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DEVELOPMENT OF SUSTAINED RELEASE MICROPARTICLES OF DICLOFENAC SODIUM USING STEARIC ACID AS POLYMER BY EMULSION/CHILLING METHOD

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ABSTRACT

Diclofenac Sodium was used as core using Stearic acid as polymer and Microparticles were prepared by Emulsion/Chilling method. The prepared microparticles were evaluated for Particles size, Percentage yield, Bulk & Tapped Density, Angle of Repose, Carr's Index, Hausner Ratio, SEM, Dissolution study. All Microparticles were obtained were discrete, Small & large sized, spherical and non spherical. Diclofenac Sodium release form microparticles followed first order kinetics and influence by the size of microparticles. Slow release of Diclofenac Sodium from Stearic acid microparticles over 18 hours was observed.

KEYWORDS: Diclofenac Sodium, Microparticles, First order kinetics.

INTRODUCTION

Controlled or sustained release delivery system is a tool for optimizing therapeutic effect, by maximizing the bioavailability of conventional drugs and reducing side effects. Controlled release dosage forms cover a wide range of prolonged action formulation, which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time.[1]

Diclofenac Sodium is a non steroidal anti-inflammatory agent, belongs to the class phenyl acetic acid derivatives, which is widely used in the long term therapy of rheumatoid arthritis.

The biological half-life of Diclofenac sodium is 1-2 hr, therefore it requires multiple dosing to maintain therapeutic drug level in blood, necessitates preparation of a controlled release formulation. Diclofenac Sodium is poorly soluble in water and practically insoluble compound in acidic solution (pKa 3.9); however, it dissolves in intestinal fluid. Gastrointestinal effects commonly observed include gastritis, peptic ulcers, bleeding, hypersensitivity reactions and renal effects. Diclofenac Sodium have many side effects like anxiety, depression, dizziness, insomnia, hypertension, edema, taste disorder, transient stinging, abdominal pain or cramps, bleeding, colitis, acute renal failure, nephritic syndrome, heart failure. The present investigation is aimed to formulate the solid lipid microparticles of Diclofenac Sodium with Stearic acid as a lipidic polymer.[2-5]

Lipid-based matrices are known to improve the bioavailability of hydrophobic bioactive, which make these matrices especially interesting as encapsulation systems. Recent advances have shown that one of the approaches to improve the half life and a bioavailability substance, such as Diclofenac sodium is to incorporate these compounds in lipid-based encapsulation systems.[6-8] Several structured lipid-based delivery systems are available to encapsulate, protect and deliver the hydrophobic bioactive compounds in the form of lipid droplets (emulsions, microemulsions, nanoemulsions and multiple emulsions), liposomes, coated particles (multilayer emulsions, colloidosomes) and solid lipid particles. Solid lipid particles, which can be produced at either the micro, or nanoscale, are generated by exchanging the liquid core (oil), composed of a conventional oil-in-water (o/w) emulsion, for a solid lipid (lipids that are solid at room temperature).[9] The aim of the study was to prepare Stearic acid Solid Lipid microparticles containing Diclofenac Sodium to achieve a sustained drug release profile suitable for oral administration.

MATERIALS AND METHODS

Materials

Diclofenac sodium and Stearic acid were kindly gift samples from Unispeed pharmaceuticals ltd., Baddi, India and Gatefoss, Mumbai, India. Tween 20, Tween 80, Span 20, Span 80 was purchased from SD fine chemicals Ltd., Mumbai, India. Potassium dihydrogen phosphate and dihydrogen phosphate were purchased from Thomas Baker (Chemicals) Pvt Ltd., Mumbai, India. Other materials used were of analytical grade and procured from commercial sources.

Drug polymer compatibility studies

Diclofenac Sodium and physical mixture of Diclofenac Sodium and Stearic acid were subjected to IR spectroscopic study using FT-IR spectrophotometer (Thermo Nicolet Ih-10corp. USA). The spectrum was scanned over the wave number range from 4000 – 400 cm^{-1}.

Preparation of Solid Lipid Microparticles

Emulsion/Chilling method

Sustained released solid lipid microparticles of Diclofenac Sodium were prepared by emulsion/chilling method. Stearic acid was melted on a hot plate under stirring at 600 rpm (in order to achieve particles with micrometric size) and Diclofenac Sodium was added to the molten excipients. The oil phase (Diclofenac Sodium + Stearic acid) was slowly added to a 1.5% (w/w) Tween 80 solution at the same temperature, followed by the quick addition of a mixture of water: propylene glycol at $0^{o}C$, maintaining the agitation at 600 rpm. The microparticles obtained were filtered and washed with water. Different compositions of Formulations are shown in Table 1.

Table 1: Composition of different formulations.

S No.	Formu-lation	Drug (mg)	Stearic acid (mg)	Propy-lene glycol (ml)	Water	Tween 20 (ml)	Tween 60 (ml)	Tween 80 (ml)	Span 20 (ml)	Span 80 (ml)	Stirring speed (rpm)
1.	F1	50	50	25	75	-	-	1.06	-	-	600
2.	F2	50	250	25	75	-	-	1.06	-	-	600
3.	F3	50	500	25	75	-	-	1.06	-	-	600
4.	F4	50	750	25	75	-	-	1.06	-	-	600
5.	F5	50	1000	25	75	-	-	1.06	-	-	600
6.	F6	50	750	25	75	1.06	-	-	-	-	600
7.	F7	50	750	25	75	-	1.06	-	-	-	600
8.	F8	50	750	25	75	-	-	-	1.06	-	600
9.	F9	50	750	25	75	-	-	-	-	1.06	600
10.	F10	50	750	25	75	1.06	-	-	-	-	1000
11.	F11	50	750	25	75	1.06	-	-	-	-	1500
12.	F12	50	750	25	75	1.06	-	-	-	-	2000
13.	F13	50	750	25	75	-	-	1.06	-	-	1000
14.	F14	50	750	25	75	-	-	1.06	-	-	1500
15.	F15	50	750	25	75	-	-	1.06	-	-	2000
16.	F16	50	750	-	100	-	-	1.06	-	-	600
17.	F17	50	750	100	-	-	-	1.06	-	-	600
18.	F18	50	750	75	25	-	-	1.06	-	-	600
19.	F19	50	750	50	50	-	-	1.06	-	-	600
20.	F20	50	750	-	100	-	-	1.06	-	-	1000
21.	F21	50	750	100	-	-	-	1.06	-	-	1000
22.	F22	50	750	75	25	-	-	1.06	-	-	1000
23.	F23	50	750	50	50	-	-	1.06	-	-	1000

EVALUATION OF MICROPARTICLES

Percentage Drug Entrapment Efficiency (% DEE)

Drug entrapment is the ratio of drug to the weight of total carrier system. Dissolved 50 mg of prepared microparticles in 10 ml of buffer solution of pH 6.8 in volumetric flask and allow it to stand undisturbed for overnight. Filtered the solution. UV absorbance of filtered solution was taken on UV-visible spectrophotometer at 282 nm.[10]

$$\% \text{ DE} = \frac{\text{Initial drug} - \text{final drug in formulation}}{\text{initial drug}} \times 100$$

Percentage Yield

The percentage yield is the ratio between the actual yield and the theoretical yield multiplied by 100%. It indicates the percent of theoretical yield that was obtained from the final product in an experiment.[11]

$$\% \text{ yield} = \frac{\text{Experimental yield}}{\text{Theoretical yield}} \times 100$$

Particle Size Analysis

The particle size of the microparticles was determined by using optical microscopy method. Approximately 100 microparticles were counted for particle size analysis by using calibrated optical microscope (Biolux cxt).[12]

$$\text{Least Count} = \frac{\text{Stage Micrometer}}{\text{Optical Micrometer}}$$

$$\text{Particle Size} = \frac{\sum nd}{\sum n}$$

Here, $\sum nd$ = no. of particles

$\sum n$ = average diameter

MICROMETRIC PROPERTIES OF MICROPARTICLES

Bulk & Tapped Density

Bulk and tapped density of microparticles is also evaluated. Weighed amounts of microparticles were taken in a 10ml measuring cylinder after shaking lightly to break any agglomerates. After observing the initial volume of microparticles the cylinder was allowed to fall under its own weight on a hard surface from the height of 2-5 cm. The tapping was continued at a rate of 100taps/min until no further change in volume was noted. Bulk density

refers to a measure used to describe a packing of particles or granules. It may also be expressed in grams per cubic centimeter (g/cm^3).

$$\text{Bulk density} = \frac{\text{mass of powder}}{\text{volume of packing}}$$

$$\text{Tapped bulk density} = \frac{\text{mass of powder}}{\text{tapped volume of packing}}$$

Angle of Repose

Angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose can range from 0° to 90°. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and shapes of the particles and the coefficient of friction of the material. The angle of repose is also gravity-dependent.[13]

$$\text{Tan } \Theta = \frac{h}{r}$$

Θ = Angle of repose

h = height

r = radius

Carr's Index

It is defined as the compressibility of powder measures the relative significance of interparticle interactions. Firstly volume occupied by powder was calculated and then final volume after tapping. The Carr's index is calculated by the formula.[14,15]

$$C = \frac{V_B - V_T}{V_B} \times 100$$

V_B is the volume occupied by given mass of powder.

V_T is the volume occupied by the given mass of powder after tapping.

Also be written as:

$$C = 100 \times \left(1 - \frac{\rho_B}{\rho_T}\right)$$

P_B is the freely settled bulk density of the powder

P_T is the tapped bulk density of the powder.

Hausner Ratio

The Hausner ratio is a number that defined as the flowability of a powder or granular material. Hausner ratio calculated by the formula:

$$H = \frac{\rho_T}{\rho_B}$$

P_B is the freely settled bulk density of the powder,

P_T is the tapped bulk density of the powder.

Surface topography by SEM

SEM photographs were taken using scanning electron microscope model (JOEL-LV-5600, USA at suitable magnification at room temperature. The shape and surface morphology of lipid based Diclofenac sodium loaded microparticles were investigated using SEM. The samples for SEM study were prepared by lightly sprinkling the formulation on a double-adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ~300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken.[16]

In vitro dissolution studies

The release rate of Diclofenac sodium from lipidic microparticles and pure drug was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of phosphate buffer 6.8 pH, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with phosphate buffer 6.8 pH. Absorbance of these solutions was measured at 289 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.[17,18]

In vitro drug release kinetic studies

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the microparticles, drug release data was analyzed according to zero order first order Higuchi square root Korsmeyer - Peppas model. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

RESULT AND DISCUSSION

Absorption maxima of Diclofenac sodium

UV absorption maximum of Diclofenac sodium in methanol was determined and exhibited characteristic absorption at 282 nm. Figure 1.2 shows the UV spectrum scan of Diclofenac sodium in methanol.

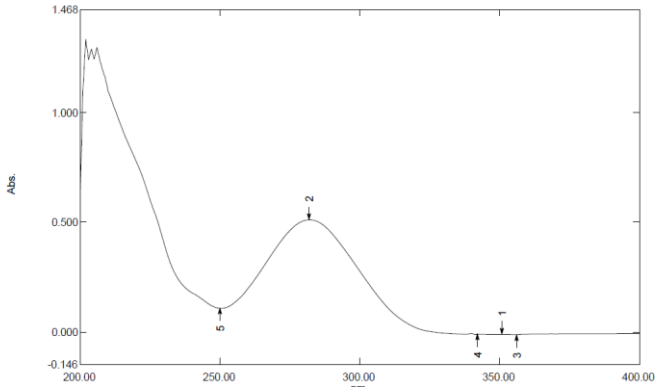

Figure 1: UV spectrum of Diclofenac sodium Standard.

Standard curve of Diclofenac sodium in methanol

Absorbance data for standard calibration curve is given in the Table 1.2. Using the absorbance of Diclofenac sodium at varied concentrations, calibration curve was constructed. The calibration equation for straight line was observed to be y=0.072x+0.020 with correlation coefficient of 0.998.

Table 2: Calibration curve data of Diclofenac in methanol.

Concentration (µg/ml)	Absorbance
0	0±0
2	0.153±0.019
4	0.223±0.021
6	0.298±0.023
8	0.374±0.021
10	0.435±0.022
12	0.494±0.035
14	0.577±0.038
16	0.633±0.042
18	0.721±0.036
20	0.805±0.045

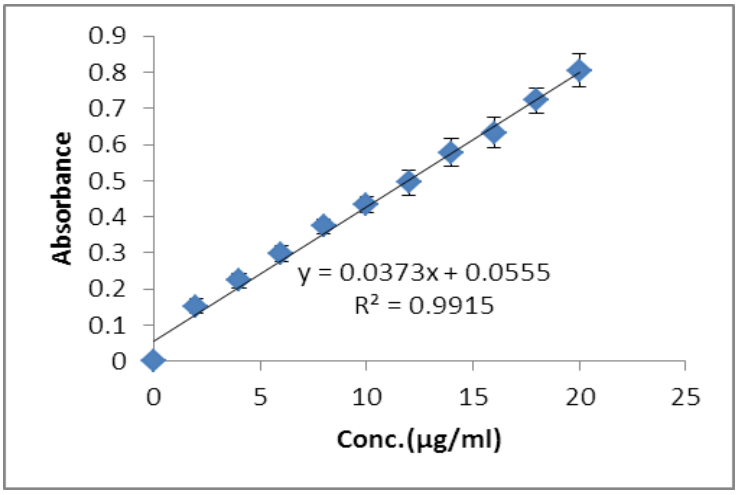

Figure 2: Calibration curve of Diclofenac Sodium in Methanol at 282 nm.

Standard curve in phosphate buffer pH 6.8

Different concentrations of standard solution were prepared and their respective absorbance was measured in UV-Visible spectroscopy. Concentration and their respective absorbance are shown in Table. The λ_{max} was found to be 276 nm. The standard curve was plotted and shown in Figure. The calibration equation for straight line was observed to be y= 0.0324x+.0093 with correlation coefficient as 0.9937 which is acceptable for the follow of Beer Lambert Law.

Table 3: Calibration data for standard curve in phosphate buffer pH 6.8.

Concentration (µg/ml)	Absorbance
0	0±0
2	0.113±0.018
4	0.195±0.019
6	0.268±0.021
8	0.325±0.019
10	0.395±0.022
12	0.454±0.025
14	0.522±0.028
16	0.583±0.032
18	0.654±0.031
20	0.726±0.035

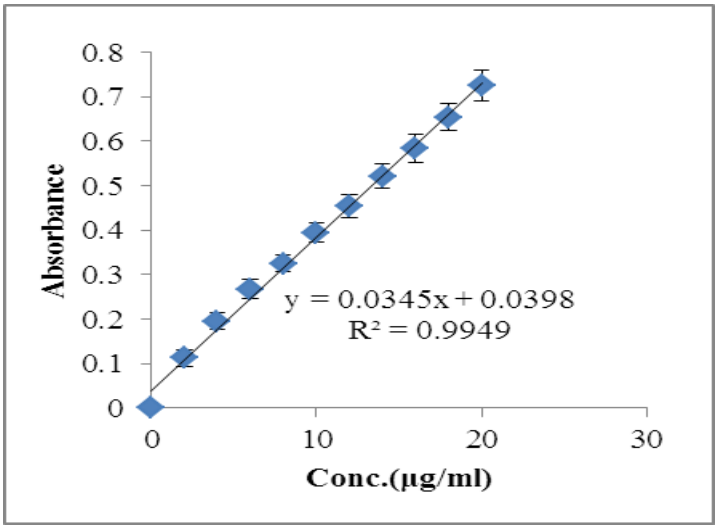

Figure 3: Standard curve of Diclofenac Sodium in phosphate buffer pH 6.8 at 282 nm.

Drug polymer compatibility studies

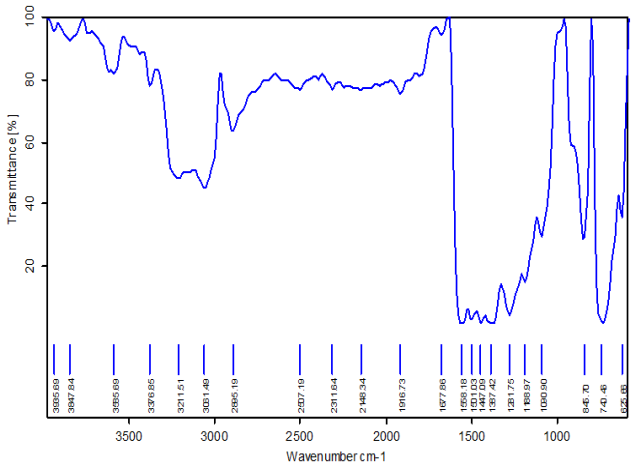

Figure 4: FTIR spectrum of Diclofenac Sodium.

Table 4: FTIR interpretation of Diclofenac Sodium.

Characteristics Peaks	Reported (cm^{-1})	Observed (cm^{-1})
N-H stretching	3430	3376.85
N-H bending	1573	1568.18
N-H bending	1505	1501.03
O-H bending	1387	1367.42
C-Cl stretching	850	845.70

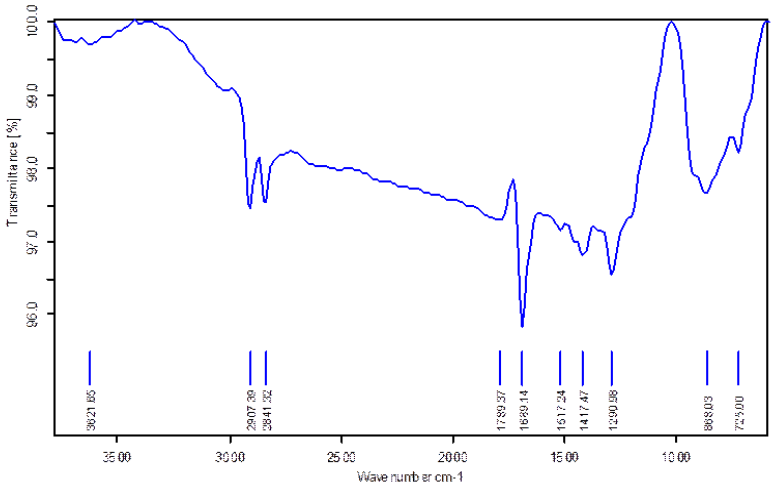

Figure 5: FTIR spectrum of Stearic Acid.

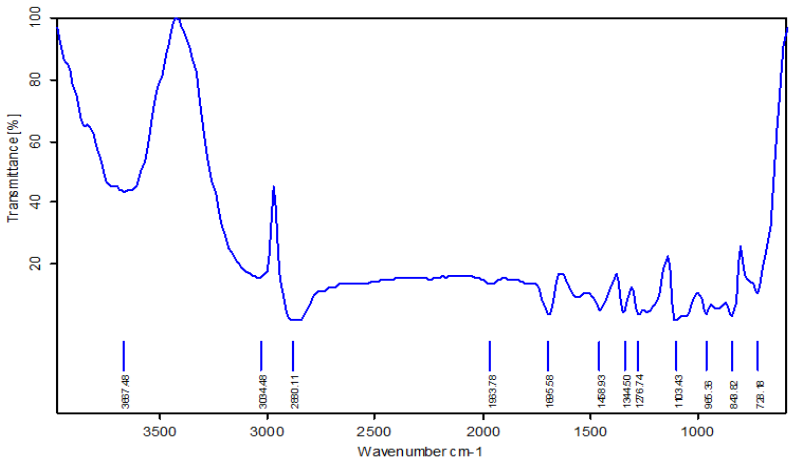

Figure 6: FTIR spectrum of Physical mixture.

Presence of characteristic peaks of Diclofenac sodium in the FTIR spectra of physical sample indicates the absence of chemical interaction between drug and excipients are employed in the study.

Method of preparation of microparticles

Emulsion/Chilling method

Sustained released solid lipid microparticles of Diclofenac Sodium were prepared. Solid lipid microparticles of Diclofenac Sodium by emulsion/chilling method. Observations of different formulations are as shown in Table 7.

Table 7: Observations of different microparticles formulations.

S. No.	Formulation	Result (Shape of Microparticles)
1.	F1	Not formed
2.	F2	Oval shaped
3.	F3	Spherical
4.	F4	Spherical
5.	F5	Spherical
6.	F6	Spherical
7.	F7	Irregular shaped
8.	F8	Spherical
9.	F9	Not formed
10.	F10	Not formed
11.	F11	Not formed
12.	F12	Not formed
13.	F13	Spherical
14.	F14	Oval shaped
15.	F15	Not formed
16.	F16	Irregular shaped
17.	F17	Not formed
18.	F18	Not formed
19.	F19	Not formed
20.	F20	Not formed
21.	F21	Not formed
22.	F22	Spherical
23	F23	Not formed

EVALUATION OF MICROPARTICLES

Drug Entrapment, percentage yield and Particle Size

The drug content and percentage yield were estimated to confirm that there is no degradation of the drug and expected amount of drug present in the product. The percentage drug entrapment efficiency and percentage yield results all solid lipid microparticles of Diclofenac prepared with Stearic acid percentage yield and particle size of all the formulation was found to be satisfactory and each formulation demonstrated high drug entrapment efficiency. The percentage yield, entrapment efficiency and particle size were found in the range of low standard deviation values in the drug entrapment efficiency indicated uniform drug distribution in all the batches as shown in table 8.

Mean particle size and size distribution of Diclofenac Sodium loaded Solid Lipid Microparticles were determined by light microscope. The results showed that the mean particle size was independent of the processing conditions. Almost all formulations studied showed a mean particle size about 4 μm with a size distribution ranging from 4.354 ± 1.54 to 7.432 ± 1.49 μm However, the mean particle size was affected by the concentration of lipids.

By varying amount of lipids, the results showed that the amount of lipid increased, the mean particle size increased as well.

Table 8: Drug Entrapment, Percentage yield and Particle size of different lipid based Microparticles.

S. No.	Formulation code	%Entrapment Efficiency	%age yield	Particles Size (mm)
1	F2	82.43 ± 1.42	41.49 ± 1.35	9.92 ± 1.54
2	F3	91.47 ± 1.18	78.43 ± 0.96	11.12 ± 1.57
3	F4	96.17 ± 1.22	89.29 ± 1.50	6.57 ± 1.61
4	F5	93.25 ± 1.19	54.11 ± 1.75	6.62 ± 1.41
5	F6	81.17 ± 1.22	85.21 ± 1.61	5.67 ± 1.54
6	F7	73.43 ± 1.55	75.45 ± 1.46	7.432 ± 1.49
7	F8	99.18 ± 1.65	53.96 ± 1.36	4.43 ± 1.28
8	**F13**	**99.3 ± 1.65**	**90.32 ± 1.29**	**4.336 ± 1.45**
9	F14	70.48 ± 1.46	42.71 ± 0.83	6.354 ± 1.54
10	F16	64.32 ± 1.48	49.46 ± 1.42	4.33 ± 1.50
11	F22	89.13 ± 1.19	11.86±0.096	4.34 ± 1.42

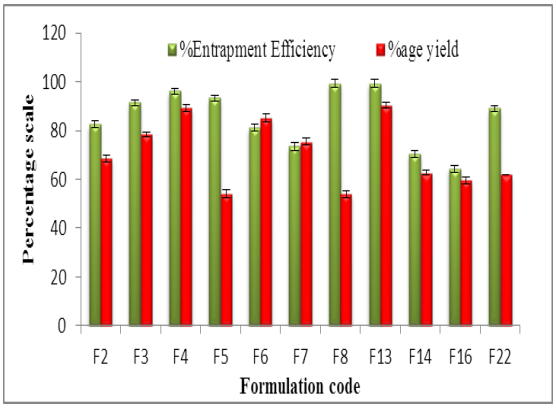

Figure 7: Percentage Entrapment efficiency and Percentage Yield of different formulations.

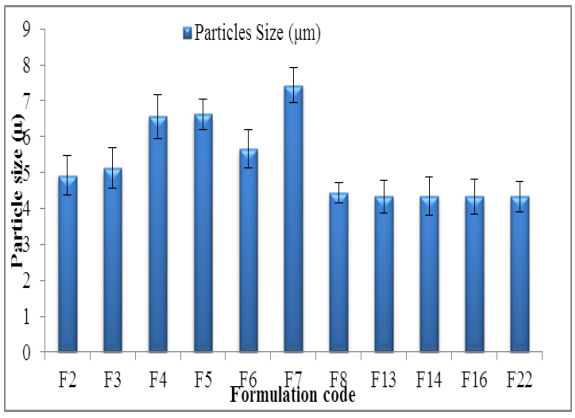

Figure 8: Particle size of different solid Lipid microparticles Micrometric properties of Microparticles.

The formulations showed good flow property index Table. Taped density in the range of 0.321 ± 0.07 to 0.823 ± 0.03, Bulk density in the range of 0.415 ± 0.04 to 0.691 ± 0.07, Angle of repose ranged from 4.67 ± 1.27 to 24.55 ± 1.77 and the Carr's index ranged from 7.53 ± 1.66 to 23.43 ± 1.4. Hausner Ratio in the range of 1.46 ± 1.10 to 2.24 ± 1.22. The results of angle of repose indicates good flow property of the microparticles and the value of Carr's index further showed support for the flow property in Table 9.

Table 9: Micrometric properties of different Microparticles.

S. No.	Formulation code	Taped density (g/ml)	Bulk density (g/ml)	Angle of Repose	Carr's Index	Hausner Ratio
1	F2	-	-	-	-	-
2	F3	0.671 ± 0.04	0.553 ± 0.05	24.55 ±1.77	16.47 ±1.16	1.57 ±1.18
3	F4	0.823 ± 0.03	0.671 ± 0.07	4.67 ± 1.27	20.23 ±1.76	1.52 ±1.07
4	F5	0.519 ± 0.06	0.684 ± 0.06	9.99 ± 1.75	7.53 ± 1.66	1.46 ±1.10
5	F6	0.469 ± 0.06	0.556 ± 0.05	16.39 ±1.24	23.43 ± 1.4	1.68 ±1.08
6	F7	0.613 ± 0.05	0.486 ± 0.07	16.52 ±1.12	13.26 ±1.56	1.63 ±1.12
7	F8	0.75 ± 0.06	0.543 ± 0.07	21.23 ±1.25	16.58 ±1.31	1.64 ±1.10
8	**F13**	**0.321 ± 0.07**	**0.415 ± 0.04**	**10.15 ±1.56**	**11.93 ±1.19**	**1.64 ±1.11**
9	F14	-	-	-	-	-
10	F16	0.531 ± 0.04	0.551 ± 0.05	16.42 ±1.76	13.25 ±1.35	1.63 ±1.12
11	F22	0.541 ± 0.09	0.691 ± 0.07	5.41 ± 1.46	16.37 ±1.69	2.24 ±1.22

Surface Morphology

Investigation by SEM on the optimized SLMs, based on Stearic acid revealed a spherical shape with a quite smooth surface; although irregular fragments were also present (Fig. 6).

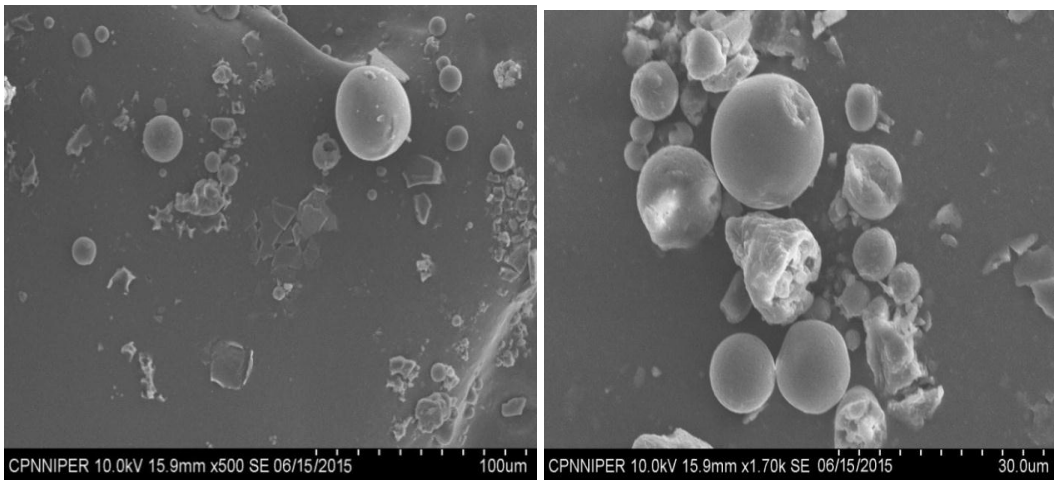

Figure 9: Scanning electron microscopy (SEM) micrograph of Diclofenac Sodium loaded lipid Microparticles.

In-vitro dissolution studies

In vitro drug release study of Diclofenac Sodium loaded microparticle.

Table 10: In-vitro drug release of F13 optimized formulation and pure drug

S. No.	Time (hr)	%CDR F13 Formulation	%CDR Pure drug
1.	0	0±0	0±0
2.	0.5	5.25±0.23	29.871±0.25
3.	1	11.834±0.46	45.794±0.32
4.	1.5	18.365±0.47	76.897±0.62
5.	2	24.851±0.77	98.231±0.86
6.	3	32.378±0.78	98.745±0.75
7.	4	38.781±1.01	98.787±0.62
8.	5	43.745±1.36	98.811±1.05
9.	6	47.298±1.89	98.845±0.96
10.	7	54.897±1.23	98.899±0.74
11.	8	59.256±1.34	98.912±0.81
12.	9	63.695±1.56	98.926±0.85
13.	10	66.589±1.25	98.956±0.74
14.	11	72.798±1.74	98.871±0.65
15	12	75.412±1.78	98.912±0.21
16	13	78.365±168	98.365±0.91
17	14	80.178±1.23	98.548±1.02
18	15	82.369±1.67	98.657±1.03
19	16	84.745±1.75	98.771±0.99
20	17	85.369±1.79	98.456±0.98
21	18	86.125±2.01	98.875±1.01

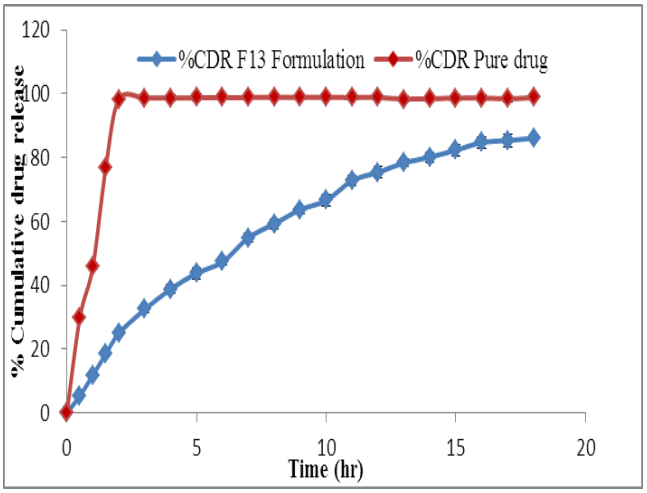

Figure 10: In-vitro drug release of F13 optimized formulation and pure drug.

Results of Diclofenac Sodium loaded microparticles in vitro release from optimized F13 formulations are illustrated in Fig. 7. It was apparent that the incorporation of Diclofenac Sodium led to significant slower release profiles compared to its pure drug where 98% was

released in 2 hrs. It was found that there was an initial rapid removal of the drug possibly by the drug associated loosely on the surface of the lipid matrix. This initial release was rapid, achieved at 2 hr and is termed as burst release. At 4th and 12th hr time intervals the drug release rate was achieved at nearly 40- 45%. The total cumulative drug releases of Diclofenac Sodium loaded microparticles was observed ~82% at the end of 12 h. Pure drug In vitro drug release curve of Diclofenac Sodium showed the rapid and sustained phase which indicates the in vitro release of Diclofenac Sodium exhibited biphasic phase.

The in vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of First order kinetics was maximum i.e 0.995 hence indicating drug.

CONCLUSION

Lipid based delivery systems like lipid microparticles offer new type of carrier system for low hydrophobic drugs. Easy availability of formulation ingredients and possible simple production techniques offer attractive option for formulation of microparticles at industrial scale. Owing to the finer particle size of microparticles, bioavailability of several problematic drugs was found to increase. Recent works demonstrate sustained release of drugs entrapped in microparticles. Hence microparticles can be considered as new formulation approach for drug moieties.

The present study focused on the development of microparticles of Diclofenac Sodium by using Stearic acid as a release retarding polymer using Emulsion/Chilling technique. The in vitro data supports the retardation of lipid profile of single dose.

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