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FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES OF NAPROXEN

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ABSTRACT

Rheumatoid arthritis can lead to severe disability in most counties worldwide including India. Naproxen is a NSAIDs used to treat various type of Arthritis. Solid lipid nanoparticles are immerged as versatile nano-sized drug carriers in this study we have prepared non-toxic, bio-compatible and easy to produced of Naproxen SLNs, Naproxen SLNs were prepared by High shear hot Homogenization technique at 65ºC temperature and 5000 rpm for 2 hrs. the globule size of Naproxen SLNs were reduced with help of probe ultra-sonicator for 10 minutes. Glyceryl Mono Stearate (GMS) was taken as a solid lipid while Tween 80 and Span80 were taken as surfactants. Various ratio between GMS with surfactants (Span80, tween80) were prepared and evaluated in term of particle size, percentage yield, Percentage entrapment efficiency (%EE) and Zeta potential. Batches Nap-SLN2,Nap-SLN3 and Nap-SLN4 were selected on the basis of above mention evaluation parameters. The particle size of these batches varies from 545nm- 682nm while % EE varies from 59 to 68%. The drug release studies of all three selected batches were performed using Franz diffusion cell for 24hrs. Batch Nap- SLN3 was optimized on the basis of linearity in different mathematical models, first order (R^2 = 0.954), Higuchi model (R^2= 0.897), Korsemeyer and Peppa"s (R^2= 0.998). Scanning electron microscopy (SEM) of optimized batch reveals it size and spherical shape, the prepared

Naproxen SLNs can provide improved and reduced in viability of GI absorption of lipophilic and poorly water soluble Naproxen.

KEYWORDS: Naproxen, Solid lipid nanoparticle, GMS, Arthritis, Probe ultra - sonication.

INTRODUCTION

Naproxen is a non-steroidal anti inflammatory drug(NSAIDs), which is used with increasing frequency in the treatment of pain, fever, inflammation and stiffness.[1] Naproxen protein binding in plasma is high and also varied and like other NSAIDs cause gastritis and peptic ulceration after oral administration. it works by inhibiting both the COX-1and COX-2 enzymes.[2]

Solid lipid nanoparticles of most developing formulations of nanotechnology, SLNs are spherical particle in nanometer range which immersed in water or aqueous surfactant solution either using lipophilic and hydrophilic drug, the physical stability and good tolerability, efficient incorporation of lipophilic drugs in the lipid core of the SLNs and easy to scale up and manufacturing. The nanoparticles posses a solid lipid core matrix that is solubilized by surfactants.[3]

Rheumatoid arthritis can lead to severe disability in most countries worldwide including India. Globally, it imposes a huge financial burden. Considering medical condition, the disease exerts medium to severe problem at various bone-joints displaying inflammation as a common symptom which often turns serious, incapacitating the individuals through pain, swelling and inflexibility at those affected joints. Statistically, women over the menopausal stage fall as the major vict ims. Among the victims of either sex, about half suffers from Osteoarthritis (OA). Next in line, are those having the problem of Rheumatic arthritis (RA). Besides OA or RA, other categories of arthritis are also briefly illustrated in addition to their epidemiological survey. But the article emphasizes mainly on OA and RA for their severe role among the major population of sufferers. The likely reasons of developing calcification and its subsequent after-effect.[4]

MATERIAL AND METHODOLOGY

Materials

Naproxen is obtained as gift sample from Herb Edge Healthcare Pvt. Ltd. Ujjain. Glyceryl

Mono Stearate purchased from Sun Labs, Span80, Tween80 and distilled water were obtained from central store of SIRT- Pharmacy, Bhopal.

METHODOLOGY

Solid lipid Nanoparticles of Naproxen Preparation

SLNs were prepared by High Shear Hot Homogenization method.[5] In this method amount of solid lipid(Glyceryl Mono Stearate) taken in a test tube and melted at 65ºC using water bath, in this melted GMS, drug (Naproxen) was added and dispersed, then made a surfactant solution (Tween80,Span80) and water, homogenized it at 5000 rpm and heated at 65ºC, then the pre-heated solid lipid and Naproxen was mixed with the surfactant solution, mixed and stirred with probe ulta-sonicator (Labmen, India) for 10 min. after the sonication process finished, the mixture was instantly immersed in an ice bath, this cooling step improve the formation of solid- lipid nanoparticles, after cooling process filter with vacuum filter and dried with Lyophilizer. The obtained SLNs collected and stored.

Table 1: Various ratios of drug and excipients for formulation of Solid lipid Nanoparticles.

Batch No.	Naproxen(gm)	GMS(gm)	Span80(gm)	Tween80(gm)	Water(gm)
Nap-SLN1	0.1	1	0.7	1.4	100
Nap-SLN2	0.1	1	0.425	1.690	100
Nap-SLN3	0.1	1	0.3	1.8	100
Nap-SLN4	0.1	1	0.225	1.8	100
Nap-SLN5	0.1	1	0.180	1.8	100

Table 2:Component and physicochemical properties of SLNs of Naproxen.

Batch No.	Particle size(µm)	% Yields	% EE	Zeta Potential(mv)
Nap-SLN1	0.760	62	58	24± 1
Nap-SLN2	0.682	68	59	38.7±0.8
Nap-SLN3	0.545	78	68	35 ±2
Nap-SLN4	0.626	75	62	24±0.5
Nap-SLN5	0.632	76	59	33.82

Evaluation of Solid lipid nanoparticles of Naproxen

Percentage Yield

In this Preparation many things will contribute to the formulation of SLN, the formation of fewer products then would be predicted due to experimental errors, incomplete formation and undesirable situations. Hence formulator need a measurement that indicate how successful

formation of SLN took place, this measurement is known as percentage yield.

% Yield = (Practical Yield/ Theoretical Yield) x 100

Naproxen Percentage Entrapment efficiency (%EE)

Entrapment efficiency Naproxen-SLNs was determined by centrifugation of samples at 10,000 rpm for 10 min. The amount of free drug was determined in the clear supernatant by UV spectrophotometer at 272nm using supernatant of non loaded nanoparticles on basic correction. The entrapment efficiency (*%EE* could be achieved by the following equation.[6]

$$(\%EE) = \frac{Total\ Naproxen\ amount - free\ Naproxen}{Total\ Naproxen\ Amount} \times 10$$

Particle size determination

Particle size of solid lipid nanoparticles of Naproxen, determined by Optical Microscopy, The image ofa particle seen in a microscope is two-dimensional and from this image an estimate of particle size must be made. Microscopic sizing involves comparing the projected area of a particle with the areas of reference circles, or *graticules*, of known sizes, and it is essential for meaningful results that the mean projected areas of the particles are representative of the particle size.[7]

Zeta Potential measurements

The Zeta potential is a physical property, exhibited by all particles in the preparation. It is an important factor to be considered in understanding the electric double layer repulsion and it can be measured by phase analysis light scattering. When an electric field is applied across an electrolyte, charged particles in preparation are attracted towards the electrode of opposite charge while vicious force act on the particle tend to oppose the movement. When equilibrium is reached, the particles move with constant velocity, also known as electrophoretic mobility, and the zeta potential can be measured.

Electron Scanning Microscopy (SEM)

Surface morphology of the specimens will be determined by using a scanning electron microscope (SEM), The samples are dried thoroughly in vaccum desicator before mounting on brass specimen studies, using double sided adhesive tape. Gold-palladium alloy of 1200 A was coated on the sample using sputter coating unit in Argon at ambient of 8-10 Pascal with plasma voltage about 20MA. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images.[8]

Determination of Naproxen release profile from solid lipid nanoparticles

Dialysis Method

In vitro release studies of solid lipid nanoparticles of Naproxen were performed by Franz diffusion cell. Dialysis membrane (egg membrane) having pore size 2.4 nm; molecular weight cut off 12,000–14,000, Was used (Membrane was soaked in double-distilled water for 12h before mounting in a Franz diffusion cell). A volume equivalent to 5 mg of Naproxen (Practically calculated) loaded SLNs formulation was placed in the donor compartment and the receptor compartment was filled with 50 ml of 7.4 PBS solution containing 0.5 %(w/v) the solubility of Naproxen in the buffer solution and prevent absorption of the Naproxen on the surface of the tube. The content of the cell was stirred with the helpof magnetic stirrer at 37ºC. Aliquots were withdrawn from receiver compartment through side tube at every hour time interval up to 24 hours in interval like 1,2,3,4,6,9,12, and 24. The same was replaced with the fresh buffer. Samples were analyzed by UV visible spectroscopy at 272nm. Dissolution data were calculated in % Drug release.

Stability Studies

Stability studies were carried out for finalized formulations by storing the formulations at two different temperatures, i.e in Environment chamber temperature and at room temperatures. The drug content was estimated at the end of every month for 1 month to find any changes in the entrapment efficiency and drug release of solid lipid nanoparticles.

***Fitting data into various kinetic models*[9]**

Zero Order Kinetics

A zero order kinetic could be used to predicted by the following equation (1)

At= Ao – Ko t

Where,

At = Drug release at time „t"

Ao = Initial Drug Concentration Ko = Zero order rate constant (hr^{-1})

When, the data is plotted as cumulative percentage drug release versus time. If the plot is linear then thedata obeys zero order Kinetics, with slope equal to Ko.

First order Kinetics

First order kinetics would be predicted by following equation (2)

Where,

Log C = log Co Kt/2.303

C = Amount of drug remained at time „t"Co= Initial amount of drug.

K = First order rate concentration (hr^{-1})

When, the data is plotted as cumulative percentage drug remaining versus time yields a straight line, indicating that the release allows first order kinetics. The constant can be obtained by multiplying 2.303 with slope values.

***Higuchi's Model*[10]**

Drug release from the matrix devices by diffusion has been described by Higuchi"s classic diffusion equation(3)

Where,

Q = [Dc /τ X (2A-c Cs t]

Q = Amount of drug release at time „t", Diffusion coefficient in the matrix, A = Total amount of drug in unit volume of matrix,

Cs = the solubility of the drug in the matrix,

c = Porosity of the matrix,

T = Tortosityt = time in hrs

The equation 3 may be simplified, if one assumes that D, c, τ, Cs, and A are constant.

Then the equation (3) becomes;Q =Kt1/2 …… (4)

When, the data is plotted according to equation(4) cumulative drug releases verus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slop is equalto „K".

Korsemeyer and Peppa's Model

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following power law equation-5.

Mt/Mα = Mtn.....(5)

Where.

Mt/Mα = the fraction of the drug related time „t"

K = Constant incorporating the structural and geometrical characteristics of the drug/ polymersystem. Diffusion exponent related to the mechanism of the release.

The equation 5 can be simplified by applying Log on both sides, we get

Log Mt/Mα = Log K+ n Log t ..... (6)

When the data plotted as log of drug released versus log time, yields a straight line with a

slope equal to"n" and the "k" can be obtained from y-intercept.

For non-ficikian release the "n" value falls between 0.5 and 1.0 while for ficikian (Case -1 Diffusion) n = 0.5 and for zero order release (case-2 Transport) n = 1.0.

RESULTS AND DISCUSSIONS

Evaluation Studies of Solid lipid nanoparticles of Naproxen

Percentage Yield: The Percentage Yield of all five formulations was evaluate

Table 3: % yield of Naproxen solid lipid Nanoparticle.

Batch No.	% yield
Nap-SLN1	62
Nap-SLN2	68
Nap-SLN3	78
Nap-SLN4	75
Nap-SLN5	76

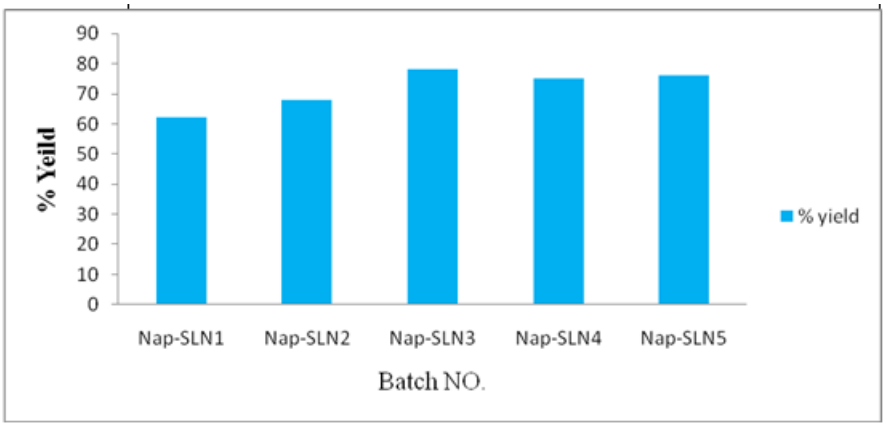

Fig 1: % yield of Nap-SLN1, 2, 3, 4, and 5 formulation of Naproxen SLNs.

Comparison of Percentage Yields of Naproxen loaded Solid Lipid Nanoparticles All the prepared formulations were evaluated for % yields. The values for all the formulations ranged from 62-78.Among all, Nap-SLN3 formulation has shown highest 78 % of % yield.

The Percentage Entrapment Efficiency of Solid Lipid Nanoparticles of Naproxen

After the preparation of Solid lipid nanoparticles of Naproxen, this nanoparticles formulation were centrifuged and harvested. The amount of drug remaining in the supernatant of the solution was then measured by a spectrophotometer. The encapsulating efficiency was determined.

Table 4: Percentage Entrapment efficiency of Naproxen solid lipid nanoparticle.

Batch No.	% Entrapment efficiency
Nap-SLN1	58
Nap-SLN2	54
Nap-SLN3	68
Nap-SLN4	62
Nap-SLN5	54

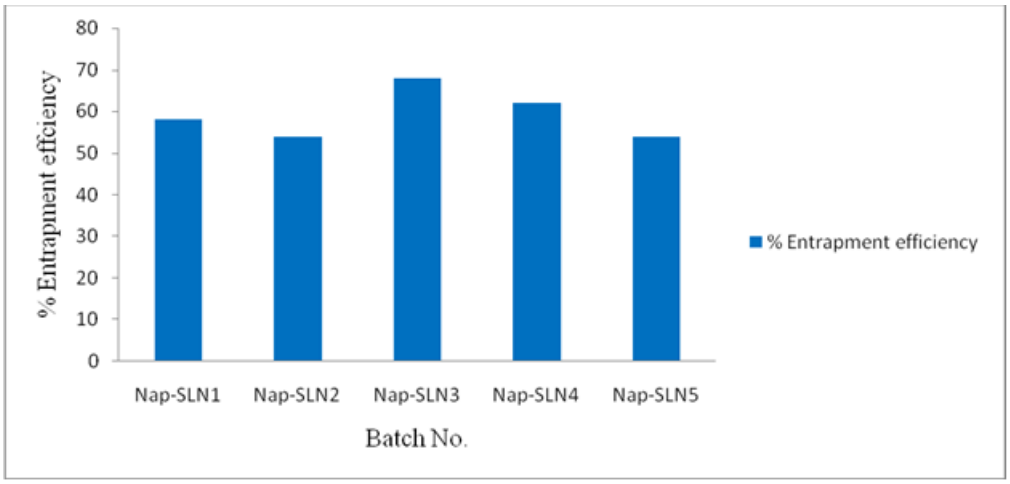

Fig 2: Comparison of entrapment efficiencies of all Batches of Naproxen SLNs.

All the prepared formulations were evaluated for entrapment efficiency. The values for all the formulations ranged from54-68 Among all, Nap-SLN3 formulation has shown highest drug content of 68.00%.

PARTICLE SIZE

Among the Five prepared formulation batches Nap-SLN3 was considered best formulation with particle size 0.545µm, particle size analysis was determined by Optical Microscope. Thus it was observed that formulations was found to be in µm range.

ZETA POTENTIAL DETERMINATION

The zeta potential value indicates the stability of nanoparticles. It was determined by Malvern Zetasizer nanoparticle analyzer. And the Zeta potential of Nap-SLN3 Batch was found- 35mV. The arbitrary value of zeta potential of nanoparticles is mV. Thus it was found that the formulation wasstable.

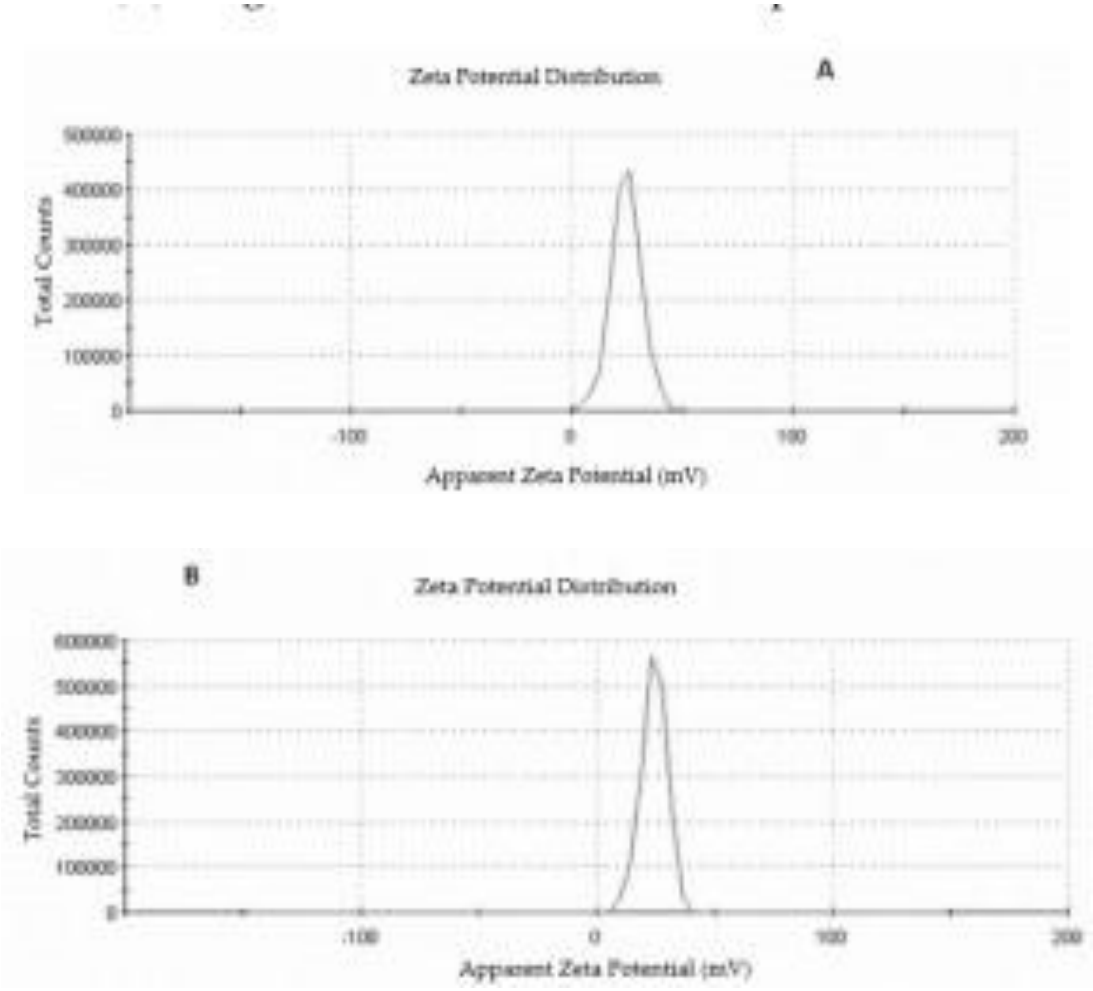

Fig 3: A and B Zeta Potential report ofNap-SLN3 formulation of Naproxen SLNs.

ELECTRON SCANNING MICROSCOPY (SEM)

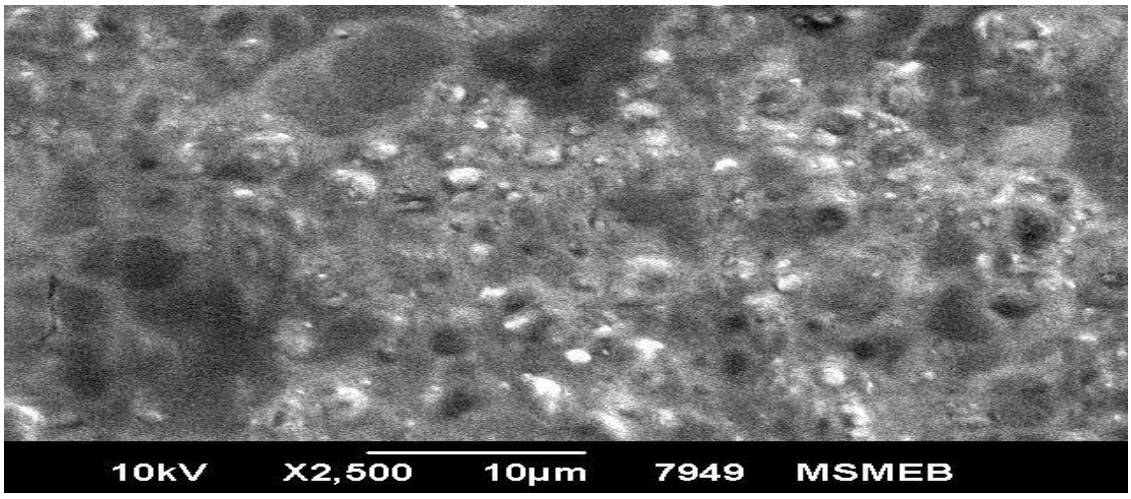

Fig 4: (SEM) micrograph of Nap-SLN3 Solid -lipid Nanoparticles of Naproxen.

In order to show microscopy image of Solid lipid nanoparticles of Naproxen,Nap-SLN3 was selected as one of the optimized Batch with narrower distribution and its microscope image

Fig:4 revels that the particle were segregated, spherical shape and uniform size.

IN VITRO DRUG RELEASE STUDIES

The drug release studies of Optimized formulations of Naproxen SLNs were conducted by means ofdissolution apparatus for a time period of 24 hrs.

Table 5: In-vitro drug release of selected Batch of Naproxen Solid Lipid Nanoparticles.

TIME	Nap-SLN2	Nap-SLN3	Nap-SLN4
0	0	0	0
1	9.4	8.2	7.2
2	16.6	14.6	12.5
3	33.9	32.8	32.2
4	50.9	48.6	47.3
6	64.6	66.8	67.4
9	75.5	76.9	77.8
12	84.5	82.2	86.2
24	92.2	93.7	89.4

All the optimized formulations were evaluated for in-vitro drug release. The values for all the formulations ranged from 9-93%. Among all, Nap-SLN3 formulation has shown highest drug re lease of 93.7%. By performing above studies with all three optimized formulations the Nap-SLN3 formulation had high % Yield, entrapment efficiency and in-vitro drug release, so the formulation Nap-SLN3 is subjected for further evaluation studies.

Fitting of data into kinetic plots of Naproxen solid lipid nanoparticles: Zero Order Release of Nap-SLN2, Nap-SLN3, Nap-SLN4.

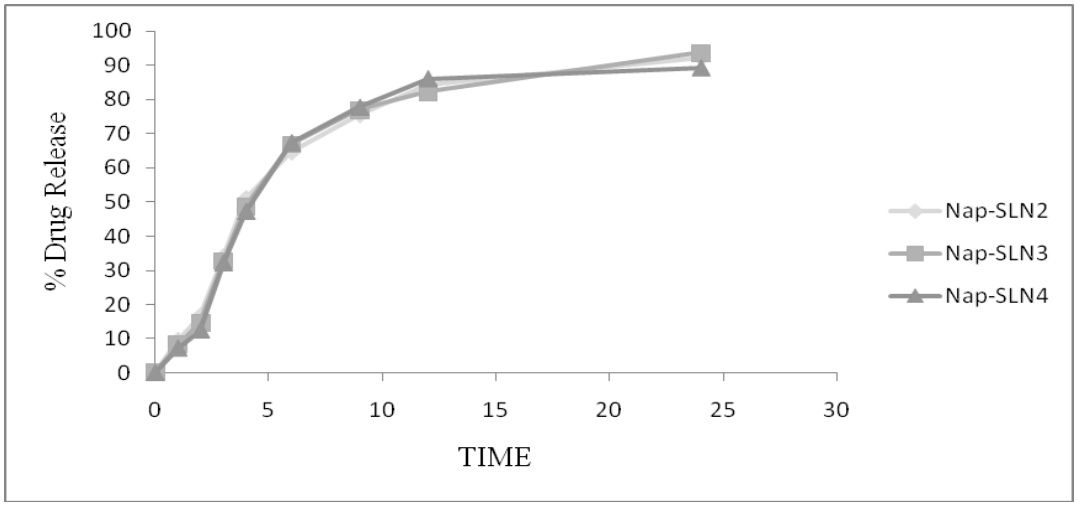

Fig 5: Zero order release kinetics of selected Solid lipid nanoparticles of Naproxen.

First Order Release of Nap-SLN2,Nap-SLN3,Nap-SLN4

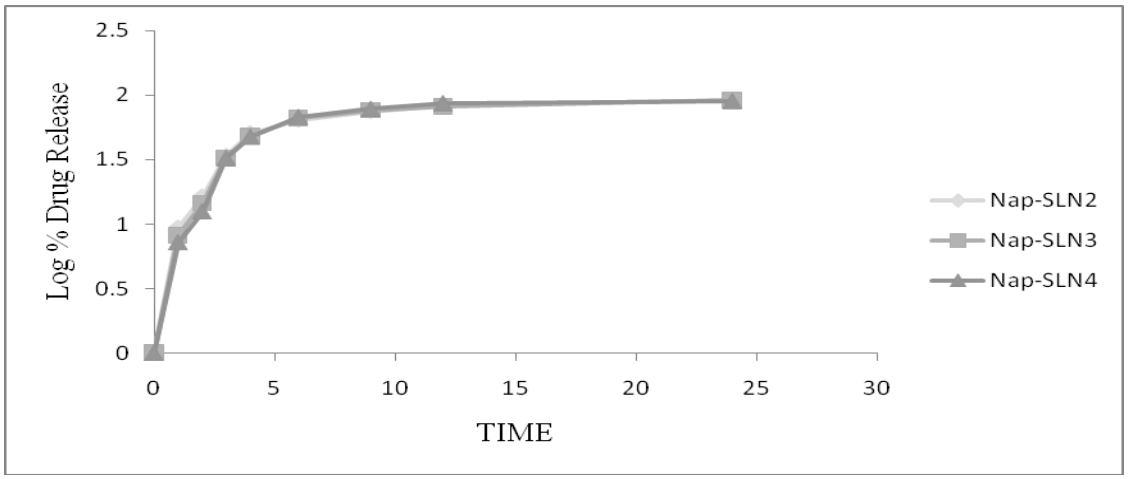

Fig 6: First order release kinetics of selected solid lipid nanoparticles of Naproxen.

Higuchi Plots of Nap-SLN2,Nap-SLN3,Nap-SLN4

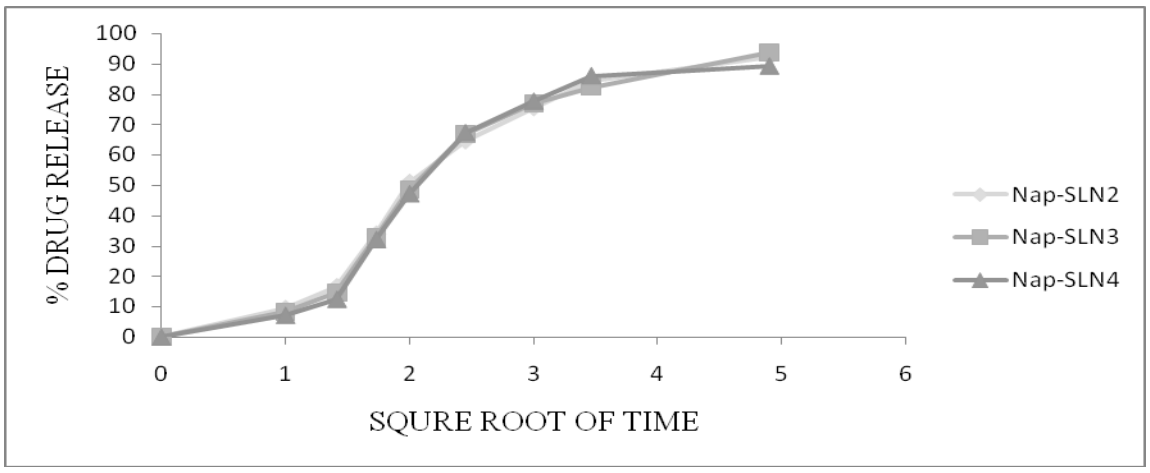

Fig.7: Higuchi Plots of Selected Solid lipid Nanoparticle of Naproxen.

Korsemeyer and Peppa's Model

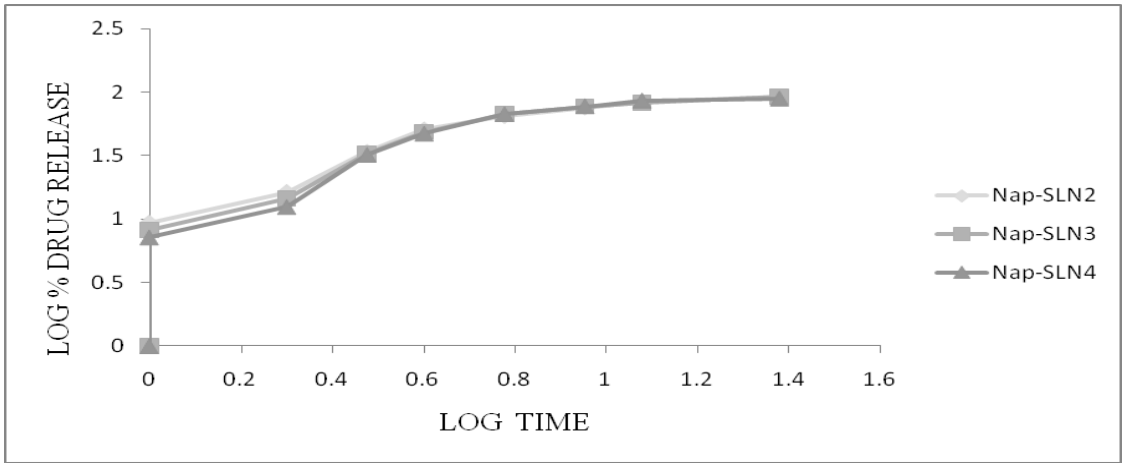

Fig 8: Peppa"s plots of selected Solid Lipid Nanoparticles of Naproxen.

Table 6: R^2 Value of Various Kinetics of selected batches of SLNs of Naproxen.

Batch Code	Zero order(R^2)	First order(R^2)	Higuchi Model(R^2)	Peppas (R^2)
Nap-SLN2	0.487	0.566	0.898	0.192
Nap-SLN3	0.524	0.954	0.897	0.998
Nap-SLN4	0.488	0.346	0.863	0.348

STABILITY STUDY

As per the guideline of ICH , Q1A(R) New drug product It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65% RH ± 5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.

Table 7: Stability Study for prepared Solid lipid nanoparticle of Naproxen.

TIME	Environmental Chamber(tem.)	Room Temperature
1 month	30ºC ± 2 65% RH ±5%	25º C RH 60%

CONCLUSION

The present study showed that solid lipid nanoparticles of Naproxen can be successfully prepared using High shear hot homogenization technique, the prepared solid lipid nanoparticles have shown good results in term of percentage yield 78%, Percentage entrapment efficiency 68%, and drug release value 93.7%, the particle size of the solid lipid nanoparticles were into range of 545 nm and zeta potential – 35mV, which represent that, the particles are in the nano range with good stability.

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