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FABRICATION AND CHARACTERIZATION OF PRONIOSOMAL GEL OF NAPROXEN SODIUM FOR TREATMENT OF INFLAMMATION AND DEGERATIVE DISORDERS OF MUSCULOSKELETAL SYSTEM

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ABSTRACT

The Aim of the study is to develop and evaluate a proniosomal gel of naproxen sodium used for the treatment of inflammatory and degenerative orders of musculoskeletal system. Proniosomal gel of naproxen sodium an cox-2 inhibitor, were prepared by coacervation phase separation method using non-ionic surfactants dissolving in minimal amount of an acceptable solvent (ethanol) and least amount of aqueous phase (water). Proniosomal gel can entrap both hydrophilic and lipophilic drugs and offers great potential to reduce side effects, frequency of dosing by providing sustained release of drug over a period of 12hrs. The prepared proniosomal gel evaluate to physical appearances, optical microscopic, surface morphology, determination of pH, drug content, in vitro drug release. A preparation with span 40:60, cholesterol, lecithin, and HPMC gave maximum drug release (95%) compared to other combination of surfactants.

KEYWORDS: Proniosomal gel, non-ionic surfactant, cholesterol, lecithin, HPMC.

INTRODUCTION

Proniosomal gels are translucent gels and liquid lamellar vesicles of vesicular bilayers. Proniosomes can be converted into niosomes upon hydrating with hot water right before the use as niosomes are associated with various drawbacks such as physical instabilities like

fusion aggregation of particles leakage of drug these are formulated into proniosomal gels. Proniosomes can deliver both hydrophilic and hydrophobic drugs. The principle advantage of proniosomes is that the amount of carrier required for maintaining the surfactant ratio can be easily adjusted. Proniosomal gels are the very recent provesicular drug delivery systems which offer the drug delivery through topical or transdermal route in versatile manner, Hence proniosomal gels are used in treatment of inflammation and degenerative disorders. Proniosomal gels are a mixture of non-ionic surfactant, Lecithin and cholesterol, HPMC.[1]

Advantages[2]

1. Proniosomes don't require any special conditions of storage as in case of niosomes and liposomes.
2. They are physically stable compared to niosomes.
3. Proniosomes are easy to apply.
4. Proniosomes are easy to handle,store and transport.
5. Proniosomes are uniform in size**.**

Classification of Proniosomes[3]

Proniosomes are divided into two types. They are:

- Dry granular proniosomes
- Liquid crystalline proniosomes

❖ **Dry granular proniosomes**

Based on the type of the carrier used and the method of preparation dry granular proniosomes Are of two types

Sorbital based proniosomes

Which is then coated with a non ionic surfactant. Such proniosones are prepared by simply spraying surfactant mixture in an organic solvent on to the s orbitol power.

a) Malto dextrin based proniosomes

Where as malto dextrin based proniosomes are prepared by fast siurry method the time required For the formation of proniosomes is independent of the ratio of surfactant concentration so, the proniosomes of high surfactant to carrier ratio can be prepared the preparation of proniosomes with sorbitol results in the formation of solid, surfactant cake,

where as the malto dextrin based on proniosomes have high surface area resulting in thin surface coating so that the re hydration process is easy.

❖ **Liquid crystalline proniosomes**

In the presence of alcohol the lecithin and non ionic surfactant as monoglyceride forms the lamellar liquid crystals at craft temperature point. The lamellar liquid crystals are coverted to niosomes by dispersing them in water this organization of lipid/water/ ethanol into lamellar liquid crystals are used in the transdermal drug delivery. The liquid crystalline proniosomes and proniosomal gels are most widely used for transdermal drudg delivery.

Chemicals

- ✓ Naproxen sodium
- ✓ Span-20
- ✓ Span-40
- ✓ Span-60
- ✓ Cholesterol
- ✓ Lecithin
- ✓ HPMC
- ✓ Ethanol
- ✓ Distilled water

Glasswares and Eqiupments

- ✓ Breakers
- ✓ Iodine flasks
- ✓ Glassrods
- ✓ Waterbath
- ✓ Motar and pestle
- ✓ Digital balance
- ✓ Volumetric flasks
- ✓ Thermometer
- ✓ Uv spectrometer

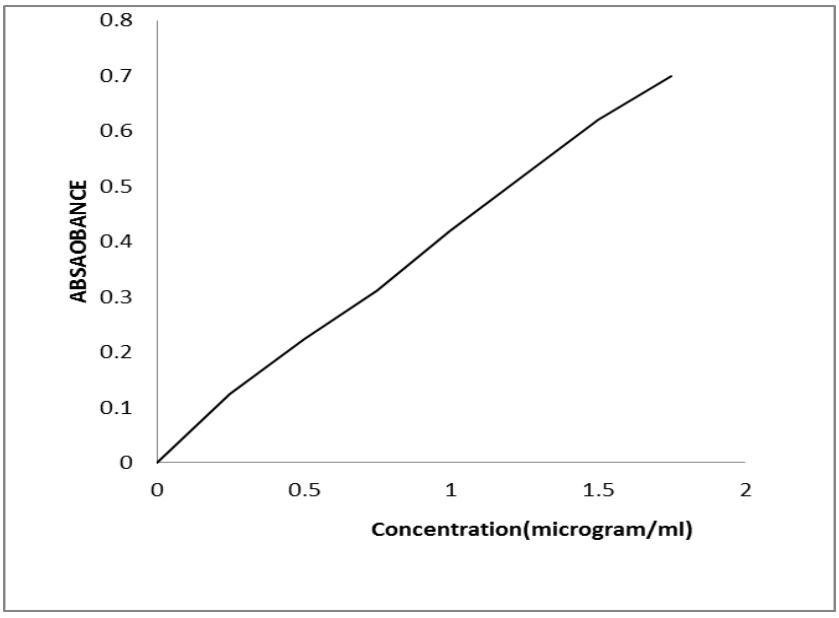
Estimation of Naproxen By Uv Spectrometric Analytical Procedure

Preparation of Standard Curve

The calibration curve of naproxen was obtained by dissolving the drug in phosphate buffer pH 7.4 and measuring the absorbance of the resulting aliquots at 230 nm, using phosphate buffer pH 7.4 as blank. Concentrations of 0.25 to 2.0µg/ml were prepared by suitable dilution of the stock solutions with phosphate buffer pH 7.4. The absorbance of the resulting aliquots was measured at 230 nm using UV spectrophotometer. A graph of Concentration vs. Absorbance was plotted. The linear regression data obtained from the calibration curve showed a linear relationship over the concentration range of 0.25 to 2.0µg/ml. The experiment was performed in triplicate and based on average absorbance; the equation for the best line fit was generated.

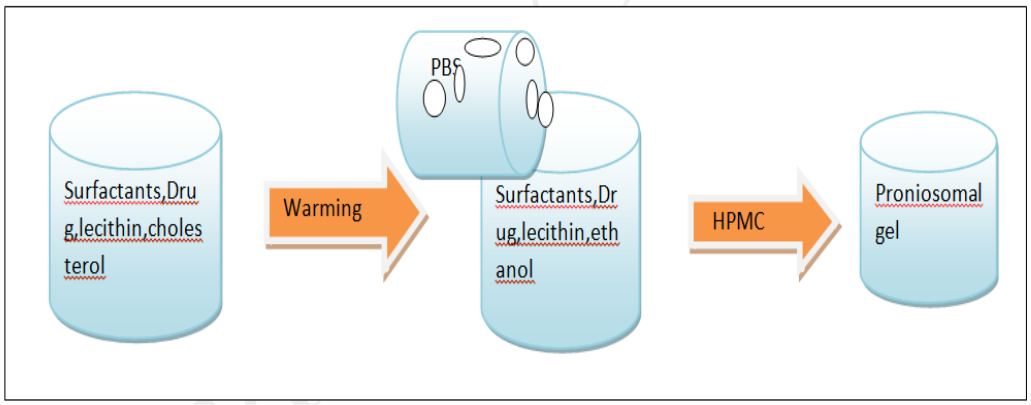
Standard Calibration Curve of Naproxen Sodium

Concentration (x-axis)	Absorbance (y-axis)
0	0
0.25	0.125
0.5	0.223
0.75	0.312
1	0.422
1.25	0.522
1.5	0.623
1.75	0.700



Preparation of Proniosomal Gel By Coacervation Phase Seperation Technique.[4,5,6,7]

- ✓ Proniosomal gel was prepared by **a coacervation-phase separation technique**.
- ✓ Precisely weighed amounts of surfactant, lecithin, cholesterol and drug were taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (1.0 ml) was added to it.
- ✓ After warming, all the ingredients were mixed well with a glass rod; the open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture was dissolved completely.
- ✓ Then the aqueous phase (phosphate buffer saline pH 7.4) was added and warmed on a water bath till a clear solution was formed which was converted into Proniosomal gel on cooling by addition of HPMC (continuously triturating).
- ✓ The gel so obtained was preserved in the same glass bottle in dark conditions for characterization.



Composition of proniosomal gel formulations are given

Table 01: Formulation Design.

Ingredients	F-01	F-02	F-03	F-04	F-05	F-06
Naproxen	220mg	220mg	220mg	220mg	220mg	220mg
Span-20	1.8ml	0.9ml	-	0.9ml	-	-
Span-40	-	0.9gms	0.9gms	-	1.8gms	-
Span-60	-	-	0.9gms	0.9gms	-	1.8gms
Lecithin	1.8gms	1.8gms	1.8gms	1.8gms	1.8gms	1.8gms
Cholesterol	0.2gms	0.2gms	0.2gms	0.2gms	0.2gms	0.2gms
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml
PBS	5ml	5ml	5ml	5ml	5ml	5ml
HPMC	0.5gms	0.5gms	0.5gms	0.5gms	0.5gms	0.5gms

Characterization of Proniosomal Gels

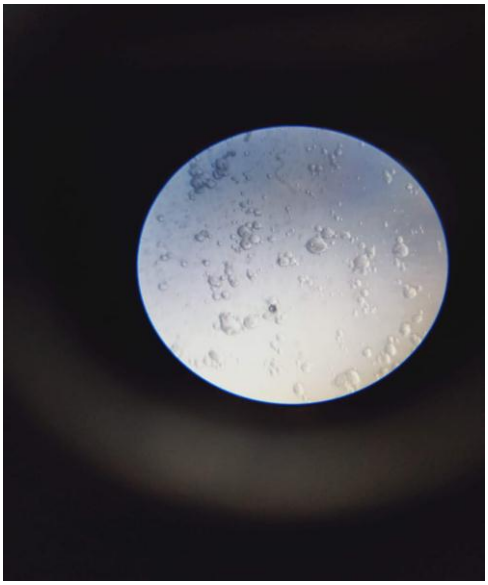
Physical Appearance or clarity[6]

The developed sodium naproxen gel where inspected visually for clarity, color in sol and gel from against white back ground (or) black back ground and appearance of various formulation was shown in the table No 1.

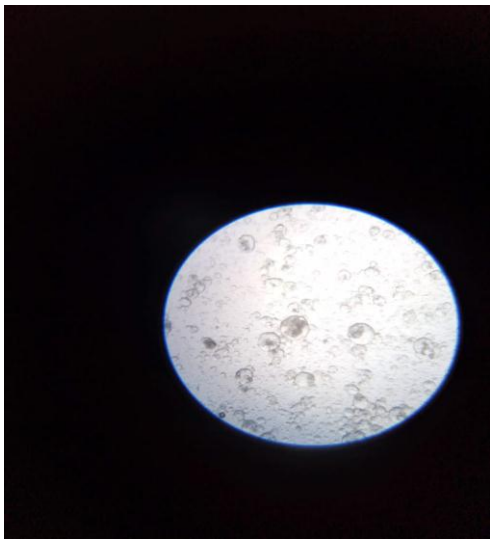
Optical Microscopic Examination

Hydration of proniosomal gel (100mg) was done by adding PBS 7.4 (5 ml) in a small glass vial with occasional shaking for 10 min. An optical microscope with a camera attachment was used to observe the shape of the prepared niosomal vesicles.

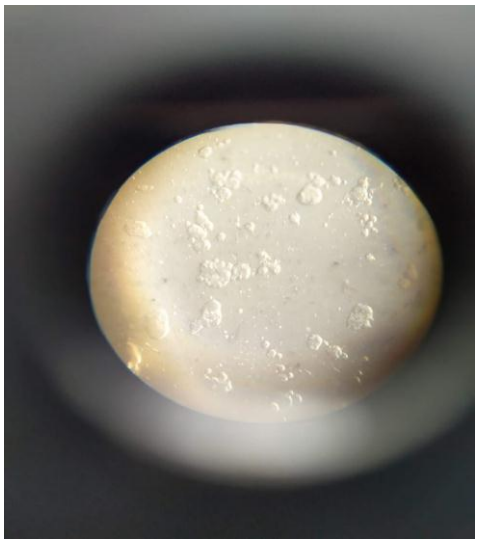
Formulation 1



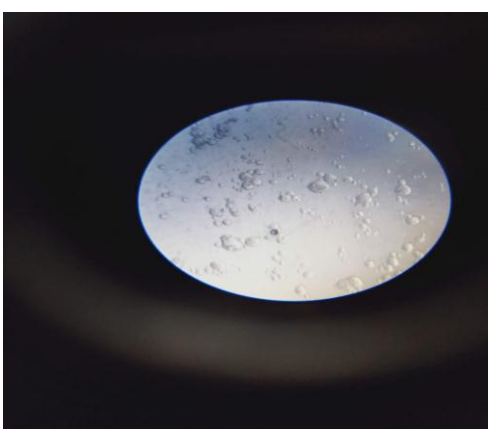
Formulation 2



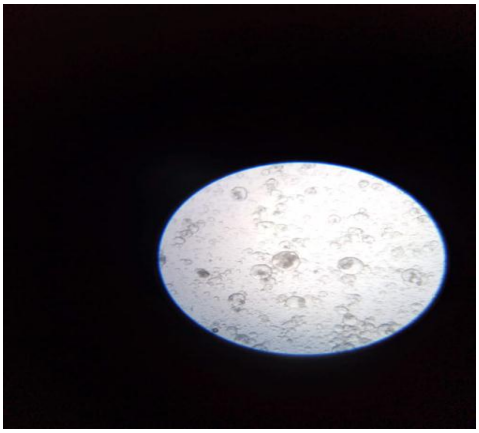
Formulation 3



Formulation 4



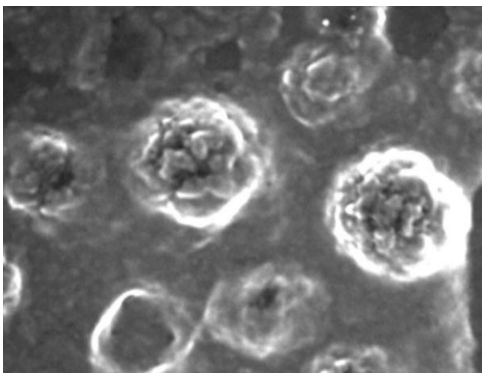
Formulation 5



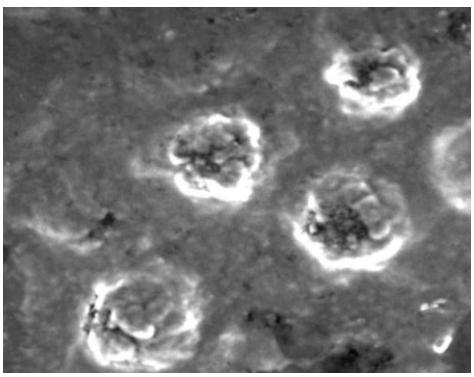
Formulation 6

Surface Morphology[4]

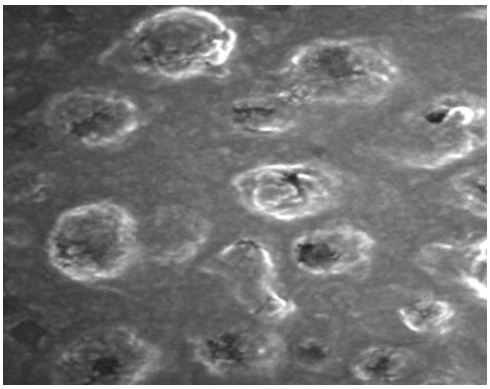
Electron micrographs were obtained using scanning electron microscope. The surface morphology (roundness, smoothness and formation of aggregates) of proniosomal gel was studied by Scanning Electron Microscopy .Hydration of proniosomal gel was done similarly as optical microscopy. One drop of niosomal suspension was mounted on clear glass slab, air dried and sputtercoated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope equipped with a digital camera, at 15 or P20 kV accelerating voltage.



Formulation 1



Formulation 2



Fomulation 3

Determination of PH[6,8]

One ml quantity of each proniosomal gel formulation was transferred to a beaker and diluted by using distilled water pH of resulting solution was determined using digital pH meter. pH meter was previously calibrated using standard buffers of pH 4 and 7 and the pH of formulation of various formulations was shown in the table No 2.

Drug content

One ml of formulation was taken in 10 ml volumetric flask, diluted with distilled water and volume adjusted to 10ml.one ml quantity from this solution was again diluted with 10ml of distilled water. finally the absorbance of prepared solution was measured at 230nm by using UV visible spectroscopy and the drug content of various formulations was shown in the table No 3

Drug Release Kinetics study

The release study employed the vertical glass Franz diffusion cells which have a diffusional surface area of 1.13 cm^2 with the receptor compartment of 10 ml volume. A cellulose dialysis membrane was soaked in distilled water overnight before cutting into suitable pieces. This soaking was conducted to ensure complete swelling of the membrane to provide a constant pore diameter throughout the experiment. The membrane was then mounted between the donor and receptor compartments before filling the receptor compartment with pH 7.4 phosphate buffer. The diffusion cells were incubated into a thermostatically controlled circulator water bath. The temperature of the receptor compartment was maintained at 37±0.5^oC and the receiver medium was continuously stirred in order to prevent any boundary layers effects. Weighrd amount of proniosomal gels containing 220 mg of naproxen sodium were loaded into the donor compartment, then it was covered with aluminum foil to prevent evaporation. At predetermined time intervals, 0, 15, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480(min) samples of 1 ml were taken from the receptor compartments and replaced immediately by fresh buffer solutions; to maintain the sink conditions constantly at constant as well. The samples were then assayed spectrophotometrically at 230 nm. All released experiments were done in triplicates. The plot of cumulative percentage dug release was plotted against time. The obtained release data was subjected to kinetic treatment according to zero, first, Higuchi, korsmeyer peppas diffusion models. The coefficient correlation (r) the order of release pattern was determined in each case. Drug release profile shown in table No 4.

Table No: 1 Appearance or Clarity.

Formulation code	Clarity
F1	Clear
F2	Clear
F3	Clear
F4	Clear
F5	Clear
F6	Clear

Table No: 2 Determination of PH.

Formulation code	Ph
F1	5.6
F2	5.7
F3	5.9
F4	6.5
F5	6.2
F6	6.4

Table No: 3 Drug content.

Formulation code	Drug content percentage
F1	98
F2	98
F3	96
F4	97
F5	98
F6	97

Table: 4 % Drug release profile.

TIME	F-01	F-02	F-03	F-04	F-05	F-06
0	0	0	0	0	0	0
0.15	33.94	36.36	35.03	36.36	35.03	35.15
0.3	38.18	38.36	43.52	43.03	38.79	38.79
0.45	46.06	44.85	52.97	59.39	43.64	43.64
1	50.91	48.48	62.06	61.82	49.70	49.70
1.5	58.18	54.55	70.18	67.88	55.76	54.55
2	63.03	63.03	73.82	72.73	61.82	60.00
3	67.88	67.88	74.30	73.94	65.45	64.24
4	70.30	70.30	75.76	76.36	69.09	67.88
5	72.73	75.15	76.97	78.79	72.73	72.73
6	75.15	78.79	88.73	81.21	75.15	77.58
7	78.18	84.85	89.09	84.85	80.00	81.21
8	80.61	90.91	95.00	92.13	83.22	85.21

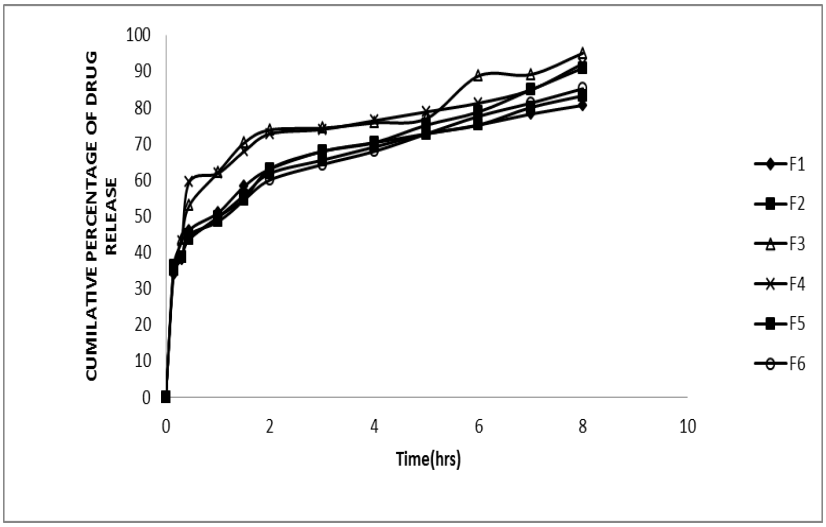


Fig No 1: graph of cumulative % drug realease v/s Time.

First order drug release

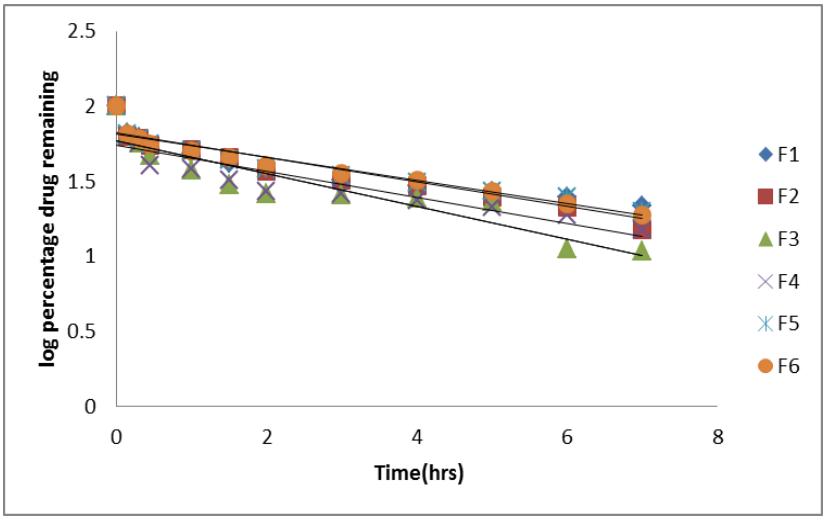


Fig No:2 graph of Time v/s log %drug remaining.

Higuchi

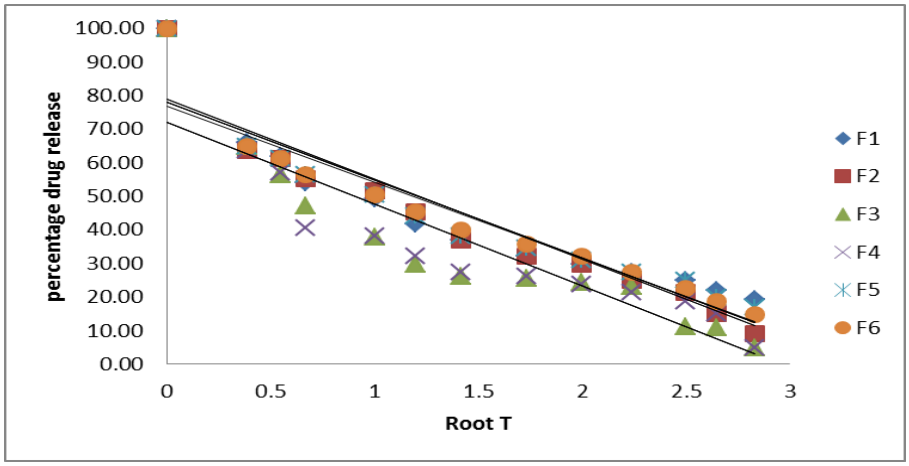


Fig No: 3 graph of Root T V/s Percentage drug release.

Peppas

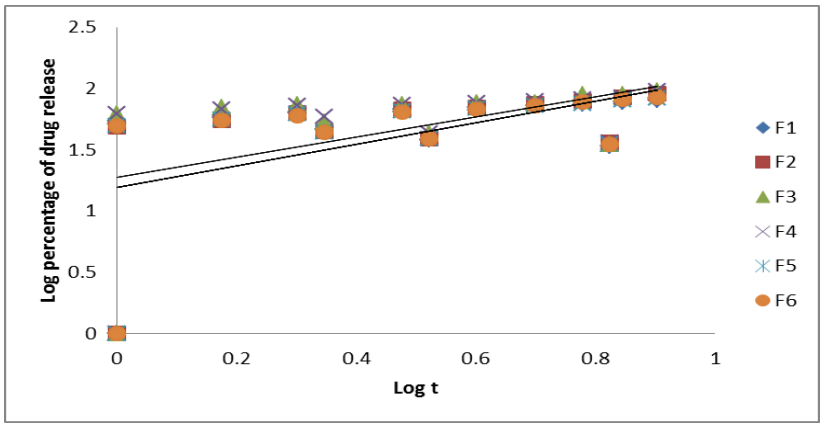


Fig No: 5 Graph of log T V/S Log percentage of Drug release.

Drug release kinetics

Zero order	First order	Higuchi	Peppas	(n)
0.9435	0.971	0.991	0.999	0.553
0.9422	0.972	0.814	0.878	0.150
0.9839	0.989	0.998	0.998	0.152
0.8205	0.984	0.996	0.998	0.577
0.9256	0.982	0.996	0.997	0.532
0.9484	0.992	0.992	0.969	0.568

CONCLUSION

In the present study, an attempt is made to prepare and evaluate Naproxen sodium proniosomal gels by coacervation-phase separation method for the treatment of inflammatory and degenerative disorders of the musculoskeletal system. The Transdermal Proniosomal Gels showed controlled drug release properties. The results of the present study indicated that

Naproxen proniosomal gel containing lecithin, cholesterol and in combination of surfactants like span 20, 40 and 60 produce sustained release of drug over a period of 12 hrs for the treatment of inflammatory and degenerative disorders of the musculoskeletal system. The proniosomal gel F3 could be an effective alternative vehicle for delivering the drug through transdermal route to avoid side effects associate with oral route.

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