IJPSR (2012), Vol. 3, Issue 09 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 May, 2012; received in revised form 02 June, 2012; accepted 29 August, 2012

FORMULATION DEVELOPMENT OF BMP-NLC ENRICHED GEL

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Keywords:
Nanostructure lipid carriers, Betamethasone Dipropionate, Gel, Nano-particle

Abbreviations:
NLC; Nanostructure lipid carriers**, SLC;** Solid lipid nano-particles**, DNA;** Deoxyribonucleic acid**, BMP-NLC;** Betamethasone Dipropionate-Nanostructure lipid carriers**, PCS;** Photon correlation spectroscopy

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ABSTRACT

NLC are innovative vehicles introduced to overcome some limitations of SLN. Particularly, NLC, composed of a solid lipid and a certain content of liquid lipid (oil), show improved drug entrapment efficiency and an increased stability during storage with respect to SLN. Furthermore, NLC, maintaining their solid state, can control the API release from the matrix. To formulate Nanostructure lipid carriers of an anti-inflammatory drug Betamethasone Dipropionate. To conduct *in vitro* Diffusion studies using dialysis membrane. To *Ex vivo* permeation study using rat skin. To conduct stability studies at 4°C and room temperature and to evaluate entrapment efficiency at various time intervals.

INTRODUCTION: Nanotechnology, shortened to nanotech is the study of controlling of matter on an atomic and molecular scale. Generally nanotechnology deals with structures of the size 100 nanometers or smaller in at least one dimension, and involves developing materials or devices within that size. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self- assembly, from developing new materials with dimensions on the nanoscale to investigating whether we can directly control matter on the atomic scale [1].

One nanometer (nm) is one billionth or 10^{-9}, of a meter. By comparison, typical carbon-carbon bond lengths or the spacing between these atoms in a molecule, are in the range 0.12-0.15 nm, and a DNA double-helix has a diameter around 2 nm. On the other hand the smallest cellular life forms, the bacteria of the genus Mycoplasma are around 200 nm in length [2].

Nanomedicine is the medical application of nanotechnology. The approaches to nanomedicine ranges from the medical use of nanomaterials, to nanoelectronics, biosensors and even possible future applications of molecular technology. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials [3].

QUICK RESPONSE CODE

IJPSR: ICV- 4.57

Website: www.ijpsr.com

Nanostructured lipid carriers are a new type of delivery system offering improved performance in terms of drug loading and long-term stability with the ability to form highly concentrated dispersions. Nanostructured lipid carriers (NLC) composed of a solid lipid matrix with a certain content of liquid lipid are a new generation of solid lipid nanoparticles [4, 9]. A SLN modified by incorporation of liquid lipid into the solid structure has been proposed as nanostructured lipid carriers (NLC) to overcome some limitations related to old generation SLN. Müller et al described NLC with a special structure for better drug accommodation in order to increase the payload and prevent drug expulsion during storage. NLC combine controlled drug release characteristics with some advantages over SLN. NLC have so far been studied for topical use, but they offer all the advantages and production aims of SLN [5, 6, 7, 8, 9].

EXPERIMENTAL WORK:

Calibration curve for Betamethasone Dipropionate: Betamethasone Dipropionate drug equivalent to 100 mg was taken and dissolved in 100 ml standard volumetric flask using methanol to get stock solution (1 mg/ml). From the stock solution, working standards of various concentrations such as 10, 20, 30, 40 and 50 µg/ml were prepared by diluting stock solution with methanol, each sample was then analyzed spectrophotometrically at 240 nm using UV spectrophotometer.

Formulation of NLC:

Hot Homogenization followed by Ultrasonication Technique [11, 12, 13]: Betamethasone Dipropionate (0.1%w/v), solid lipid (Dynasan 118) and liquid lipid (Captex 355), Phosphatidyl choline were dissolved in 10 ml of 1:1 mixture of chloroform and methanol. Organic solvents were completely removed and drug embedded lipid layer was melted by heating at 70°C. An aqueous phase was prepared by dissolving the Tyloxopol in double distilled water at 70°C. Hot aqueous phase was added to the oil phase and homogenization was carried out at 8000 rpm for 3 min.

Course hot oil in water nanoemulsion obtained was ultrasonicated for 15 min. BMPNLC was obtained by allowing hot nanoemulsion to cool to room temperature.

Formulation of NLC based Gel [14, 15, 16, 17]**:** Gels were prepared using Carbopol 934P (1%). For the preparation of gel forming polymer was dispersed in double distilled water containing glycerol (5%). Aqueous BMP-NLC dispersion (20%) and gel were mixed in a high speed stirrer at approximately 1000 rpm for 5 min.

Measurement of particle size of NLC [18, 19, 20]**:** Average size and polydispersity index of different formulations of BMP-NLC were measured by photon correlation spectroscopy (PCS) using Malvern Zetasizer at fixed angle of 90° at room temperature. The NLC dispersion was diluted 1:100 with the aqueous phase of the formulation to get a suitable kilo counts per second (Kcps)

Estimation of Drug Content: 0.2 ml of formulation was diluted to 10 ml with ethanol using standard volumetric flask. Final dilution was made with mobile phase and the samples were analyzed spectrophotometrically at 240 nm [8].

Estimation of Entrapment Efficiency [21]**:** 5 ml NLC equivalent to 50 mg of the drug was taken and diluted with 25 ml of acetonitrile. 1 ml was taken from the solution and diluted to 25 ml. the absorbance was measured UV spectrophotometrically at 240 nm. The amount of drug entrapped was then calculated

The entrapment efficiency was calculated by the following equation

Entrapment efficiency = $Wa - Ws/Wa \times 100\ \%$

Where Wa = weight of drug added in system; Ws = weight of supernatant

***In vitro* Release Studies** [22]**:** *In vitro* release studies were performed using modified Franz diffusion cell. Dialysis membrane having pore size 2.4 nm, molecular weight cut-off between 12,000–14,000 was used. Membrane was soaked in double distilled water for 12 h before mounting in a Franz diffusion cell.

Phosphate buffer pH 7.4 containing 0.5% w/v of Tyloxopol was used as release media. NLC dispersion (1 ml) was placed in the donor compartment and the receptor compartment was filled with 0.5% Tyloxopol in phosphate buffer; pH 7.4 (12 ml). During the

experiments, the solution in receptor side was maintained at 37°C±0.5°C and stirred at 800 rpm with Teflon-coated magnetic stirring bars. At fixed time intervals, 100 µl of the sample was withdrawn from receiver compartment through side tube and analyzed by UV.

***Ex vivo* permeation Studies** [23, 24]**:** Rat skin obtained. It was washed and the hair was removed from skin. A part of skin was mounted over a Franz diffusion cell of diffusional area of 3.56 cm^2 BMP-NLC dispersion (0.5 ml) was applied on the skin surface and the compartments were clamped together. The temperature was maintained at 37°C by placing diffusion cell in a water bath. 1 ml sample were withdrawn at predetermined time interval (1, 2, 4, 8, 12, 18 and 24 hr) from receptor compartment and replaced with an equal volume of phosphate buffer 7.4. The amount of Betamethasone Dipropionate was estimated by UV spectrophotometrically.

Evaluation of Topical Preparations:

1. **Rheological studies on the Gel** [25, 26]**:** Brookefield Synchro-Lectric Viscometer (Model RVT) with helipath stand was used for rheological studies. The sample (30 g) was placed in a beaker and was allowed to equilibrate for 5 min before measuring the dial reading using a T-C spindle at 1, 2, 3, 4 and 5 rpm. At each speed, the corresponding dial reading on the viscometer was noted. The spindle speed was successively lowered and the corresponding dial reading was noted. The measurements were carried in duplicate at ambient temperature. Direct multiplication of the dial readings with factors given in the Brookfield viscometer catalogue gave the viscosity in centipoises.

2. **pH:** The pH measurements were done by using a digital type pH meter by dropping the glass electrode completely into the gel system so as to cover the electrode.

3. **Stability studies:** All the formulations were subjected to stability testing for three months at a room temperature and 4°C±2°C. It was analyzed for the entrapment efficiency.

RESULTS AND DISCUSSION:

1. **Standard curve of Betamethasone Dipropionate:** A standard plot of Betamethasone Dipropionate was plotted for the concentration of 10, 20, 30, 40 and 50 µg/ml with the absorbance measured at 240 nm. The calibration equation for the standard graph was found to be y = 0.025x+0.027 and the regression coefficient (R^2=0.996) was used in all the calculations. The standard plot of Betamethasone Dipropionate is given in **fig. 1**.

TABLE 1: STANDARD PLOT OF BETAMETHASONE DIPROPIONATE

Sr. No.	Concentration (µg/ml)	Absorbance(nm)
1	10	0.299
2	20	0.584
3	30	0.788
4	40	1.022
5	50	1.324

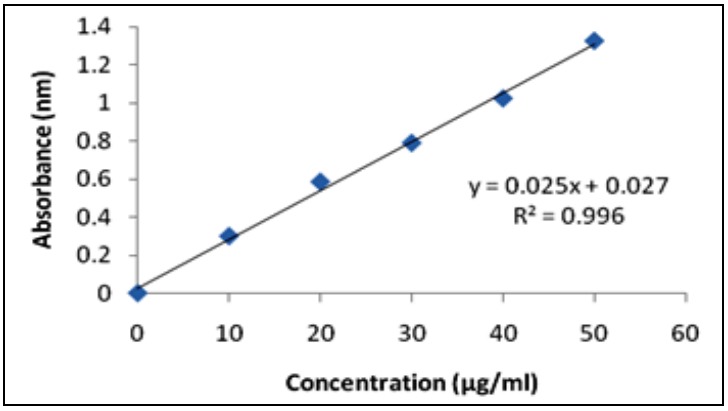

FIG. 1: STANDARD PLOT OF BETAMETHASONE DIPROPIONATE

2. **Preparation of Nanostructured Lipid Carrier of Betamethasone Dipropionate (BMP-NLC):** Hot homogenization followed by ultrasonication method was used for the preparation of BMP-NLC. Dynasan 118 (Glyceryl tristerate) and Captex 355 was used as the lipid phase due to its biodegradability and toxicological acceptability. Phosphatidyl choline (soya lecithin) was selected as the emulsifier, as it is physiologically acceptable, hydrophobic, neutral phospholipids, Tyloxopol was used as the surfactant and steric stabilizer. The NLC dispersion obtained were quite stable and milky in appearance.

3. **Preparation of gel enriched with optimized BMP-NLC formulations:** Gels were prepared using Carbopol 934P (1.0%). For the preparation of gel, the gel forming polymer was dispersed in double

distilled water containing glycerol (5.0%). Aqueous BMP-NLC dispersion and gel were mixed in a high speed stirrer at approximately 1000 rpm for 5 mins to yield gel containing a final concentration of 0.5% BMP-NLC.

TABLE 2: COMPOSITION OF BMP-NLC ENRICHED GEL FORMULATION

Ingredients	BMP-NLC enriched gel		
	F1B	F2B	F3B
Betamethasone Dipropionate (%)	0.1	0.1	0.1
Dynasan 118 +Captex 355 (%)	1	3	5
Phosphatidylcholine (%)	2	2	2
Tyloxopol (%)	3	3	3
Carbopol 934 (%)	1	1	1
Glycerol (%)	5	5	5

The gel formulations are designated as F1B, F2B and F3B. The composition of the NLC enriched gel.

4. **Measurement of particle size of NLC:** Dynamic light scattering is a technique used for particle sizing of samples, typically in the sub-micron range. Photon correlation spectroscopy (PCS) determines hydrodynamic diameter of the nanoparticles via Brownian motion by employing light scattering technique. The technique measures the time dependent fluctuations in the intensity of scattered light from a suspension of particles undergoing random, Brownian motion. Analysis of these intensity fluctuations allows for the determination of the diffusion coefficients, which in turn yield the particle size. Average particle size of optimized BMP-NLC formulations was shown in the table 3. In all the formulations, the average particle sizes were between342.6 to 522.4 nm. F1 shows least particle size i.e. 342.6 nm.

TABLE 3: PARTICLE SIZE OF OPTIMIZED BMP-NLC FORMULATIONS

Formulations	Average particle size (nm)
F1	522.4±5.32
F2	342.6±6.13
F3	380.4±6.98

5. **Drug content and entrapment efficiency:** 5 ml of the optimized formulations (F1, F2 and F3) was taken and diluted to 25 ml with ethanol (96%). 1 ml was taken from that solution and diluted to 25 ml. the concentration was measured by UV spectrometer at 240 nm. The amount of drug entrapped in the nanosphere was then calculated in terms of mg/ml. the concentration of Betamethasone Dipropionate in the optimized formulations ranged from 0.778 to 0.803 mg/ml.

   The entrapment efficiency of all the optimized formulations was calculated in terms of %. The value ranged from 81.65 to 85.50. The average standard equation y = 0.021x+0.169 and the regression coefficient (R^2=0.983) was used for calculation.

TABLE 4: DRUG CONTENT AND ENTRAPMENT EFFICIENCY

Formulations	Average drug content (mg/ml)	Average entrapment efficiency (%)
F1	0.778	81.65
F2	**0.803**	**85.50**
F3	0.790	83.34

6. ***In vitro* release of Betamethasone Dipropionate from the optimized BMP-NLC formulations:** The *in vitro* release of BMP from the optimized NLC formulations was studied using Franz diffusion cells with dialysis membrane. In order to compare the release profile if BMP from different formulations; a solution of BMP (1 mg/ml) in ethanol was prepared. The release of BMP from the solution form was compared with that of the NLC formulations.

   The release studies for the optimized BMP-NLC formulations were carried out for 24 hrs. It was observed that all the formulations sustained the release of BMP for 24 hrs with more than 50 % of the drug being released within 12 hrs with F2 showing the highest release of 85.45% in 24 hrs. The faster release of drug from NLC could be due to short diffusion path owing to an enriched of drug in the outer region of the NLC or drug deposition on the particle surface.

   Factor contributing to a fast release are the large surface area, a high diffusion coefficient due to small molecular size, low viscocity of the matrix and a short diffusion distance for the drug.

TABLE 5: AVERAGE PERCENTAGE OF DRUG RELEASED IN 1% NLC CONTAINING PHOSPHATE BUFFER (pH 7.4) FROM OPTIMIZED BMP-NLC FORMULATIONS

Time (hrs)	Cumulative percentage of drug released					
	F1		F2		F3	
	Avg (%)	S.D.	Avg (%)	S.D.	Avg (%)	S.D.
1	5.14	1.125	8.14	2.021	4.29	1.982
2	7.31	2.560	9.05	2.322	6.88	2.226
4	10.78	1.230	15.10	1.782	8.20	1.983
6	16.41	1.400	17.75	1.221	13.87	0.938
8	19.50	0.998	20.42	1.453	17.81	1.479
12	26.60	1.155	30.95	3.781	23.05	1.472
24	74.55	1.870	85.45	2.321	77.03	2.143

7. ***In vitro* release kinetics:** The release data were analyzed on the basis of Korsmeyer-Peppas equation and Higuchi kinetics. The release rates k and n of model were calculated by linear regression analysis using Microsoft Excel 2007 software. Coefficients of correlation (R^2) were used to evaluate the accuracy of the fit. The R^2**,** k and n values are given in **table 6**.

   In order to describe the kinetics of the drug release from NLC preparation, mathematical modelling have been proposed, where zero order model describes the system were independent of the concentration, Higuchi model tell us about the mode of the release and a semi empirical equation was proposed to describe the drug release mechanism which is so called Korsmeyer-Peppas law.

On calculating and comparing R^2 values for Higuchi and Peppas kinetic models, it was found that there was no good fit to the Higuchi model, so the formulations were best fitted into the Korsmeyer-Peppas model. The fundamental of diffusion, according to the model, is based on Fick's laws, which describes the macroscopic transport of molecules by a concentration gradient. But in non-Fickian case, the drug release varies with time t according to the power law, which has been given in **table 7**.

The release of Betamethasone Dipropionate from all the formulations has shown upper case II transport mechanism.

TABLE 6: THE VALUES OF R^2, k, AND n FOR BMP-NLC FORMULATIONS

Formulation	Zero order	Higuchi	Korsmeyer-Peppas		Mechanism
	R^2	R^2	R^2	n	
F1	0.968	0.820	0.864	1.027	Super case II
F2	0.960	0.811	0.808	1.005	Super case II
F3	0.946	0.810	0.879	1.040	Super case II

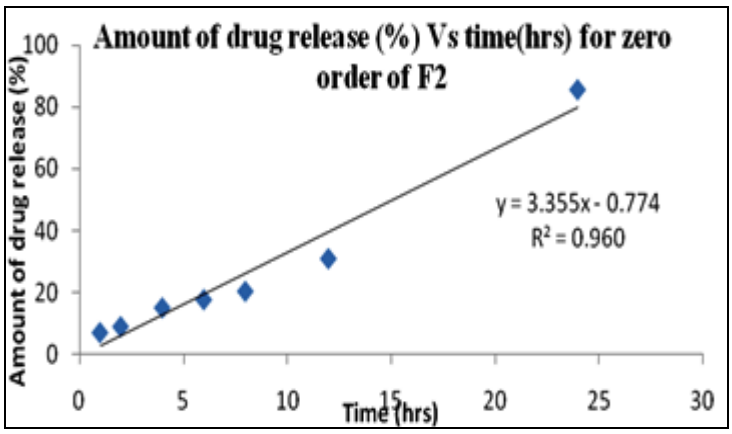

FIG. 2: AMOUNT OF DRUG RELEASE (%) VS TIME (HRS) FOR ZERO ORDER MODEL FOR F2

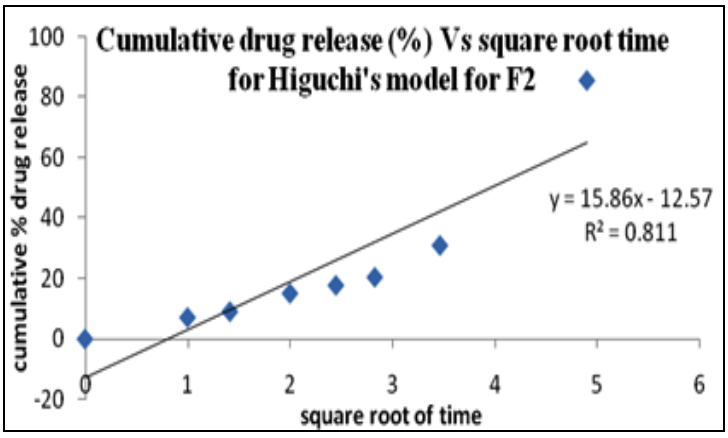

FIG. 3: CUMULATIVE DRUG RELEASE (%) VS SQUARE ROOT TIME FOR HIGUCHI'S MODEL FOR F2

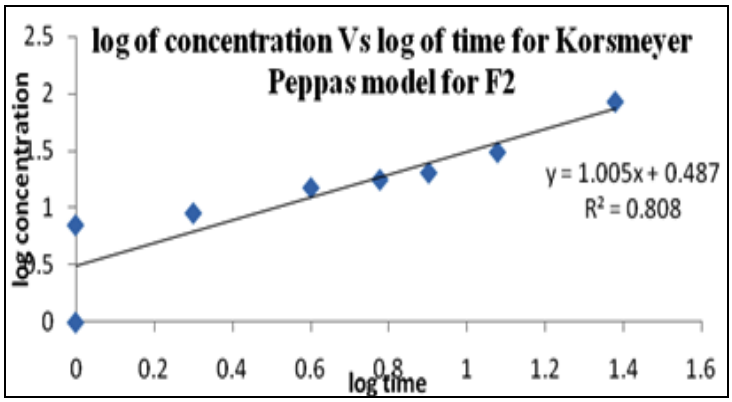

FIG. 4: CUMULATIVE DRUG RELEASE (%) VS SQUARE ROOT TIME FOR KORSMEYER PEPPAS MODEL FOR F2

TABLE 7: DRUG TRANSPORT MECHANISMS AND DIFFUSIONAL EXPONENTS

Diffusional Exponent, n	Type of transport	Time dependence
0.5	Fickian diffusion	$t^{1/2}$
0.5 < n <1	Anomalous transport	t^{n-1}
1	Case II transport	Time independent
n>1	Super case II transport	t^{n-1}

8. ***Ex vivo* drug permeation from BMP-NLC and BMP-NLC enriched gels through excised rat skin:** The formulation F2 had shown the maximum drug release through the membrane was further studied for drug release by using rat skin. The *ex vivo* skin permeation of BMP-NLC were shown in **table 8.** BMP-NLC exhibited 81.53% of cumulative percentage of drug permeation in 24 hrs. The results of the drug permeation from F2 through the rat skin confirmed that BMP was released and permeated through the rat skin.

TABLE 8: EX VIVO DRUG PERMEATION FROM BMP-NLC THROUGH EXCISED RAT SKIN

Time (hrs)	Amount of BMP permeated (µg/cm²)		
	F1	F2	F3
1	4.71	5.14	3.43
2	6.45	7.31	6.02
4	9.92	10.33	7.34
6	18.63	30.65	13.00
8	23.45	37.68	16.93
12	28.29	44.31	17.45
24	70.30	**81.53**	76.89

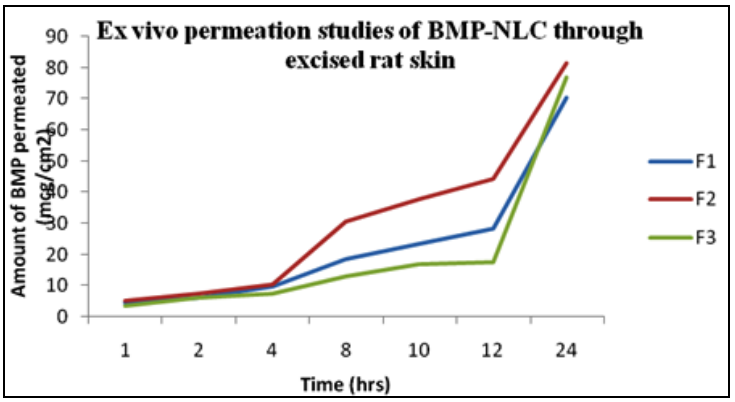

FIG. 5: *EX VIVO* DRUG PERMEATION BMP-NLC THROUGH EXCISED RAT SKIN

The *ex vivo* studies have been shown that the amount of drug permeated at the end of 24th hr from the F9 gel formulations was found to be 80.65 µg/cm^2 which were lesser when compared to that of the F2 BMP-NLC dispersion.

TABLE 9: *EX VIVO* DRUG PERMEATION FROM BMP-NLC ENRICHED GEL THROUGH EXCISED RAT SKIN

Time (hrs)	Amount of drug permeated (µg/cm²)		
	F1	F2	F3
1	4.20	4.29	5.14
2	5.17	5.60	6.03
4	8.19	9.48	7.35
6	14.24	21.11	8.25
8	17.75	29.80	12.15
12	27.39	43.45	22.60
24	72.29	**80.65**	74.38

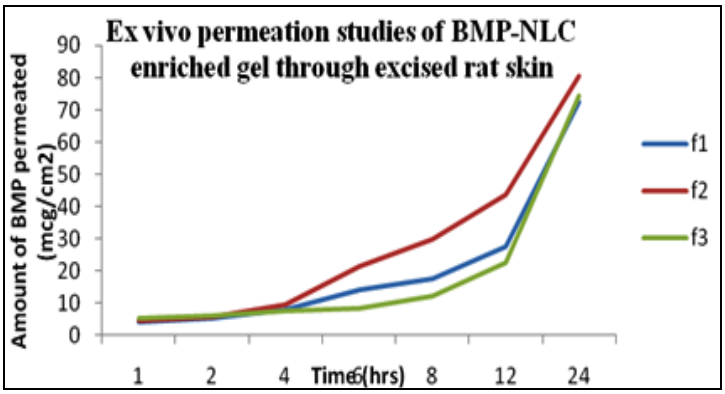

FIG. 6: *EX VIVO* PERMEATION STUDIES OF BMP-NLC ENRICHED GEL THROUGH EXCISED RAT SKIN

Evaluation of Topical Preparations:

1. **Rheological Properties:** With a view to study the rheological behaviour of the NLC formulations, viscosity measurements were made at several shear rates. The results obtained were used to construct rheograms. The moment of turning the spindle in

the sample, the structural arrangement of the sample were temporarily changed, and during the rearrangement, the particles were oriented more parallel to the spindle surface, so the hindering of the spindle rotation was decreased. The faster the rotations, more the structure was destroyed and less the structure of molecule slides in together, the lower the viscosity.

TABLE 10: RHEOLOGICAL BEHAVIOUR OF NLC ENRICHED GEL FORMULATIONS

Shear rate (rpm)	Viscosity (cps)		
	F1B	F2B	F3B
1	9	11	11
2	3.4	4.3	5.6
3	2.2	1.4	2.7
4	0.97	0.89	0.75
5	0.76	0.53	0.68

The viscosity of the NLC formulations gradually decreased as the shear rate was increased from 1 to 5 rpm, which characterizes shear thinning behaviour. From the rheograms obtained, the NLC incorporated gels may be concluded as pseudo plastic system.

2. **pH:** The pH measurements were done by using a digital type pH meter by dropping the glass electrode completely into the gel system so as to cover the electrode, and it was found that the pH of gel is near about pH 7.

TABLE 11: pH OF DIFFERENT FORMULATIONS

Sr. No.	Formulations	pH
1	F1B	6.94
2	F2B	6.96
3	F3B	6.96

3. **Stability studies:** To assess the stability of the NLC formulations, they were stored at room temperature and at 4°C. Entrapment efficiency of the formulations on day 1, day 60 and day 90 were compared as the measure of stability. The impact of storage on the entrapment efficiency on different time intervals is shown in **table 12.** The entrapment efficiency of the formulations did not show much difference at the end of 60 days when stored at 4°C but showed a decrease in 6-7 % at the end of 90 days. When stored at room temperature, there was a decrease in entrapment efficiency of 4-5 % at the end of 60 days.

TABLE 12: STABILITY STUDIES ON ENTRAPMENT EFFICIENCY OF BMP-NLC FORMULATIONS

formulations	Entrapment efficiency					
	4°C			Room Temperature		
	Day 1	Day 60	Day 90	Day 1	Day 60	Day 90
F1	81.65	79.46	75.97	81.65	80.12	77.89
F2	85.50	81.73	78.51	85.50	84.23	82.74
F3	83.34	82.57	79.53	83.34	80.73	78.34

SUMMARY AND CONCLUSION: Lipid nanoparticles, due to the safety of component materials and the controlled release abilities, possess a great potential and have generated a large interest in the industrial and academic worlds. In fact, they have been proposed and investigated for many different applications and all the administration routes.

An attempt was made to formulate Betamethasone Dipropionate Nanostructured lipid carrier enriched gel using Tyloxopol as surfactant and Phosphatidylcholine as an emulsifier with optimum concentration of 3.0 % and 2.0 % respectively, as at this concentration formulations least particle size and high entrapment efficiency.

Process variables like homogenization time and ultrasonication time were optimized so as to get minimum particle size and optimized formulation is prepared by hot homogenization followed by ultrasonication method. *In vitro* release and *ex vivo* permeation were determined and results obtained shows satisfactory results. Gels were then prepared from optimized formulations and evaluated for its rheological studies, pH and stability studies at various time intervals.

From the results, it is observed that formulation F2 which is having 3.0% lipid concentration, 2.0% Phosphatidyl choline and 3.0% Tyloxopol concentration shows least particle size (342.60 nm), high entrapment efficiency (85.50%) and average drug content (0.803 mg/ml). Cumulative percentage of drug release of F2 formulation was found to be 85.45% and 81.53 µg/ml of drug permeated through excised rat at the end of 24 hours by super case II mechanism, while gel of formulation F2 shows highest drug permeation (80.65%) through excised rat skin at the end of 24 hrs and stable at room temperature.

As permeation of drug from rat skin was quite good so it indicate that, it can be applicable for human use too.

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How to cite this article:
Nighojkar PA, Devi SKU, Pund KV, Gadakh RT and Shinde MG: Formulation development of BMP-NLC enriched gel. *Int J Pharm Sci Res*, 2012; Vol. 3(9): 3522-3529.