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FORMULATION AND IN-VITRO EVALUATION OF SOLID LIPID NANOPARTICLES CONTAINING DEXAMETHASONE

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ABSTRACT

The present study aims on preparing dexamethasone loaded solid lipid nanoparticles (SLNs) to reduce the dose, frequency of dosing, reduce side effects and to increase the bioavailable fraction of drug (<30% orally in general). A total of 16 formulations were prepared (8 for each lipid *i.e.* Stearic acid and Palmitic acid; SF1-SF8 and PF1-PF8 respectively) Optimized formulations were characterized for particle size analysis, , drug entrapment efficiency and *in vitro* drug release study. The particle size of SF1, SF2, SF6, PF1, PF2 and PF6 was measured to be 124.5 nm, 136.4 nm, 154.4 nm, 130.4, 167.5 and 146.2 nm respectively using Microscopic method, which was in desired range. SLN formulations were found to be stable with drug entrapment efficiency was reported to be approximately 90% for selected formulations. From *in vitro* drug release study, the % cumulative drug release after 24 hrs from SF1, SF2, SF6, PF1, PF2 and PF6 was recorded to be 93.44, 90.20, 85.58, and 92.33, 89.44, 88.58 respectively. Mechanism of drug Release was found to follow Higuchi diffusion model; Fickian diffusion for SF batch formulations and non-Fickian diffusion for PF batch formulations. The highest cumulative % drug releasing formulation from each batch (*i.e.* SF1 andPF1) was chosen for further evaluations. The SLNs appeared to be less dense in the core with a well-defined shell. The successful incorporation of Dexamethasone into SLNs opens a wide scope of the study of the delivery system with respect to sustained and targeted drug delivery. However the *in vivo* studies are yet to be carried out to confirm the potential of formulated SLNs.

KEYWORD: Dexamethasone, Stearic acid. Palmitic acid, Solid Lipid Nanoparticles.

INTRODUCTION

In the recent years, with the advent of Nanomedicine, engineered tunable devices with the size in the order of billions of meters have been proposed as an intriguing tool potentially able to solve the unmet problem of enhancing drug transport across the BBB. Amongst different devices, nanoparticles (NPs) technology is rapidly advancing. Nanotechnology refers to structures with a size range of 1–100 nm in at least one dimension. Nanotechnology is the application of science and technology to control matter at the molecular level. At the nanoscale level, the properties of matter are significantly different from their macroscopic bulk properties. Nanotechnology also refers to the ability for designing, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale. One area where nanotechnology has the potential to make a significant impact is drug. This impact has already been felt with the translation of several nanoscale drug delivery systems into the clinic, although the full potential of these systems is only starting to be explored. Nanoscale drug delivery vehicles have shown the ability to encapsulate a variety of therapeutic agents such as small molecules (hydrophilic and/or hydrophobic), peptides, protein-based drugs, and nucleic acids. Because of their unique size range, nanoparticles exhibit "enhanced permeability and retention effect" (EPR) which confirm their potential in specific targeting so as to maximize the therapeutic effects and minimize the undesirable effects.

Amongst various nanoparticles, solid lipid nanoparticles (SLNs), introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric nanoparticles. SLNs are small sized lipid nanoparticles composed of biocompatible and biodegradable solid lipids. Their matrix is composed of physiological lipids which reduce the danger of acute and chronic toxicity. Irrespective of their small size (10-1000nm), they offer a high drug loading capacity, larger surface area and thus enhanced bioavailability. These characteristics make SLNs an interesting drug delivery system.

Topical corticosteroids such as dexamethasone (DEX), which is a highly potent and long-acting glucocorticoid, are considered as the first-line therapy for symptomatic oral precancerous lesions and are effective in their

management. This is due to their antiinflammatory effects and anti-immunologic properties of suppressing T lymphocyte function. It is a Food and Drug Administration (FDA)-approved immunosuppressive corticosteroid clinically used to treat various inflammatory diseases. Although corticosteroids can be administered systemically, local therapy remains the treatment of choice as it can be applied to lesions with minimal systemic absorption and potential for serious side effects such as hypertension, hydroelectrolytic disorders, hyperglycemia, peptic ulcers, edema, and glucosuria restricts.

So the aim of the present study was to prepare Dexamethasone loaded SLNs by solvent evaporation followed by homogenization technique and to evaluate the physicochemical properties of obtained Dexamethason loaded SLNs, such as mean particle size, zeta potential, drug entrapment efficiency, in vitro drug release and drug release kinetics evaluation. The effects of composition of lipid materials and surfactant mixture on particle size, zeta potential, drug entrapment efficiency, and in vitro drug release behavior were investigated in detail. FTIR and DSC analyses were performed to investigate the status of the lipid and the drug.

2. MATERIALS AND METHODS

Dexamethason was received as a gift sample from Balaji drugs distributors Pvt. Ltd; Maharashtra (India). Tween 80 was purchased from Qualikems Fine Chemicals Pvt. Ltd. Span 60 was purchased from Loba Chemie, Mumbai. The other chemicals were of analytical reagent grade and were used as received.

2.1. PREFORMULATION STUDIES

2.1.1. Melting Point

Melting point of the drug was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in digital melting point apparatus and the temperature at which the drug melted was noted down.

2.1.2. Assay

Assay of the drug was performed by UV spectrophotometric method. Dexamethason (10 mg) was dissolved in few ml of phosphate buffer (pH 6.8) and volume was made up to 100 ml in the volumetric flask using phosphate buffer (pH 6.8). From this stock solution 1 ml solution was withdrawn and diluted up to 10 ml in volumetric flask (10µg/ml). The absorbance of the solution was measured at scanned wavelength (241.2 nm) using UV spectrophotometer.

2.1.3. Calibration Curve

Accurately weighed 10 mg of Dexamethasone was transferred into a 10 ml volumetric flask. A few mL of pH 6.8 phosphate buffer was added to it and shook well. The solution was sonicated for 1 minute in bath sonicator and diluted up to the mark with pH 6.8 phosphate buffer to have a stock solution. From this stock solution, further dilutions were made.

2.2. Preparation of Dexamethasone Loaded Solid Lipid Nanoparticles

Dexamethasone, stearic acid / palmitic acid, and span 60 were dissolved in ethanol to prepare the lipid phase. The aqueous phase was prepared by mixing tween 80 in distilled water with magnetic stirrer. Ethanol from lipid phase was evaporated and when a wet mass was left, then this drug-embedded lipid layer was slowly poured in aqueous solution homogenizing at 10,000 rpm for 10 minutes. The composition of stearic acid and palmitic acid formulation batches are given in Tables 1 and 2 respectively.

Table 1: Composition of Stearic acid formulations.

Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
Dexamethasone	10	10	10	10	10	10	10	10
Stearic Acid (mg)	100	200	100	200	100	200	100	200
Span 60 (mg)	50	50	100	100	50	50	100	100
Tween 80 (mL)	0.50	0.50	0.50	0.50	0.75	0.75	0.75	0.75
Ethanol (mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled water	25	25	25	25	25	25	25	25

Table 2: Composition of palmitic acid formulations.

Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
Dexamethasone	10	10	10	10	10	10	10	10
Palmitic acid (mg)	100	200	100	200	100	200	100	200
Span 60 (mg)	50	50	100	100	50	50	100	100
Tween 80 (mL)	0.50	0.50	0.50	0.50	0.75	0.75	0.75	0.75
Ethanol (mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled water	25	25	25	25	25	25	25	25

2.3. Characterization of Formulated SLNs

2.3.1. Measurement of Particle Size: The average particle size of the Dexamethasone loaded SLN formulations were estimated using microscopy method. The number of particles present in the size range, the average particle size were determined.

2.3.2. Drug Entrapment Efficiency

The percentage of entrapped Dexamethasone was determined spectrophotometrically at 241.2 nm. After centrifugation of the aqueous suspension, the amount of the free drug was detected in the supernatant and the amount of entrapped drug was determined as the result of the initial drug minus the free drug. The entrapment efficiency can be calculated using the following formula:
%EE = {(Total drug content - Free drug content)/Total drug content} X 100

2.3.3. In Vitro Drug Release Study

Drug release study was carried out in phosphate buffer pH 6.8 for 24 hours. The buffer was prepared using the method quoted before. In vitro drug release study was carried out by incubating 10 mL of formulation in 50 mL pH 6.8 phosphate buffer maintained at 37°C with continuous stirring with a magnetic stirrer. The samples (2 mL each) were withdrawn periodically and the equal volume of medium was replaced after each withdrawal. The samples collected were then analyzed for the amount of drug released by measuring absorbance at 241.2 nm using a UV-Visible double beam spectrophotometer.

2.3.4. Drug Release Kinetics

The cumulative amounts of Dexamethasone release from the polymeric nanoparticles at different intervals were fitted with zero-order kinetic model, first order kinetic model, Higuchi model and Korsmeyer- Peppas model to characterize the mechanism of drug release.

3. RESULTS AND DISCUSSION

3.1. Preformulation Studies

Dexamethasone is a white to cream colored crystalline powder in appearance with a reported melting point of 260-264°C.

3.1.2. Assay

Assay of the drug was performed by UV spectrophotometric method at a scanned wavelength of 241.2 nm. The drug content was found to be in the range of 98.99-99.82%, which is within acceptable limits.

3.1.3. Calibration Curve

Absorbance of each solution was recorded at 241.2 nm against pH 6.8 phosphate buffer as blank. The calibration curve of absorbance vs. concentration was plotted and correlation co-efficient and regression equation for Dexamethasone were determined. The drug was found to show linearity in a concentration range of 10 to 100 µg/ml. The calibration curve is shown in Fig. (1).

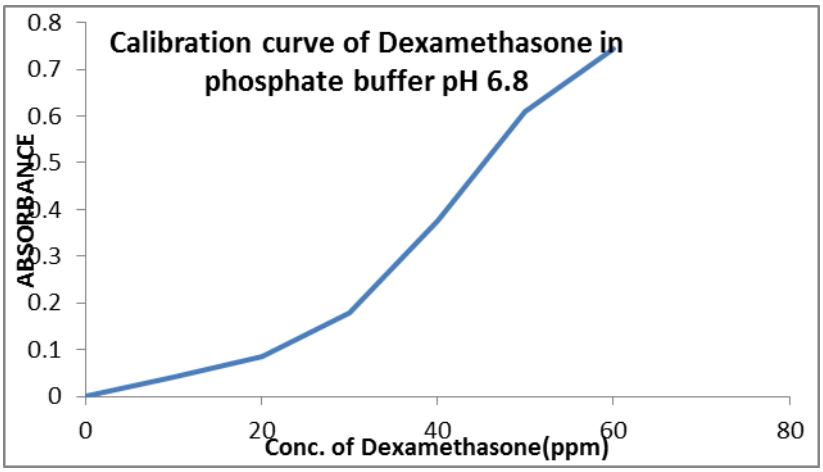

Fig. (1). Calibration curve of drug in pH 6.8 phosphate buffer.

Measurement Particle Size

Since our aim was to achieve SLNs with particle size small enough for brain applications, one of the first tasks was to identify the experimental parameters that govern the particle size. The formulations were characterized for particle size analysis. amongst which only six formulations (three of each lipid) i.e. SF1, SF2, SF6 and PF1, PF2, PF6 were found to be in required nanometer (nm) size range and other formulations were found to possess particle size beyond 250 nm.

Table 3: Particle size and PDI of Stearic acid formulations (SF Batches).

Sr. No	Formulation	Particle Size (nm)
1	SF1	124.5
2	SF2	136.4
3	SF3	204.2
4	SF4	220.3
5	SF5	318.5
6	SF6	154.4
7	SF7	254.6
8	SF8	407.5

Table 4: Particle size and PDI of Palmitic acid formulations (PF Batches).

Sr. No	Formulation	Particle Size (nm)
1	PF1	130.4
2	PF2	167.5
3	PF3	218.6
4	PF4	236.5
5	PF5	340.3
6	PF6	146.2
7	PF7	272.4
8	PF8	418.4

Drug Entrapment Efficiency

The entrapment efficiency of prepared SLNs was determined by UV-Visible spectrophotometer. At 291.2 nm λmax absorbance was determined and after calculations, the entrapment efficiency was computed which is given in the table below. Lipids show positive influence on entrapment efficiency; this result can probably be attributed to the high affinity of the lipophilic drug for the lipid material as well as the presence of span 60. The selected formulations were able to entrap ~90% or more drug. The results are tabulated below (Table 5).

Table 5: Entrapment Efficiency of selected formulations.

Sr. No.	Formulation	Entrapment Efficiency (%)
1	SF1	93.44
2	SF2	90.20
3	SF6	88.58
4	PF1	92.33
5	PF2	89.44
6	PF6	88.08

In Vitro Drug Release Study

Cumulative amount of drug release was plotted against time to obtain release profile. It was observed that there was an initial rapid release followed by slower release rate. This initial burst rate may be due to the desorption of drug associated with the surface of nanoparticles and the slower release in the later stage was attributed to the fact that solubilized drug can only be released slowly from the lipid matrices due to dissolution and diffusion. All the 6 formulations were able to release the drug at a sustained release up to 24 hours in phosphate buffer pH 6.8. The release pattern observed in Stearic acid and Palmitic acid formulations is shown in Figs. (**2** and 3) respectively and dissolution data is tabulated below (Table 5)

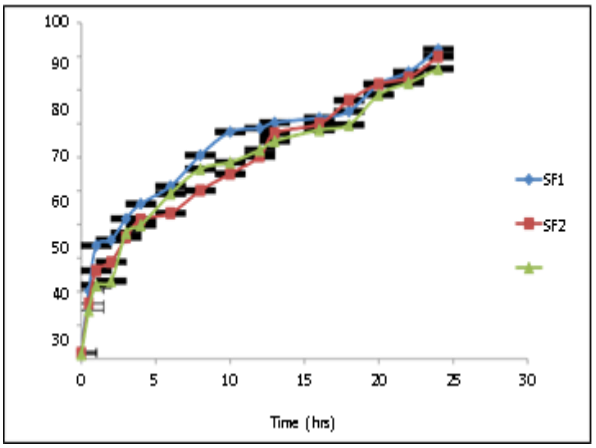

Fig. (2). % Cumulative drug release of Dexamethasone loaded SLNs from Stearic acid batch (selected formulations). The error bars indicate the standard deviation of three tests.

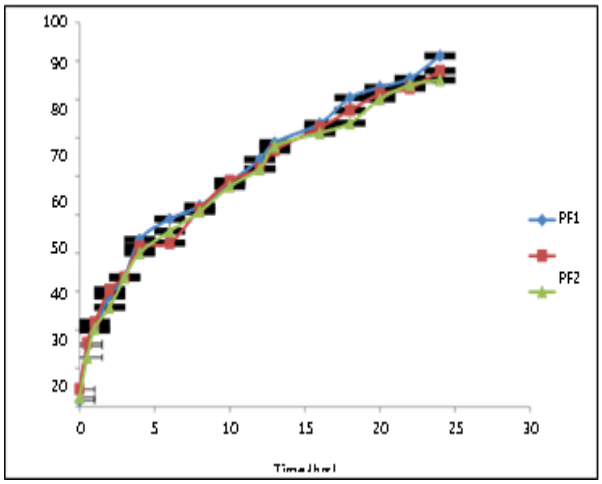

Fig. (3). % Cumulative drug release of Dexamethasone loaded SLNs from Palmitic acid batch (selected formulations). The error barsindicate the standard deviation of 3 tests.

Table 7: % cumulative drug release of Dexamethasone loaded SLNs.

Time	% Cummulative Drug Released					
	SF1	SF2	SF6	PF1	PF2	PF6
0 min	00	00	00	00	00	00
30 min	2.44	1.79	1.40	2.55	4.55	4.19
1 hr	18.24	16.49	17.18	16.80	16.54	12.83
2 hr	35.71	33.11	30.20	20.40	20.99	19.44
3 hr	38.39	36.91	37.44	29.86	29.48	24.42
4 hr	44.14	42.14	43.51	34.53	32.92	34.48
6 hr	53.38	51.22	54.68	43.66	40.76	39.19
8 hr	59.90	57.11	56.11	46.89	41.61	44.65
10 hr	65.40	63.91	60.60	53.72	50.55	49.83
12 hr	70.25	72.05	62.14	59.95	57.46	56.11
14 hr	72.44	74.19	65.10	65.40	60.50	60.95
16 hr	75.48	77.20	70.11	70.77	65.55	68.46
18 hr	78.16	81.15	72.34	78.19	71.76	76.58
20 hr	80.02	82.24	76.44	82.33	76.64	79.97
22 hr	83.90	85.11	80.90	88.94	82.58	82.38
24 hr	93.44	90.20	85.58	92.33	86.44	85.58

1.1. Drug Release Kinetics

The prepared SLNs were subjected to the drug release kinetics and release mechanism. The formulations were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi and Korsmeyer pappas. All the formulations (SF1, SF2, SF6, PF1, PF2 and PF6) were analyzed for the drug release mechanism. The data revealed a better fit to the Higuchi diffusion model with n value less than 0.43 *i.e.* Fickian diffusion for SF batch formulations and the drug release was dependent on time. On the other hand, Higuchi anomalous diffusion (non-Fickian) was observed for PF batch formulations owing to n value > 0.43<1 which could be attributed to the fact that the diffusion refers to combination of both diffusion and erosion controlled rate release.

The results are presented in Tables (8 and 9) and Figs. (4 and 5) below.

Formulations	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	$K(h^{-1})$	R^2	$K (h^{-1})$ 1	R^2	$K (h^{-1/2})$ H	R^2	N	R^2
SF1	3.003	0.906	0.038	0.963	16.71	0.984	0.256	0.968
SF2	3.062	0.937	0.034	0.966	16.82	0.991	0.321	0.975
SF6	2.991	0.902	0.030	0.976	16.72	0.988	0.405	0.973

Table 9: Drug release kinetics for Palmitic acid formulations.

Formulations	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	K (h^{-1})	R^2	K (h^{-1}) 1	R^2	K ($h^{-1/2}$) H	R^2	N	R^2
PF1	3.223	0.928	3.223	0.928	17.84	0.996	0.464	0.982
PF2	3.046	0.937	3.046	0.937	16.77	0.996	0.496	0.989
PF6	3.109	0.929	3.109	0.929	17.21	0.997	0.464	0.984

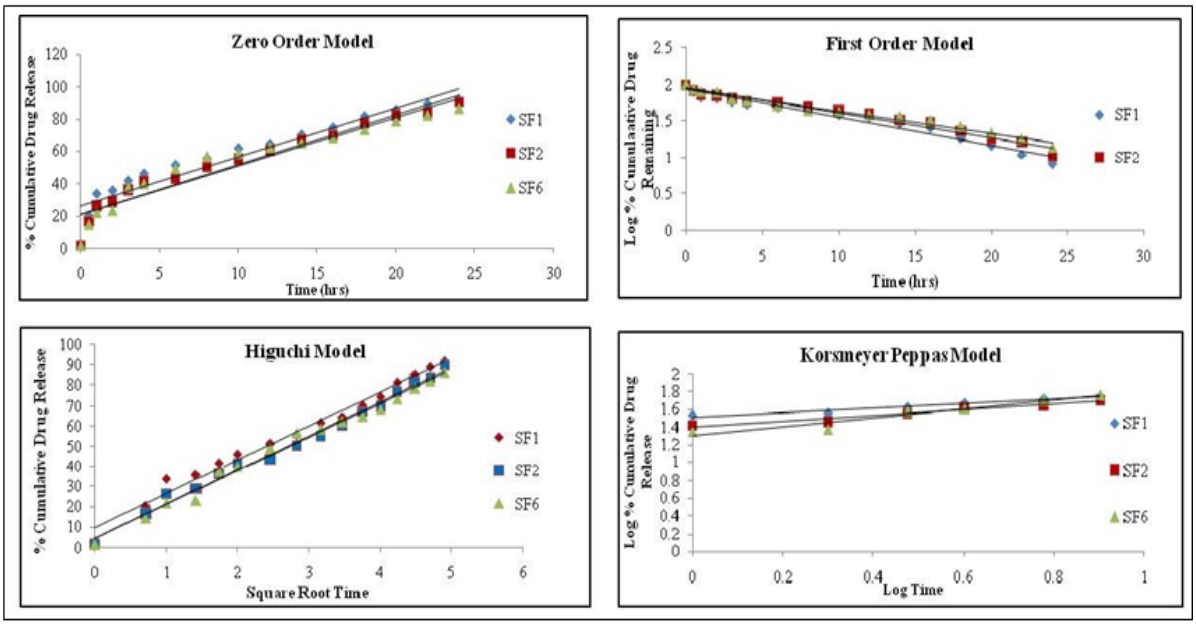

Fig. (4). Kinetics of drug release for Stearic acid formulations- a). Zero order model; b). First order model; c). Higuchi model; d).Korsmeyer-Peppas model.

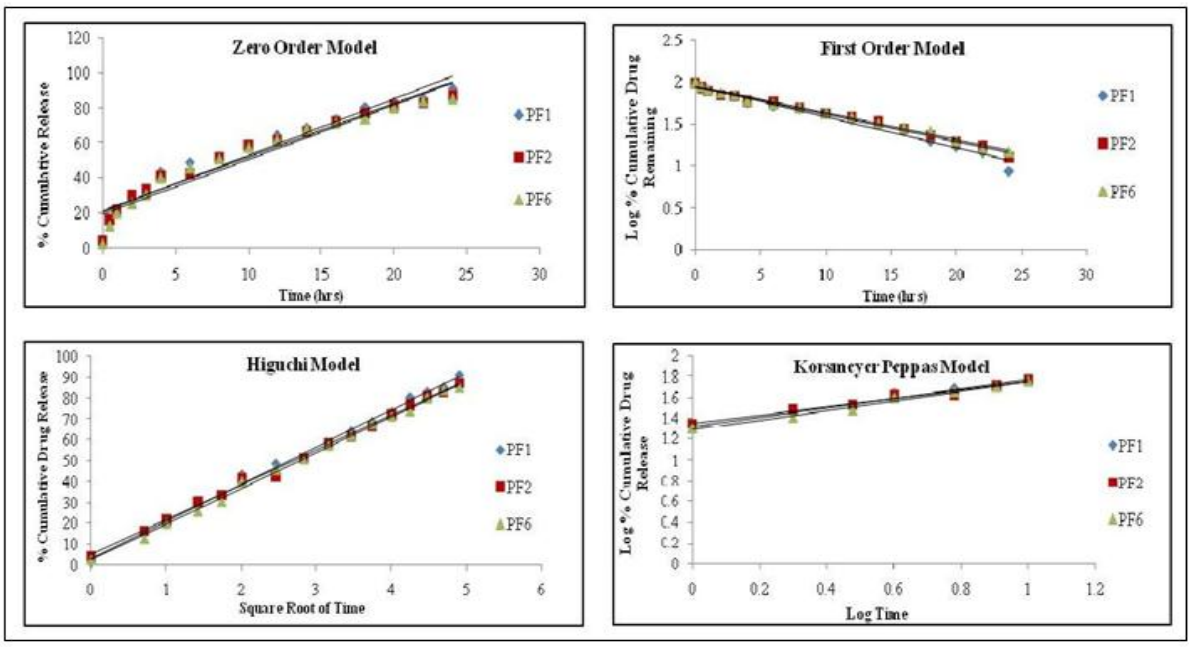

Fig. (6). Kinetics of drug release for Palmitic acid formulations- a). Zero order model; b). First order model; c). Higuchi model; d).Korsmeyer-Peppas model.

CONCLUSION

A total of 16 formulations were prepared (8 for each lipid *i.e.* Stearic acid and Palmitic acid; SF1-SF8 and PF1-PF8 respectively) Optimized formulations were characterized for particle size analysis, drug entrapment efficiency and *in vitro* drug release study. The particle size of SF1, SF2, SF6, PF1, PF2 and PF6 was measured to be 124.5 nm, 136.4 nm, 154.4 nm, 130.4, 167.5 and 146.2 nm respectively using Microscopic method, which was in desired range. SLN formulations were found to be stable with drug entrapment efficiency was reported to be approximately 90% for selected formulations. From

in vitro drug release study, the % cumulative drug release after 24 hrs from SF1, SF2, SF6, PF1, PF2 and PF6 was recorded to be 93.44, 90.20, 85.58, and 92.33, 89.44, 88.58 respectively. Mechanism of drug release was found to follow Higuchi diffusion model; Fickian diffusion for SF batch formulations and non-Fickian diffusion for PF batch formulations. The highest cumulative % drug releasing formulation from each batch (*i.e.* SF1 and PF1) was chosen for further evaluations.. The SLNs appeared to be less dense in the core with a well-defined shell. The successful incorporation of Dexamethasone into SLNs opens a wide scope of the study of the delivery system with respect to sustained and targeted drug delivery. However the *in vivo* studies are yet to be carried out to confirm the potential of formulated SLNs.

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