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Formulation and invitro evaluation of novel gel containing liquid crystals of diclofenac in the treatment of arthritic disorders

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ABSTRACT

Present study was focused on the formulation and invitroevaluation of novel gel containing liquid crystalline gel. Aim of the study is to develop Diclofenac liquid crystalline gel for managing pain and inflammation using liquid crystalline form. The invitro release profile of the developed liquid crystalline gel was higher as compared to marketed and conventional gel. This is prepared by using tween 80, cetosteryl alcohol and glycerol. Formulation LCG-1 to LCG-4 differs in the ratio of tween 80 and cetosteryl alcohol. Preformulation studies for pure drug were conducted andformulation was evaluated on the basis of viscosity, encapsulation efficiency and invitro drug release study using Franz diffusion cell. FTIR study of pure drug, polymer and the formulation proves there is no chemical interaction between them. Formulation LCG-3 had appropriate viscosity 1536.78, highest encapsulation efficiency 87.82±0.36.Theinvitro release study found to have zero order release profile compare to all other formulation that indicates the predominant mechanism of drug release is diffusion. Invitro comparative evaluation of the liquid crystalline gel with that of 3 marketed samples (gel, emulgel and ointment) proves that liquid crystalline gel formulation has the sustained release capability compare to others.

KEY WORDS: Diclofenac, liquid crystalline gel, Tween 80, Cetostery alcohol

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INRODUCTION

Diclofenac gel form is available in the market and can be used mainly for mild to moderate pain, rheumatoid arthritis, osteoarthritis. These formulations are available with short half-life. By adopting the drug, Diclofenac to a liquid crystalline form the half-life can be increased with sustained release action. Due to high viscosity of the liquid crystalline gel, the contact time of the drug with that of the infected areacan also increase.Diclofenac will inhibit prostaglandin synthesis which mediates poor patient compliance. So topical administration is an alternative method for Diclofenac oral administration,thus this formulation can be more effective in pain, rheumatoid arthritis [1,2,4]. Formulation developed for topical delivery must be pleasant to touch and feel it must not produce any irritation.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly outcome of a drug. The common side effect of oral dose include abdominal pain,gastro intestinal bleeding,dizziness, head ache, swelling. The drug application to the skin mainly aims to prevent disorder, avoid first pass metabolism and to treat deep tissues such as muscles and vein [2]. This system of liquid crystalline gel show faster drug release compare to other gel, Emulgel, Ointment

A gel is a solid jelly-like material that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute cross- linked system, which exhibits no flow when in the steady- state.Liquid crystals (LCs) are matter in a state which has properties between those of conventional liquids and those of solid crystals. Liquid crystals can be divided in to Thermotropic,lyotropic and Metallotropic phase.

The characteristic orientation order of the liquid crystal state is between the traditional solid and liquid phases and this is the origin of the term mesogenic state.Thermotropic phases are those that occur in a certain temperature ranges. Many Thermotropic LCs exhibit a variety of phase as temperature is changed.lyotropic liquid crystal are of surfactant molecules. A lyotropic crystal consists of two or more component that exhibit liquid-crystalline properties in certain concentration ranges. Metallotropic Liquid is based on low-melting inorganic phases [5].

ADVANTAGE OF LIQUID CRYSTALLINE OVER GEL FORMULATION

- These LC forms allow drug solubilisation with a proper choice of self-association structure.
- Both oil and water soluble drugs can incorporate and in high concentration.
- This will increase drug solubility, decrease drug degradation and to control drug release rate.
- Due to high viscosity this will provide the drug to highly localized in tissues

METHODOLOGY

PREFORMULATION OF DICLOFENAC

Organoleptic property

The drugwas visually inspected to find the organoleptic property like colourodour and appearance

Determination of solubility of Diclofenac

Excess drug(100 mg) was added to 15ml of each fluid taken in a 25ml Stoppered conical flask and the mixtures were shaken for 24hrs at room temperature(28+-1) on rotary flask shaker. After 24 hours of shaking, 2ml sample were withdrawn at 2 hour interval and filtered immediately using a 0.45 disc filter. The filtered sample were diluted suitably and assayed for Diclofenac by measuring absorbance at 276nm. Shaking was continued until two consecutive estimations are the same.The solubility experiments were replicated four times each (n=4).

Melting point determination

The melting point of Diclofenac was determined by using melting point apparatus.

Determination of partition coefficient

30 ml of water and 30ml n-octanol solution were taken to the separating funnel. 100mg of drug(Diclofenac) was added to it and shaken for 1 hour. 1ml of aqueous layer was removed and transferred into a 100ml standard flask and made up to the mark with water. The absorbance was measured at 276nm by using water as blank.

UV spectroscopy:

Determination of λ max

Diclofenacwas accurately weighed and dissolved in distilled water to make 1mg/ml. The solution was then suitably diluted to 100ml using distilled water to get a final solution of concentration 100µm/ml. UV spectrum was recorded in the wavelength range 200-400nm.

Preparation of calibration curve for Diclofenac

Stock solution of Diclofenac(100µg/ml) was prepared in water. The solution of Diclofenac was transferred into a series of 10ml volumetric flask up to the mark with water to get the concentration in the range of 10-50µg/ml. The absorbance of all the resulting solutions was measured at 276nm.

FORMULATION OF DICLOFENAC LIQUID CRYSTALINE GEL

Liquid crystals(LC) gel was prepared by melting cetosteryl alcohol and tween 80 together and water is added to approximately same temperature followed by cooling slowly and mixing at 500rpm stirrer.Diclofenac was mixed in mixture of cetosteryl alcohol and tween80 and glycerol in different ratio [10].

Table 1: Formulation of Diclofenac liquid crystalline gel

SLN CODE	DRUG (mg)	TWEEN 80 (ml)	CETOSTEARYL ALCOHOL (mg)	GLYCEROL (ml)	WATER (ml)
LCG – 1	100	5	5	0.5	15
LCG – 2	100	2.5	7.5	0.5	15
LCG – 3	100	7.5	2.5	0.5	15
LCG – 4	100	5	10	0.5	15

LCG –liquid crystalline gel

COMPARISON OF LIQUID CRYSTALLINE GEL WITH MARKETED PRODUCTS

compare vitro release study of liquid crystalline gel with the marketed formulation like (Gel, Emulgel, Ointment) These drugs are mainly used for the treatment of mild to moderate pain and treatment of osteoarthritis, rheumatoid arthritis .

EVALUTAION OF GEL

Evaluation of Diclofenac gel pH and viscosity

The pH is measured using pH meter and viscosity by brook field viscometer[11].

Determination of %entrapment efficiency

The % entrapment efficiency (%EE) of Diclofenac in LCG formulations were determined by centrifugation of the colloidal sample at 14000 rpm at 25ºC for 30 min. The free Diclofenac in the supernatant is estimated by UV spectroscopy at 276nm [4].

$$EE\% = \frac{\text{Amount of Diclofenac found in liquid crystalline}}{\text{Amount of Diclofenac added during preparation of liquid crystalline gel}} \times 100$$

I
nvitro release study.

In vitro release studies of Diclofenac was performed in Franz diffusion cell that has receptor compartment with an effective volume approximately 70ml and effective surface area of permeation of 3.14sq cms. The cellophane

membrane was mounted between the donor and receptor compartment. A weighed amount of gel is placed on one side of the membrane; the receptor medium was phosphate buffer pH 7.4. The receptor compartment is surrounded by a water jacket to maintain the temperature at 37 ± 0.5ºC. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by a Teflon coatedmagnetic bead fitted to a magnetic stirrer. At each sampling interval, sample is withdrawnand is measured at 276nm [15].

FTIR Spectra of Diclofenac sodium:

IR spectra of physical mixture of drug and excipients were recorded by KBr method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide pellet. The potassium bromide-drug pellet of approximately 1 mm diameter was prepared by grinding 3-5 mg of physical mixture of drug-excipients with 100-150 mg of potassium bromide in pressure compression machine. The sample pellet was mounted in IR compartment and scanned at wavelengths 4000 cm-1 to 400 cm-1

RESULT AND DISCUSSION

FORMULATION AND EVALUATION OF LIQUID CRYSTALLINE GEL

Pre formulation studies of Diclofenac

Colour and appearance

The formulation shows white in colour with semisolid consistency. It was observed that gel formulation shows good spread ability and viscosity.

Organoleptic property

Diclofenac drug is white to off white colour having bitter taste, odourless powder which is of hygroscopic and crystalline form

Determination of solubility of Diclofenac

The solubility of the received sample of clindamycin was examined in various solvents aqueous and organic. Diclofenac was freely soluble in water, slightly soluble in methanol and insoluble in chloroform.

Melting point determination

The melting point of pure Diclofenac was determined by melting point determining apparatus, and the melting point was found out to be 284ºc.

Determination of Partition coefficient

Partition coefficient of Diclofenac was determined by using water and n-octanol as solvents. It was found to be 13.1

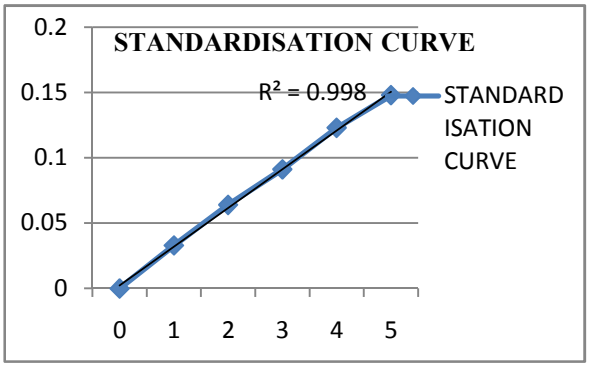
Determination of λmax

The λ max of Diclofenac was determined by using UV spectrophotometer. The λmax was found to be 276 nm.

Table 2:Calibration curve of Diclofenac

Concentration(mcg/ml)	Absorbance at276nm
0	0
1	0.033
2	0.064
3	0.0912
4	0.123
5	0.148

Graph1:Calibration curve of Diclofenac



EVALUATION TEST

Table3: The formulations are subjected to various evaluation test and results are tabulated.

S. NO	Formulation Code	PH	Viscosity (CPS)	Encapsulation Efficiency
1	LCG-1	8.12	1354.67	85.46±0.15
2	LCG-2	6.52	2132.45	95.32±0.3
3	LCG-3	8.06	1536.78	87.80±0.36
4	LCG-4	7.82	982.25	63.25±0.26

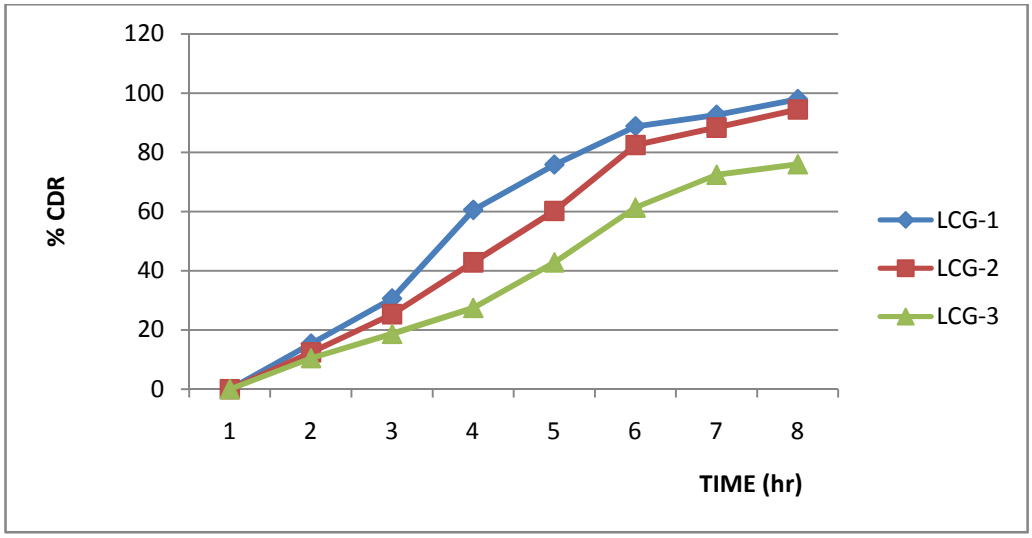
LCG –liquid crystalline gel

Table 4:In vitro release study(%CDR of Diclofenac from liquid crystalline gel of best 3 formulation)

Time	LCG-1	LCG-2	LCG-3
1	0	0	0
2	15.35	12.45	10.45
3	30.62	25.34	18.67
4	60.53	42.85	27.45
5	75.82	60.21	42.85
6	88.78	82.45	61.34
7	92.63	88.36	72.45
8	97.95	94.45	75.98

LCG- liquid crystalline gel

Graph:2 In vitro drug release of diclofenac from liquid crystalline gel



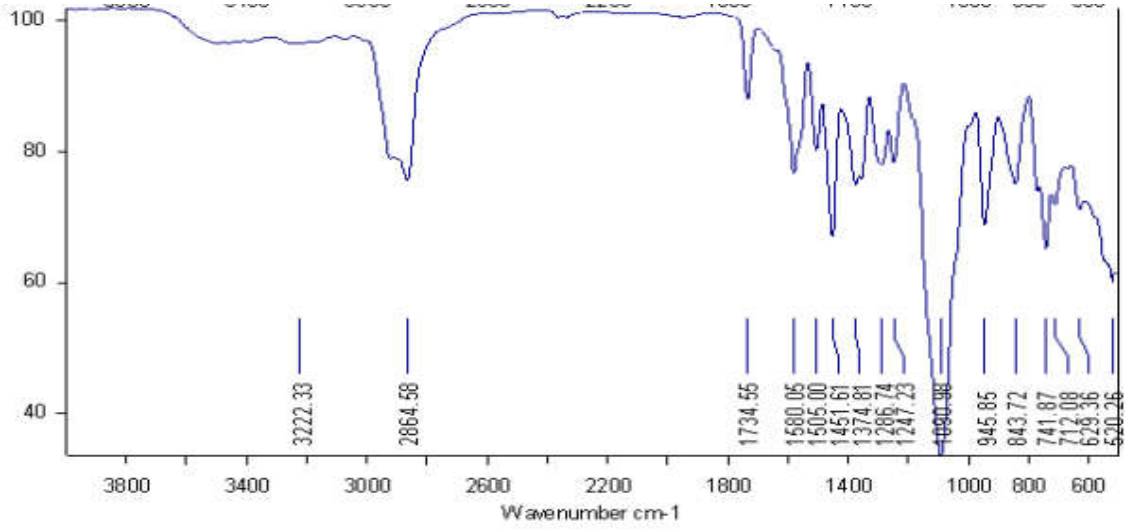


Figure-1 IR spectra ofDiclofenac LC gel form

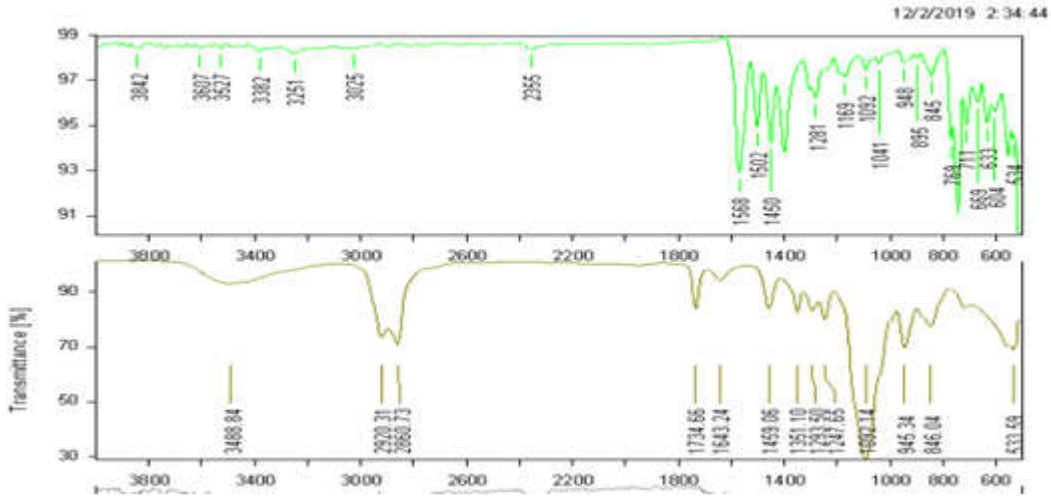


Figure -2 IR spectra of Diclofenac sodium pure drug, IR spectra of tween 80(polymer interactive study)

The FTIR spectra of Diclofenac, Tween 80 are depicted in figure(2). FTIR spectra of DiclofenacHCL figure (1) shows characteristic peaks at 1286cm amide group, 741cm C-Clstretching, 1734cm acid.

From the FTIR spectra of Diclofenac and the polymer it is evident that there is no chemical interaction between the drug and polymerin the formulation

OPTIMIZATION OF BEST GEL

Out of three formulations LCG-3 exhibited good release pattern. LCG-1releasesits 90% of drug with in 4hr and shows saturation effect. LCG-2 releases its 94% of drugin 8 hrs. LCG-3 releases only 75% of its drug in 8hrs and show sustained release. So LCG-3 had been optimized as the best formulation. To describe the exact mechanism and order of drug release, curve fitting analysis was done with LCG-3

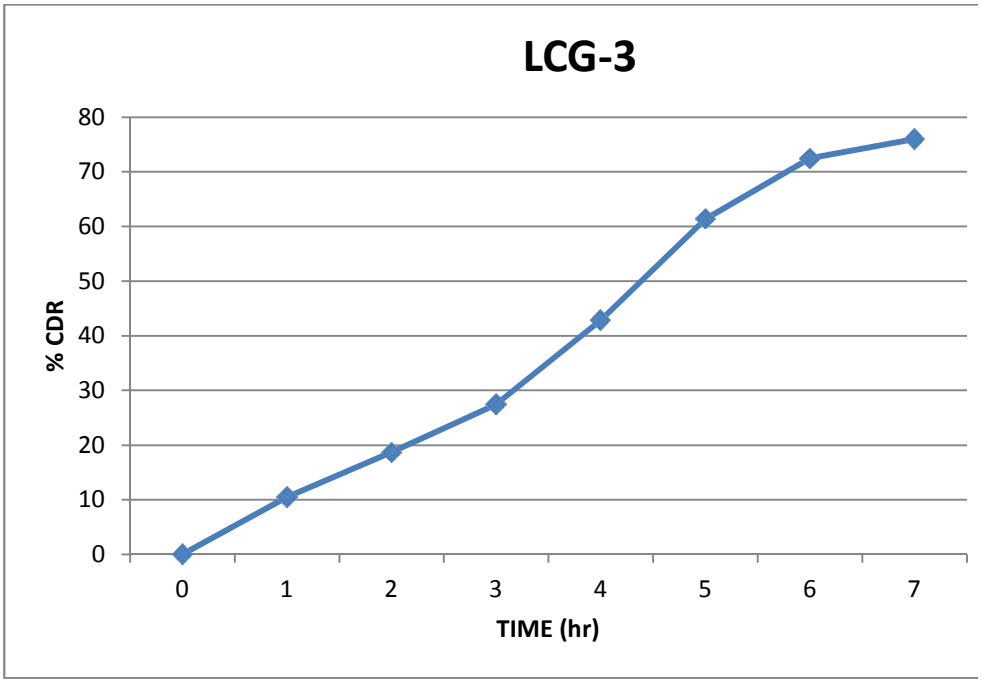
CURVE FITING ANALYSIS

1) **Zero order kinetics**

Table5 :Zero order kinetics of LCG3

Sl no	TIME (HRS)	LCG-3 %CDR
1	0	0
2	1	10.45
3	2	18.67
4	3	27.45
5	4	42.85
6	5	61.34
7	6	72.45
8	7	75.98

Graph3: zero order kinetics of LCG-3

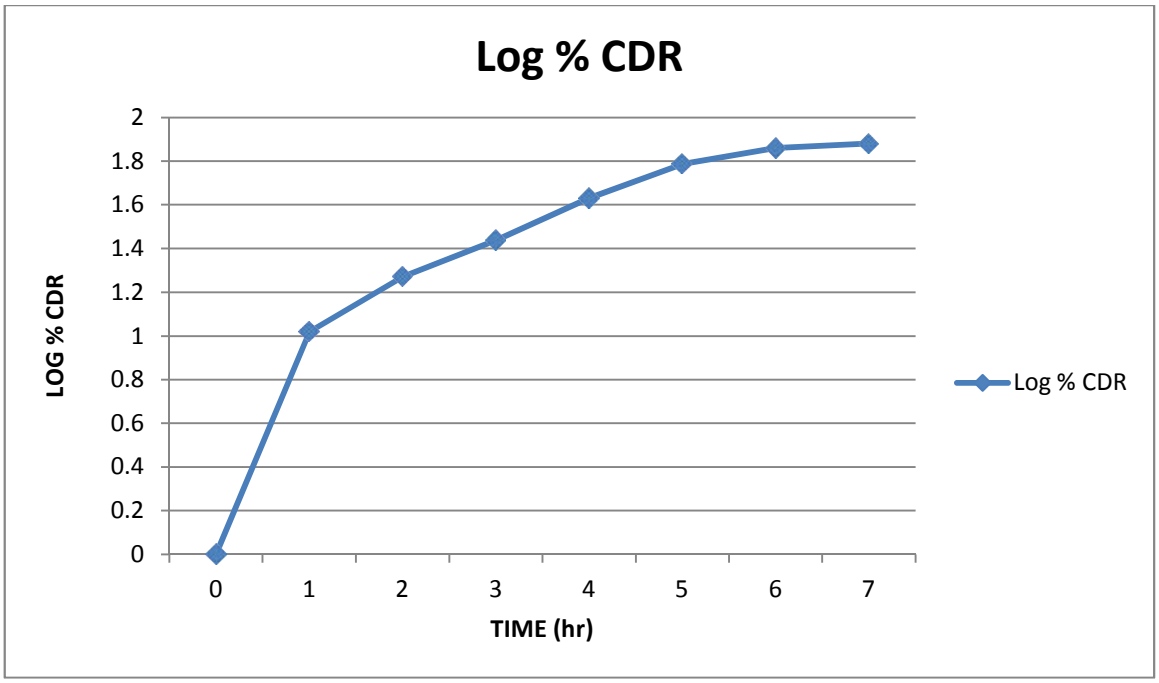


2) First order kinetics

Table6: First order kinetics of LCG3

Slno	Time (HRS)	Log % CDR LCG-3
1	0	0
2	1	1.019
3	2	1.271
4	3	1.438
5	4	1.631
6	5	1.787
7	6	1.860
8	7	1.880

Graph4: first order kinetics



3) Higuchi model

Table7: Higuchi model LCG3

Sl no	Square root time	LCG-3 %CDR
1	0	0
2	1	10.45
3	1.414214	18.67
4	1.732051	27.45
5	2	42.85
6	2.236068	61.34
7	2.44949	72.45
8	2.645	75.98

Graph5: Higuchi model LCG-3

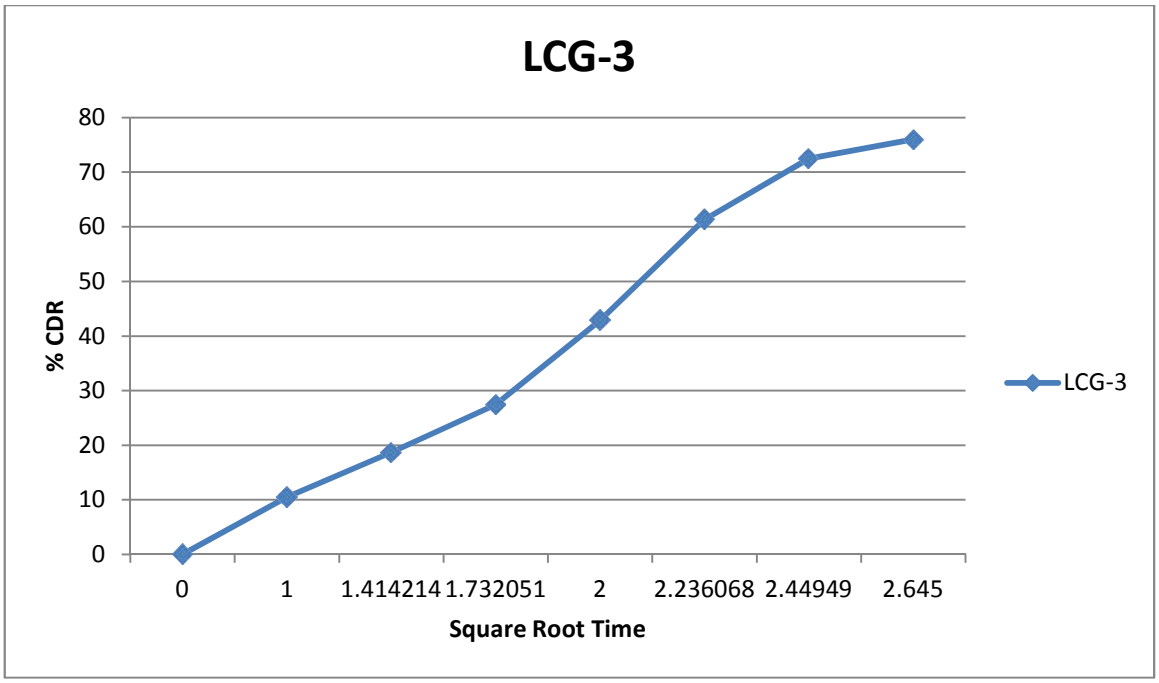
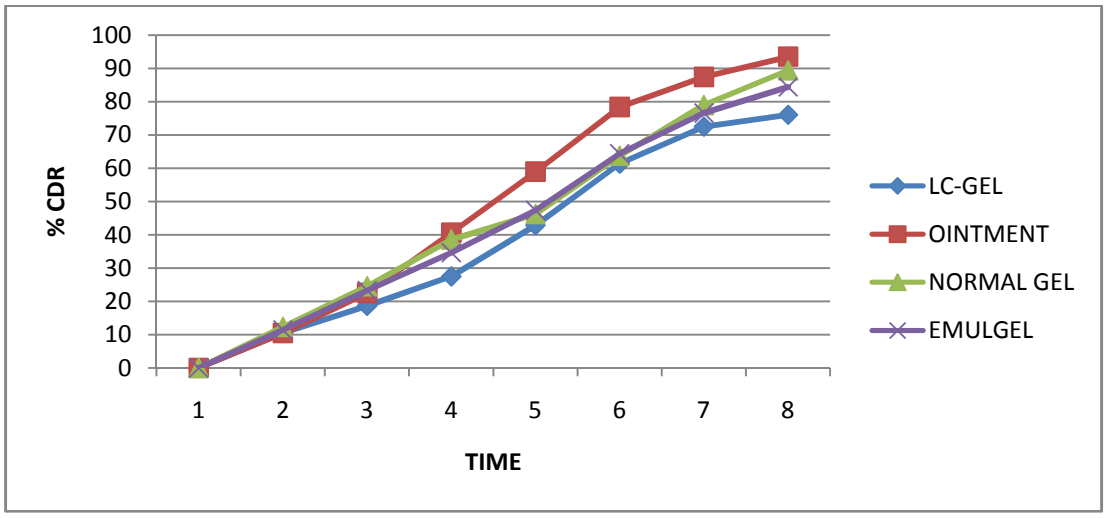


Table8: Invitro comparison of formulated drug with marketed formulations.

TIME	LC-GEL	OINTMENT	NORMAL GEL	EMULGEL
1	0	0	0	0
2	10.45	10.43	12.32	11.45
3	18.67	22.53	24.52	23.22
4	27.45	40.62	38.56	34.61
5	42.85	58.92	46.22	47.33
6	61.34	78.35	63.72	64.32
7	72.45	87.36	78.92	76.54
8	75.98	93.45	89.33	84.35

Graph6: Invitro comparison of formulated drug with marketed formulations



DISCUSSION

Preformulation studies

Preformulation studies were carried out and the drug was found to be white to off white crystalline powder which is hygroscopic in nature. The drug was found to be odourless bitter in taste. Considering solubility, the drug is freely soluble in water. From FTIR studies proves there is no chemical interaction between drugs and polymer

Liquid crystalline gel

Liquid crystalline was prepared from the formulation and whose encapsulation efficiency was determined. The LCG2 have encapsulation ability (EE) 95.32% and LCG3 have EE 87.80%. For more optimizing the invitro release study was conducted.LCG2 haveinvitro release of 94.45% in about 8 hours.LCG3 release only 75% of drug in 8 hours. LCG2 was not suitable for inserting gel into cosmetic cream because of high viscosity.SoLCG3 has been optimized as the best formulation. The invitro release profile of liquid crystalline gel Vs marketed products are plotted by time in x axis and % CDR in y axis.Invitro comparison of the sample with that of marketed product founds that liquid crystalline formulation has sustained action compares to other formulation

CONCLUSION

The preformulation studies were performed using the pure drug found to be useful for the formulation. The formulation was prepared using fusion method. The formulation were subjected to evaluation procedures and found that this

formulation was have sustained releasing ability of about 75.98% in 8 hour. This is also having high encapsulation efficiency.

Zero order plot of optimized formulation (G3) indicated that the release mechanism is concentration independent(R = 0.995). Higuchi's plot for the formulation revealed that the predominant mechanism of drug release is diffusion(R=0.898).

Optimized formulation shows sustained action compares to other 3 marketed formulations.

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