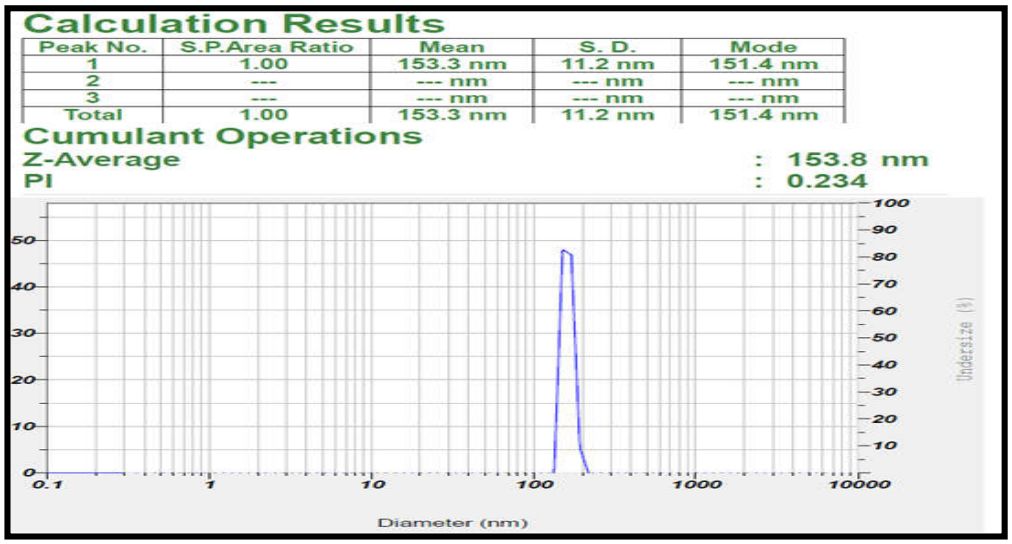


Figure 1. The particle size and particle size distribution of optimized formulation NLCs

Figure 2. The zeta potential of optimized formulation NLC 1

Zeta potential

The zeta potential of the optimized formulation was found to be 31.1mV. Which is the indicative of the stability of the formulation. The zeta potential of the optimized NLCs is found to be 31.1 Mv.

FT-IR: The FT-IR studies are done to check that what changes are done of drug with lipid. FT-IR studies of pure Curcumin Drug (CUR), physical mixture of drug: lipid (Stearic acid), and Optimized batch (NLC 1) were performed. The FT-IR Spectrums of pure Curcumin Drug (CUR), physical mixture of drug: lipid (Stearic acid), and Optimized batch (NLC 1) were shown in Fig 9.5, 9.6, 9.7 respectively. The principle peaks obtained through FT-IR study were shown in Table No: 9.4

X-ray diffraction studies: CUR powder was highly crystalline as evident from sharp peaks seen at the 2θ value in the x-ray scan (Fig 9.17). Characteristic diffraction peaks at 8.50^0, 17.16^0, 25.50^0, and 24.50^0 were observed with intense peak at 24.50^0. Fig 9.18 shows the XRD patterns of freeze-dried CUR loaded NLC showing that peak intensity is reduced indicating reduction in crystallinity.

The absence of these characteristics reflections in lyophilized NLCs demonstrated the total solubilization of drug within the lipid phase.

Scanning electron microscopy (SEM): The SEM of Curcumin and NLC 1 was shown in fig 9.19. From the fig A it is clearly seen that Curcumin particles were irregular shaped smooth and rough surface, while in case of fig B the NLC particles are found to be spherical shape. This change is due to the entrapment of the drug into the lipid matrix.

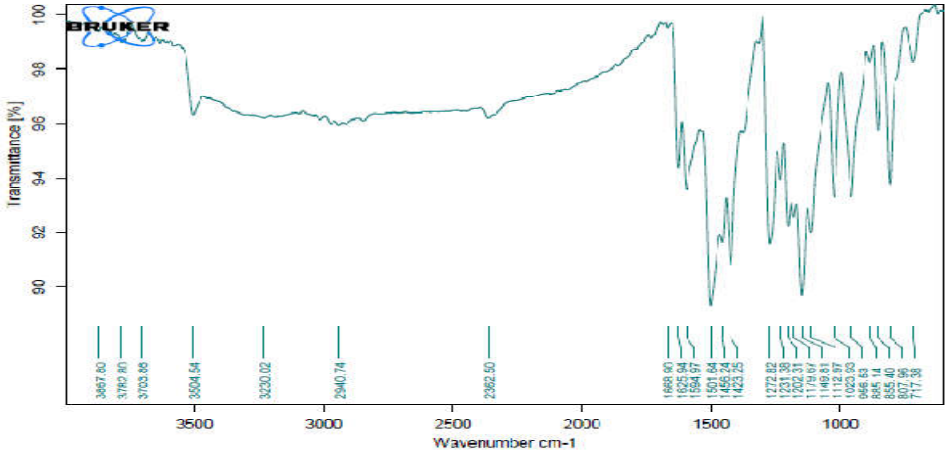


Fig. 3. FTIR Spectra of pure drug curcumin

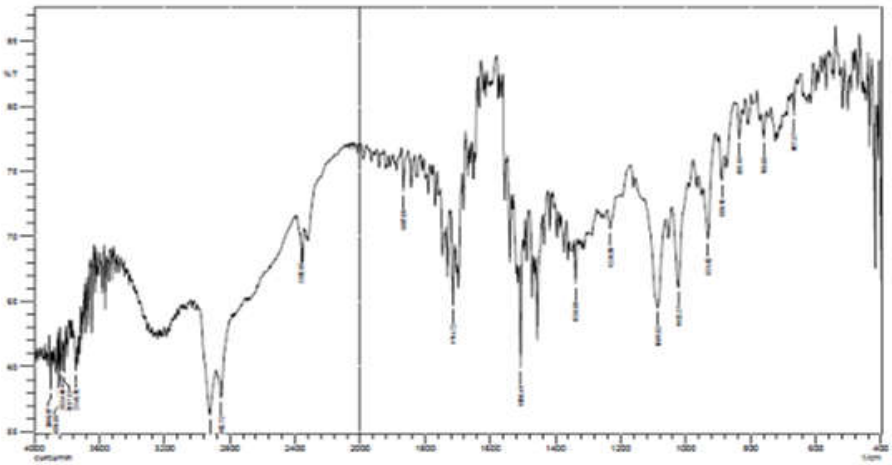


Fig. 4. FTIR Spectra of Curcumin NLC 1

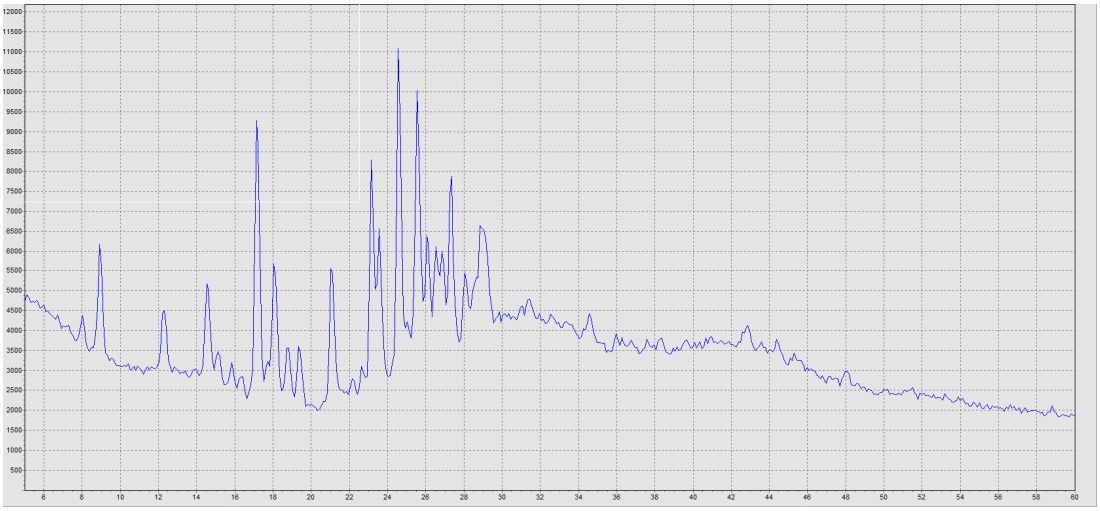


Fig. 5. XRD of pure drug Curcumin

Transmission electron microscopy: TEM image of pre drug and optimized formulation NLC 1 is shown in Fig 9.20. It was observed that NLC 1 exhibited a nanometric size, spherical shape and had narrow size distribution. There was no large difference between the particle size of NLC 1 from TEM images (160 nm) and PSA (153 nm). TEM analysis is done by SAED method which shows images in amorphous form.

In-vitro dissolution of NLC: In vitro dissolution of Nanostructured Lipid Carriers were carried out by using USP Apparatus type XXIV (TDT 08L Electro lab, Mumbai, India) at 100 rpm in two different media water and phosphate buffer saline pH 6.8 (7:3 ratio buffer : methanol).The results of in vitro dissolution of Nanostructured Lipid Carriers were shown in Table 9.7, 9.8.

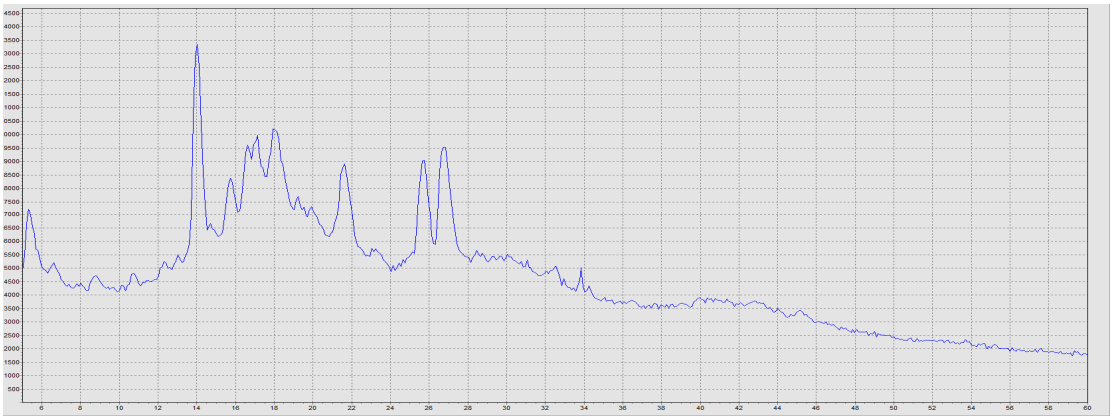
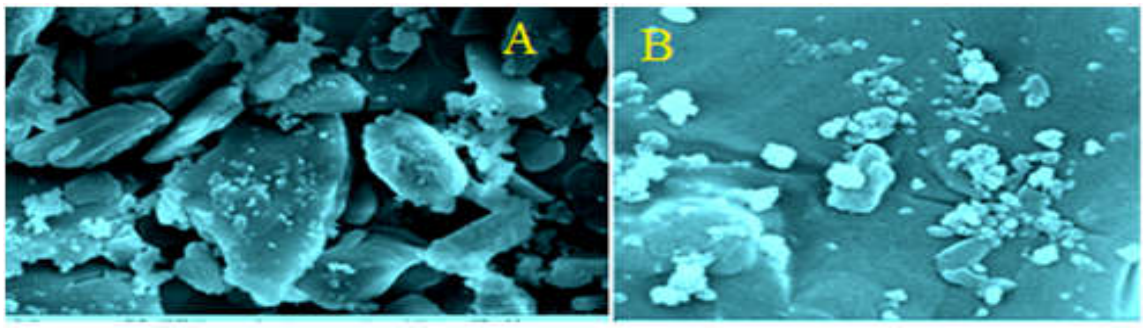
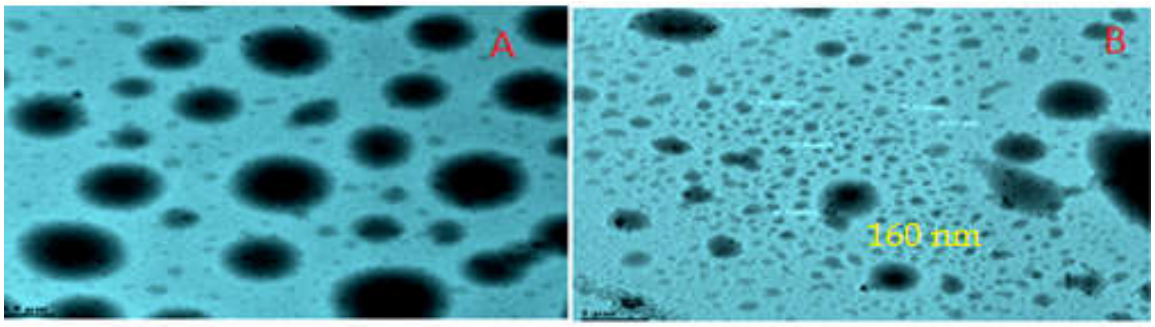


Fig. 6. XRD of Curcumin NLC 1



SEM Image of pure drug SEM Image of CUR-NLCs

Figure 7. SEM images of pure drug (A); NLC (B)



TEM Image of pure drug **TEM Image of CUR-NLCs**

Figure 8. TEM image of Pure drug (A); NLC (B)

Table 2. In-vitro dissolution of NLCs in phosphate buffer saline pH 6.8

Time	Pure drug (% CDR)	NLC 1 (% CDR)	NLC 2 (% CDR)	NLC 3 (% CDR)
05 min	03.30	05.75	05.50	05.44
15 min	06.15	11.54	11.04	10.96
30 min	09.79	18.07	16.74	16.62
45 min	13.64	24.73	22.78	22.68
1.0 HR	17.92	31.89	29.45	29.36
02hr	22.58	39.14	36.62	36.60
04 hr	27.53	46.41	43.86	43.88
06 hr	33.22	53.71	51.16	51.19
08 hr	39.37	61.05	58.48	58.52
10 hr	45.97	75.12	75.12	65.88
12 hr	53.27	89.23	79.91	73.28

From the results of in-vitro dissolution studies in two different medias water and phosphate buffer saline ph 6.8, it can be concluded that after formation of Nanostructured lipid carriers, the drug release is enhanced. Out of all NLCs formulation NLC 1 shows highest drug release.

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