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FORMULATION AND OPTIMIZATION OF NANOGEL OF DICLOFENAC DIETHYLAMINE FOR TRANSDERMAL DRUG DELIVERY.

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ABSTRACT
The aim of this study is to formulate nanogel of diclofenac by double emulsification method. The formulations are characterized for the particle size which should be below than 400 nm. .A formulation of nanogel consisting an emulsifier phase of Tefose63, a co-emulsifier Labrafil1944 and Transcutol P was found to be ideal, with mean particle size of 228 nm with a high capacity of solubilisation for diclofenac. The drug entrapment in the formulations was found satisfactory. The optimization of nanogel was carried out by using factorial design and the formulations are characterized for in vitro drug diffusion, skin permeability, rheological properties and in vivo animal study. The in vivo animal studies showed significant improvement in the activity for the formulation in comparison with the conventional marketed formulation. The formulation showed optimal permeability properties, stability and possessed a sustained drug release during the study period. The nanogel formulation showed the promising alternative to oral administration for diclofenac diethylamine.

KEYWORDS: nanogel, Labrafil1944 and Transcutol P .

1.0 INTRODUCTION
Transdermal route for Drug delivery system proposed an impressive route than conventional drug delivery through oral and injectable route by increasing patient compliance and avoiding first pass metabolism respectively and enhances therapeutic efficiency and maintain steady plasma level of the drug **(Langer R.,2004).** The skin provides a "reservoir" that sustains delivery of drug over a period of days. The permeation of drug through the stratum corneum may follow the intercellular, transcellular or appendageal route (**E. Nahas. *et al.*, 2011**) The intercellular route is the more common pathway of the drug permeation through the skin. Transdermal delivery provides controlled, constant administration of the drug; it allows continuous participation of drugs with short biological half-lives and reduces the non desirable side effects. Today, the clinical use of transdermal delivery is limited because few drugs can be delivered transdermally at a feasible rate**(J. A. Kumar. *et al.*, 2010).** This difficulty is due to the stratum corneum of skin acts as an efficient barrier that limits penetration of drugs through the skin, but now various forms of novel drug delivery systems are developed to increase the series of drugs available for transdermal delivery like transfenac,ethosomes ,nanoparticels ,liposomes,microsphers, Lipid based nanocarriers etc.

In order, the use of nanocarriers has emerged as an attractive and precious alternative for delivery of lipophilic and hydrophilic drugs throughout the stratum corneum with the opportunity of having a local or systemic effect. The main aim is to developed a carrier system having particle size less than 500 nm for the deep penetration of drug in lower layers of skin .Particle size greater than 500 nm fails to penetrate the stratum corneum. **(S. P. Denyer.*et al.*, 1985**). The effective barrier properties of the skin may prevent the entry of drug molecules from the external environment. Nanosized drug in suitable form like gels can also be used for topical application of drug. Nanosized gel provides constant and prolonged therapeutic effect, reduced the dosing frequency and thereby improves the patient compliance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs to reduce pain and inflammation Diclofenac is one of the most potent and commecially non-steroidal anti-inflammatory agents, has been recommended orally for the treatment of rheumatoid arthritis and osteoarthritis. It having antiinflammatory, antipyretic and analgesic activity. The oral administration of diclofenac causes gastrointestinal ulcers and gastrointestinal bleeding. Due to gastrointestinal bleeding it may cause anemia **(H. A. Benson.,2005)**. The major disadvantage is insufficient bioavailability of drug and serious side effects of drug These adverse effects are mainly due to the poor agent specificity,resulting from the drug binding to certain (e.g.,prostaglandin) receptors. Transdermal delivery

avoids these side effects, increases patient compliance and bypasses first pass metabolism and maintains the plasma drug levels for longer period of time **(R. Kumar.,2007).**Therefore, an improved formulation of diclofenac nanogel is desirable which gives high degree of permeation through the skin for the treatment treatment of locally inflamed skin without the use of chemicals enhancer and solvents to achived desired action **(Changez M., 2002).** Therefore, it is needed to develop a topical vehicle system that does not require the use of chemical enhancers to facilitate drug permeation through the skin. So the nanosized gel are developed which is one of the most potential techniques for enhancement of transdermal permeation of drugs.

2.0 MATERIAL AND METHOD

2.1 Materials

Diclofenac diethylamine was gift sample from Laborates Pharmaceuticals, Panipat, India. Tefose 63, Labrafil m1944 and Transcutol P was a gift sample from Gatefose Pvt Ltd, Mumbai. Ethyl alcohol was purchased from Loba Chemie Pvt. Ltd., Mumbai. Menthol was purchased from Kayal Enterprises, Methylsalicylate was purchased from Alta laboratories, Mumbai.
Carbopol 940 was purchased from Corel pharma, Gujrat.

2.2 Formulation and optimization of Diclofenac diethylamine

2.2.1 Selection of emulsifier and co emulsifier

The solubility of diclofenac diethylamine in various solvents (TranscutolP, Ethyl alcohol) emulsifier (Tefose 63),co- emulsifier (Labrafil1944) was determined by dissolving an excess amount of drug in 2ml each of the selected solvent and emulsifying agents in 5mL capacity stoppered vials separately and mixed using a vortex mixer. The mixture vials were then kept in a shaker for 72hour to equilibrate. The equilibrate samples were removed from the shaker and centrifuged at 3000 rpm for 30min.The supernatant was taken and filtered through a 0.45µm membrane filter. The concentration of drug was determined in each solvent emulsifying agents by using UV spectrophotometer. The components are selected on the basis of highest solubility.

2.2.2Preparation of Diclofenac nanogel

Nanogel was formulated by double emulsification method. Carbopol 940, methylparaben and propyl paraben (phase 1) were dispersed in water phase. Then heated it about (70-80° C) for 20 minutes at 700-800 rpm (Mechanical stirrer).Then Tefose 63, labrafil 1944 (phase2) was also heated at same temp i.e (70-80° C).After that phase1 was poured into phase2 under overhead stirrer(LKA RW20) at same temp . Formation of o/w emusion .cooled the emulsion for 60 minutes .After that diclofenac diethylamine, menthol, methylsalicylate, Transcutol ant ethyl alcohol (phase 3) were weighed and mixed by stirring and heated at (30-40° C). Then gradually poured phase 3 to the above cooled emulsion. Formation of o/w/o emulsion .complete cooling was done and homogenized the nanogel on a rotor stator with constant stirring at 5,000-8,000 rpm using (T-10 basic Ultra Turrax) for one hour.

2.2.3Optimization of Nanogel

The nanogel of diclofenac diethylamine was optimized for different parameters such as surfactant: co-surfactant ratio, polymer ratio to obtain the minimum particle size and PDI.

2.2.4 Characterization and evaluation of the formulation

The diclofenac enriched gels were characterized for their physicochemical properties such as color, odor and pH.

2.3 Measurement of particle size of the formulation

2.3.1 Particle size and size distribution analysis

The mean particle size of the prepared nanogel was obtained by using particle size analyzer. The particle size analyzer Malvern Mastersizer 2000 MS (Malvern Instruments UK) is a new generation of instruments that use photon correlation spectroscopy (PCS), which determines particle size by measuring the rate of fluctuations in laser light intensity scattered by particles as they diffuse through a fluid, for size analysis measurements. For the measurement of size and polydispersity index (PDI), 1mL of nanogel was diluted in double distilled water and placed into cuvetts of zeta sizer and measurements were recorded. Size and PDI of nanogel was determined **(Phatak Atul., 2012) .**The average particle size was measured after performing the experiment in triplicates**(Shah, P. *et al* ., 2010)**.

2.3.2 Determination of Zeta potential

Zeta potential for nanogel was determined using zetasizer hsa 3000 (Malvern instrument ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment **(Phatak Atul., 2012)**.

2.3.3 Morphology

Transmission electron microscopy (TEM) is a microscopy technique where by a beam of electrons is transmitted through an ultra-thin specimen, interacting with the specimen a sit passes through. An image is formed from the interaction of the electrons transmitted through the specimen. The samples were prepared by putting a 20-µl droplet of the nanogel on to a 200 mesh colloidon-coated copper grid, and letting the nanogel settle for 3–5 min. Then, the excess fluid was removed by wicking it off with an absorbent paper. The samples were negatively stained in PTA solution for 3–5 min. The samples were then viewed on a Hitachi H-7500, 200kV transmission electron microscope and photographed digitally on a 4k×4k CCD camera.

2.3.4 pH

The pH of the nanogel was determined at 25°C using pH meter (LabIndia). Firstly the electrode was calibrated

using the standard buffer solution pH 4, pH 7, pH 9, and then the electrode was dipped in the nanogel and the readings were taken in triplicate **(Lakshmi P K. *et al.*,2011).**

2.3.5 Viscosity

The viscosity of nanogel was measured using a Brookfield rotational viscometer (LV2, Brookfield Inc.,USA) equipped with the spindle no. C75-1. The measurement was performed at ambient temperature as per reported procedure in triplicate **(Pal. *et al.*,2007).**

2.3.6 Drug Entrapment efficiency

Total amount of drug present in nanogel was determined by adding 10 mg of gel in 10 ml of methanol. Drug was extracted in methanolic phase solution, filtered the solution and absorbance was determined by UV spectrophotmetrically at 277nm

% Entrapment = entrapped drug / total drug ×100

2.3.7 *In –Vitro* drug release study

Dialysis membrane technique was used to study in-vitro release of drug from the prepared nanogel Formulations. The receptor medium used was filled with freshly prepared phosphate buffer pH 5.5. Dialysis membrane (Molecular weight cut off- > 12, 000, Hi media LA393-10MT) previously soaked overnight. 500mg of formulation was placed in the donor compartment in conical flask .This flask was taken in incubator shaker and speed of the shaker was maintained at 60 rpm at 37°c.. Aliquots of 3 ml were withdrawn at pre-determined time intervals (0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hrs) and immediately replaced by same volume of the fresh medium after each sampling. The drug content in the sample was determined spectrophotometrically at 277nm.

2.3.8 Stability studies

Stability studies of nanogel were conducted for 3 month at room (25±2°c), refrigerated (5± 3°C) and at accelerated stability studies (40°±2°c). Characterization parameters were particle size, PDI and drug release.

2.3.9 *Ex –vivo* skin permeation studies

This study was carried out using Franz diffusion cell .Penetration was studied using abdominal skin of wistar rats. Animals were sacrificed to obtain the skin. Hairs from the abdominal part of skin removed and skin was excised from abdomen using surgical blade Skin samples washed with normal saline and cut into appropriate sizes**.** Skin placed on Franz diffusion cell, maintained at 37 ^{0}C with continuous stirring. 500 mg gel applied on donor side.60ml saline phosphate buffer (pH 5.5) used as acceptor media. 3 ml sample removed from the acceptor media at regular time interval for a period of 24 hrs and replaced with same amount of buffer to maintain sink condition. Samples analyzed at 277nm using UV-spectrophotometry (**K.Dua *et al.*, 2010).**

2.3.10 Skin retention studies

After performing skin permeation studies, skin was carefully removed from the Franz diffusion cell. Formulation on the skin was scraped using spatula. It was dissolved in sufficient amount of methanol to extract out the polymer. After extraction, the resulting solution was filtered and amount of drug content in filtrate was determined using UV-spectrophotometer at 277 nm **(Agarwal & Katare, 2002).**

2.3.11 Pharmacodynamic studies

The anti-inflammatory activity of drug in nanogel in wistar rats by using carragenan induced paw Edema Method. For in vivo pharmacokinetic studies, female Wistar rats weighing (175 ± 25 g) will be used. The animals were divided into three groups (n = 18).The distilled water (vehicle), conventional gel and optimized nanogel applied externally to each rat of every group. Thirty minutes later the rat was challenged by a subcutaneous injection of 0.01 ml1% w/v solution of carragenan into planter side of the left hind paw. The paw was marked with ink at the level of lateral malleolus .The paw volume is measured plethysmographically immediately after injection and again after 0.5,1,1.5,2,4 and 6 hours after challenge .The % inhibition of edema induced by carragenan was calculated in each group by (following equation). Difference in paw volume between v control and v treated was taken as a measure of edema. **(S. V. Satyananayana., 2008)**

Parameters to be assessed

Percent of inhibition of edema = V control – V treated / **V control x 100**

Where, V control = mean edema volume of rats in controlled group

V treated = edema volume of each rat in test

3.0 RESULT AND DISCUSSION

3.1Selection of Surfactants and co-surfactants

Diclofenac showed maximum solubility in PolyethyleneGlycol 400(TEFOSE63) (43mg/mL) and Labrafil 1944(24 mg/mL) as shown in the **Figure 1.** Among the various surfactants and cosurfactant evaluated, the maximum solubility of drug was found in Tefose63 so it was selected as surfactant. Instead of its solubility Tefose63(PEG400,PEG 6 Sterate)is a non-ionic emulsifier and solubilizer, with HLB value 9-10. Non-ionic surfactants are considered to be less toxic than ionic surfactants and therefore Tefose63 was selected.

Among the various co-surfactants (Ethanol, isopropyl alcohol, labrafil1944, propylene glycol) evaluated, the solubility of drug in different Coemulsifier was observed to be maximum with labrafil, with HLB value -4 .This was the probable reason for the selection of labrafil and it is also a good penetration enhancer and solubilizing agent.

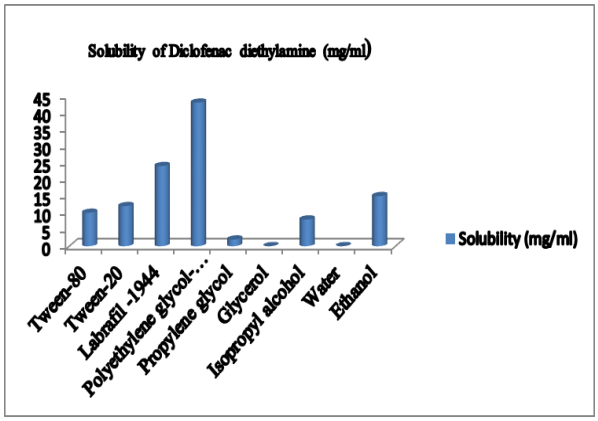

Fig 1: Selection of Surfactant and co-surfactants.

3.3.1 BOX BHENKEM DESIGN ANDOPTIMIZATION

The optimization was conducted using box-benkemdesign. In this study, a 3^3 factorial study was used to optimize the nanogel. In order to optimize the formulation, the amount of polymer concentration and emulsifier: coemulsifier concentration was selected as independent variables. Each factor was set at a high level and low level To achieve our goal 13 formulation of nanogel were optimized by 3^2 boxbenken design. The response of the design was analyzed using Design Expert. The dependent variables i.e. particle size, entrapment efficiency, Polydispersibility index was calculated. All the recordings were done in triplicates(*n=3)

Table1:Independent and dependent variables

Factors	**Units**	**Level used actual (Coded**		
		1.5	**Medium**	**High**
Polymer ratio	% w/v	1:1	2	2.5
Emulsifier:Co emulsifier ratio	% w/v		2:1	3:1
Dependent variables	**Units**	**Constraints**		
Particle size	nm	Optimum		
PDI	Nil	Optimum		
Entrapment efficiency	Percentage	Maximum		

Table2: Tabular representation of calculated dependent variables using box bhenkem design

CODE	Polymer ratio	Emulsifier: coemulsifier ratio	Particle size±SD* (nm)	PDI± SD*	Entrapment efficiency
F-1	0	-1	628.4	.336	42.2
F-2	-1	-1	355.2	.374	60.3
F-3	0	0	267.5	.290	74.1
F-4	0	0	268.3	.291	74.4
F-5	0	0	268.7	.292	74.6
F-6	0	1	228.4	.113	77.3
F-7	1	0	590.7	.357	40.7
F-8	1	-1	962.6	.704	44.8
F-9	0	0	268.4	.297	74.7
F-10	0	0	268.9	.296	74.8
F-11	-1	0	265.4	.549	68.7
F-12	1	1	319.2	.312	52.6
F-13	-1	1	249.2	.257	70.7

3.3.2 Analysis of experimental results and validation of experimental design

The selected independent variables like amount of polymer concentration and emulsifier: coemulsifier concentration influenced the particle size, PDI, entrapment efficiency. For each dependable variable, the response polynomial coefficients were determined in order to determine the effect of each response. Analysis of experimental result was done by using the Stat-EaseDesign Expert. After filling the data in the design, quadratic model were suggested to run the design. Model F-value, and p-value for average particle size, PDI, entrapment efficiency were obtained from ANOVA. A second order polynomial regression equation which fitted to the data is as following equation.

$$Y = b0 + b1A + b2B + b3C + b12\,AB + b13\,AC + b23\,BC + b11A2 + b22B2 + b33C2$$

Where Y = measured response associated with each factor level combination;
b0 = is an intercept;
b1 to b33 = regression coefficients computed from the observed experimental values of Y. A, B, and C = coded level of independent variables.

The term (AB, AC, BC) and (A2, B2, C2) represents the interaction and quadratic terms. The polynomial equations of three dependable variables can be given as follows.

Particle size - 228.4+167.12A-191.57B-134.35AB+103.43A^2 +103.78B^2
PDI- .11 +0.032A-0.012B-0.069AB+0.17A^2+0.055B^2
Entrapment efficiency- 77.3 -10.27A+8.88B-0.65AB-11.53A^2-6.48B^2
From above equation particle size 284.4 nm, PDI 0.29 and entrapment efficiency 72.1were predicted which was closed to observed values. To further analyze the effect of variables on the responses, response surface plots were generated.

The relationship between the dependable variables and two independent variables was further elucidated by constructing 3-D response surface shown in Figure-2, 3, 4 the response surface showed the effect of amount of polymer and emulsifier and co-emulsifier ratios at different levels on studied response (particlesize ,PDI,entrapment efficiency).

The particle size recorded at minimum polymer(2%w/v) amount and high ratios of emulsifyingagents(3:1 w/v).

3.3.3 Response Surface analysis for particle size,PDI and entrapment efficiency

Effect of polymer and emulsifying agent on particle size

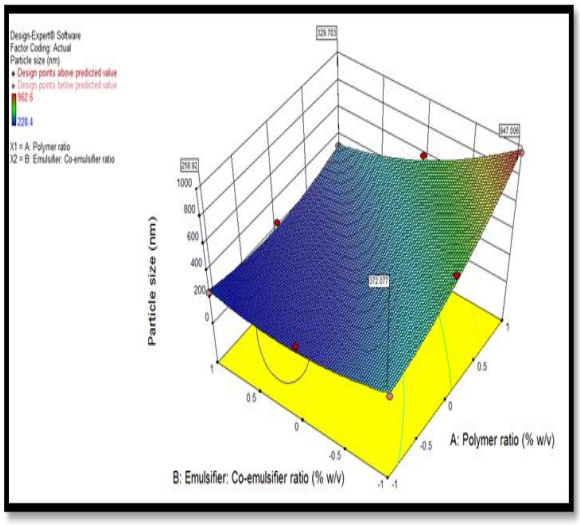

Fig2: Effect of polymer and emulsifying agent on particle size
With the increase in polymer ratio and decrease in the emulsifier and co emulsifier ratio there in increase in particle size.

Effect of polymer and emulsifying agent on PDI

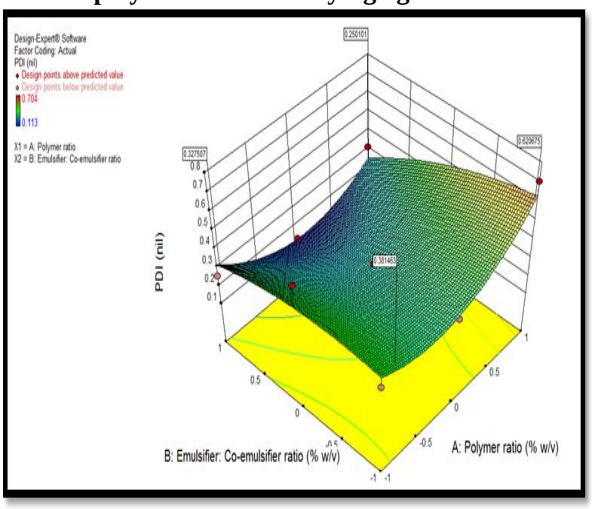

Fig 3: Effect of polymer and emulsifying agent on PDI
With the increase in polymer ratio and decrease in the emulsifier and co emulsifier ratio there in increase in PDI

Effect of polymer and emulsifying agent on entrapment efficiency

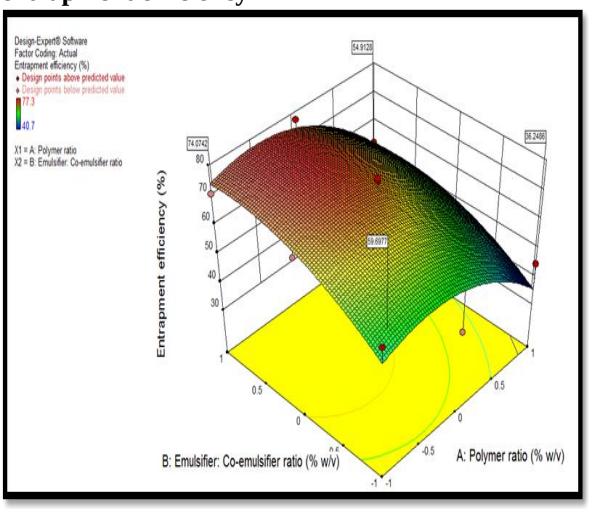

Fig 4: Effect of polymer and emulsifying agent on entrapment efficiency
With the increase in polymer ratio and decrease in the emulsifier and co emulsifier ratio there in decrease in entrapment efficiency.

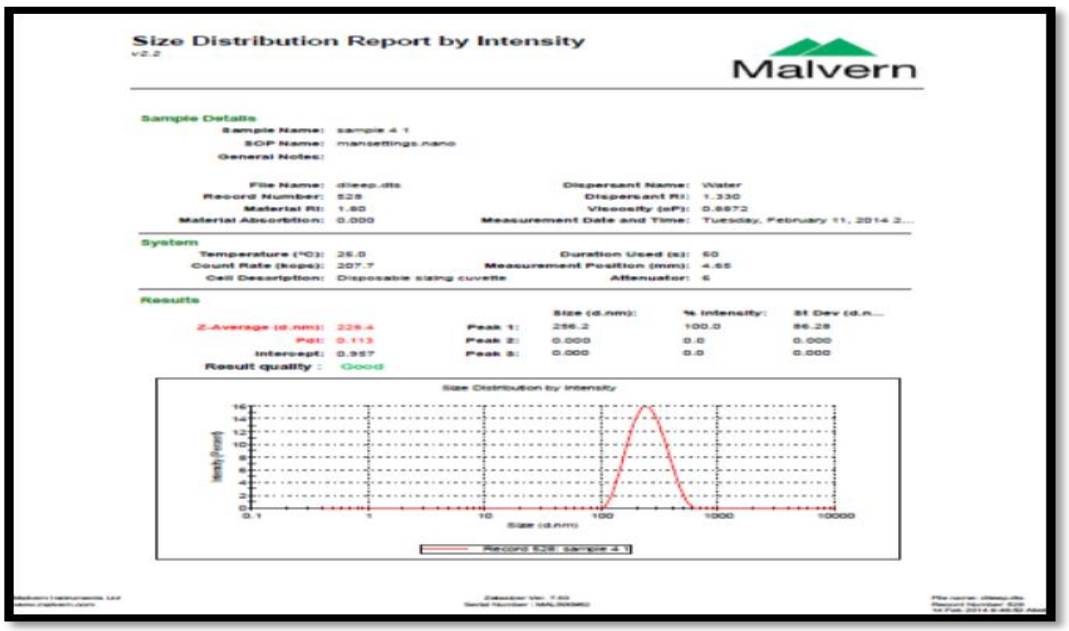

Figure 5: Particle size and size distribution studies final optimized formulation

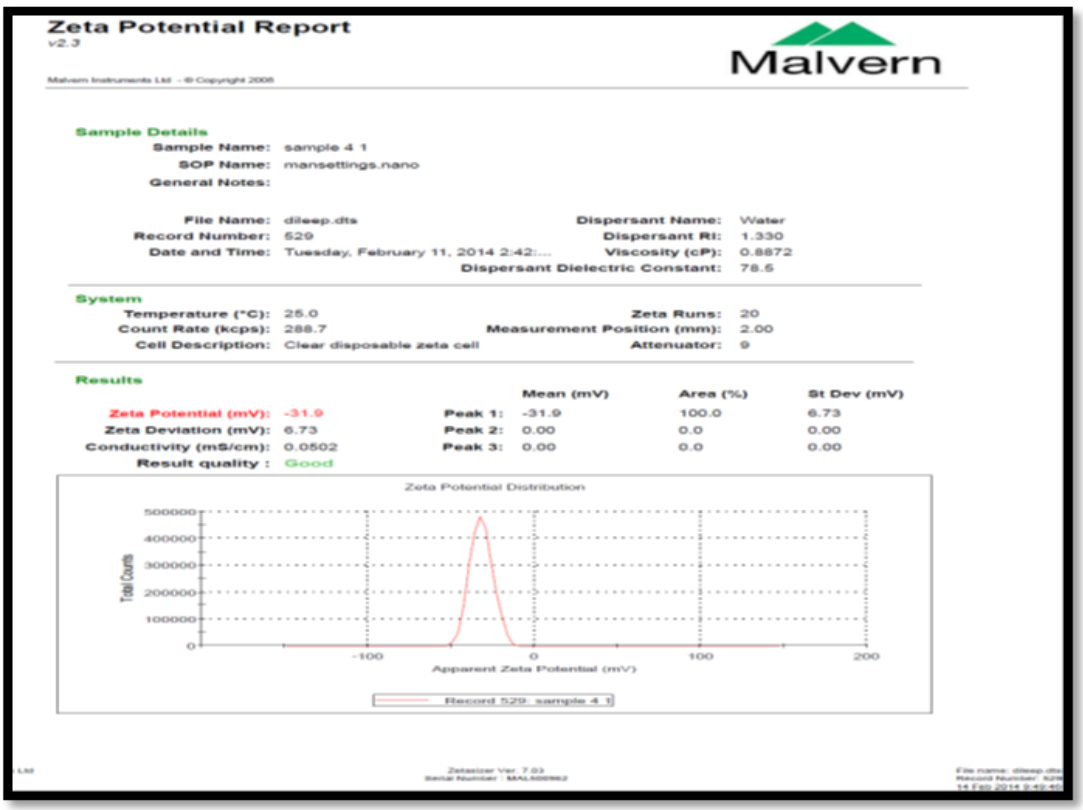

Fig6: Zeta potential of final optimized formulation

The particle size should be within the range due to the concentration of emulsifier and co-emulsifier and other ideal charactertistics which leads to the permeation in deep layers of skin. It is uniform and topically suitable for the dosage form.

3.3.4 Morphology

The morphology of the reconstituted nanogel formulation was observed using TEM and motic microscopy. The shape of final formulation was regular, uniform and spherical. The droplets of nanogel were found to be equally distributed and in agreement with the results obtained from particle size analyzer. The droplets of formulation in TEM were found to be in the range near 150 nm. The range of size in motic was found to be 20-50 µm.The results are shown in **Figure 7(a),(b) and Figure 8.**

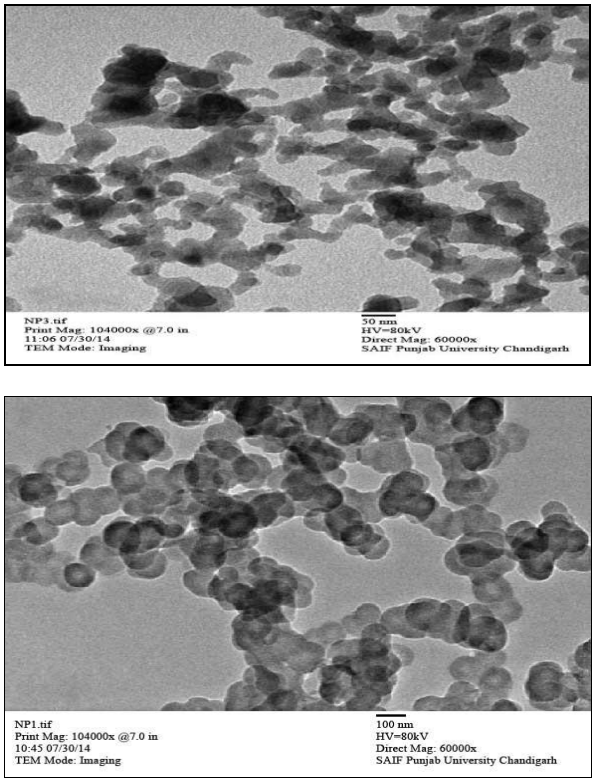

Fig 7(a),(b): TEM images of Nanogel

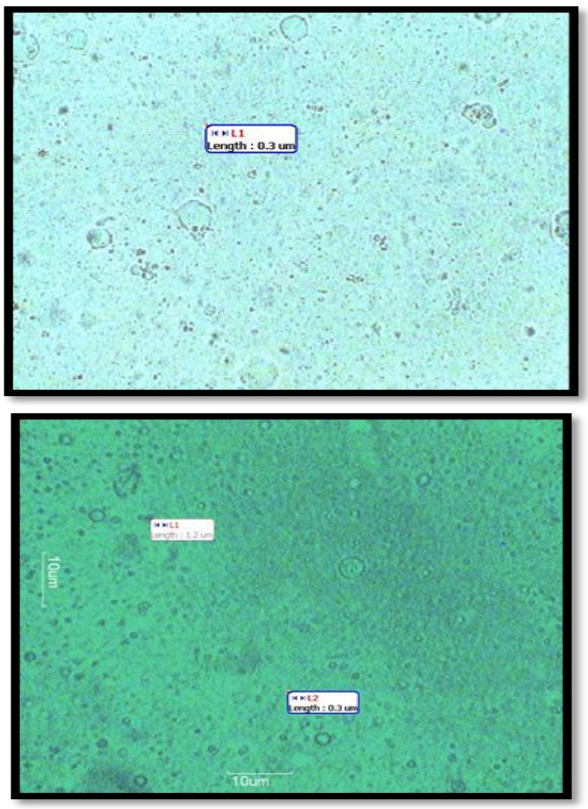

Figure 8: Motic images of final formulation

3.3.5 Viscosity

The rheogram of the formulation showed the pseudoplastic behavior which shows Gel-Sol-Gel conversion. Rheogram showed as the shear rate increases, viscosity will decrease with time. Rheogram of nanogel showed in **Fig 9 (a and b).**

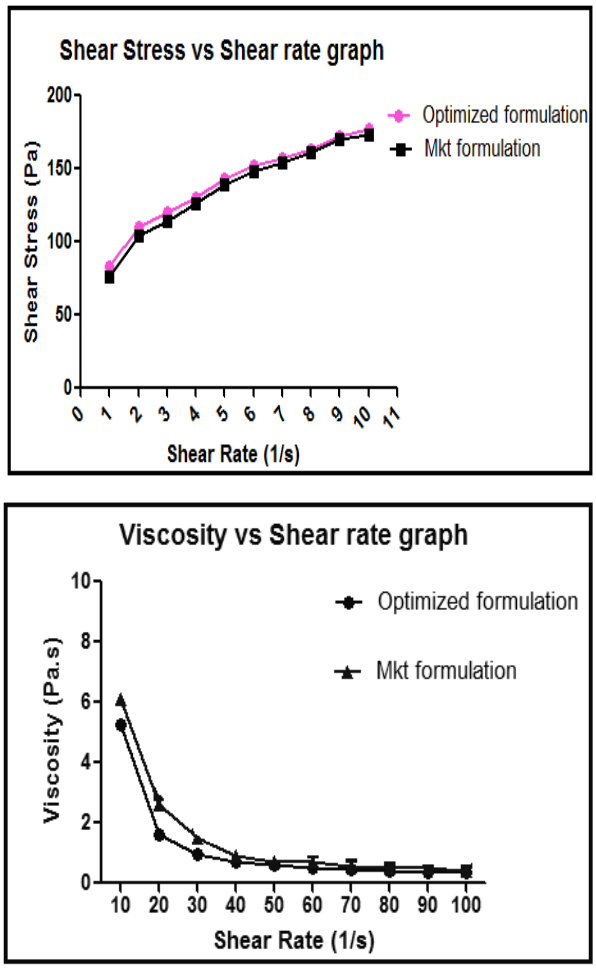

Fig 9 (a and b): Rheograms of Optimized and marketed formulation

The nanogel show non-newtonian behaviour. It reduces the surface tension of water due to their molecular relaxation processes and good for topical administration of drugs.

3.3.6 pH determination

The mean pH of the nanogel was 5.2±0.5. All measurements were carried out in triplicate. pH of topical formulation should less than 7 as pH of skin is 5.5 so the formulation pH should compatible with skin pH.

3.3.7*In*-vitro release study of nanogel

The release of drug from nanogel was observed by dialysis bag method. At the end of 12hours, the release of drug from the nanogel was significantly greater (49.14 ± 2.165) than that for marketed gel(36.24 ± 2.675) as shown in **Figure10.**

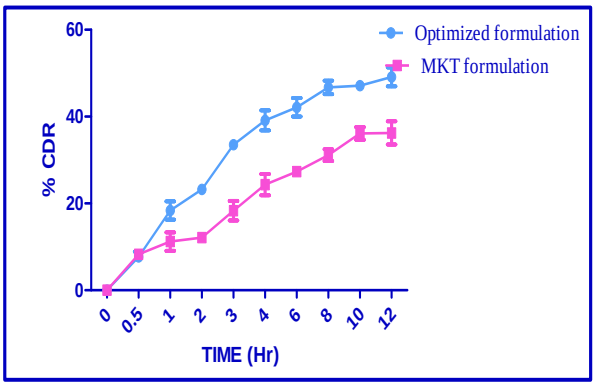

Fig 10 : *In-vitro* drug release profiles of optimised formulation and marketed formulation

Kinetics of drug release of optimised formulation and marketed formulation is shown in **Table 3 and Figure 11 & 12.** R^2 value is maximum in case of first order (0.9433) for optimized formulation and in case of higuchi order (0.9294) for marketed formulation.

Table 3: Drug release kinetics of both formulations

Kinetic approach	0 order	1st order	Higuchi	Peppas
Optimized formulation	0.7958	0.8478	**0.9529**	0.685
MKT Formulation	0.9401	**0.955**	0.9092	0.750

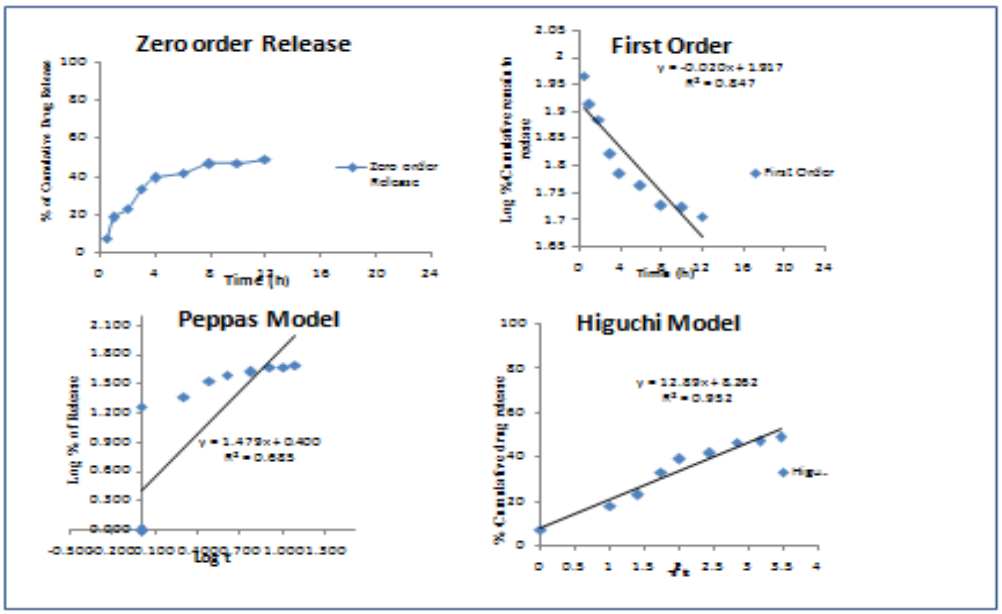

Figure:11: Drug release kinetics of nanogel

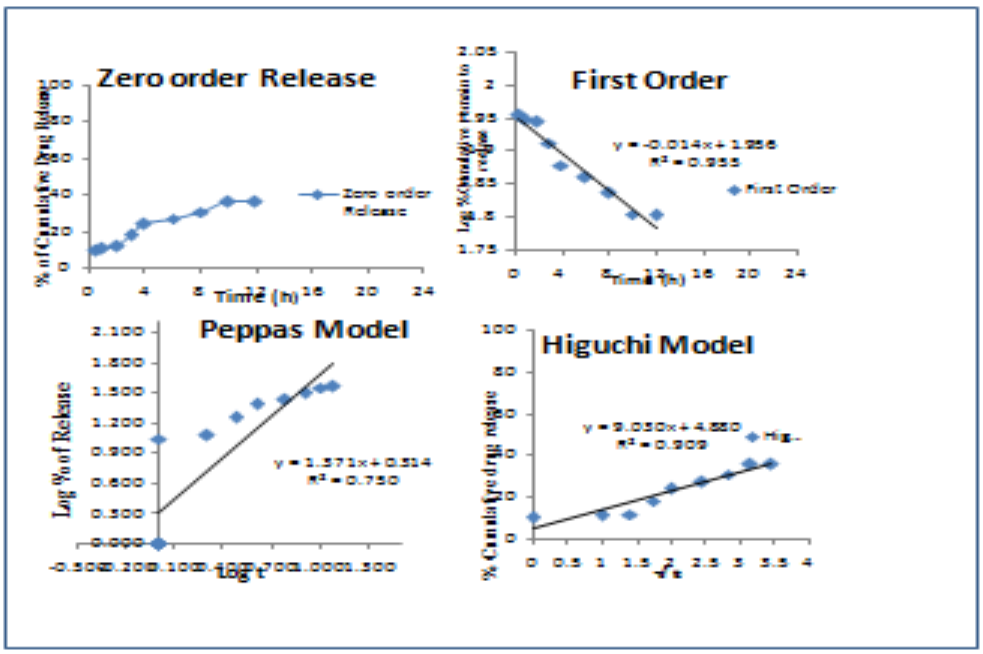

Figure.12: Drug release kinetics of marketed gel.

3.3.8 *In-vitro* skin permeation studies

Cumulative percentage of drug permeated in 12 hrs from nanogel gel was 36.24 ± 1.234 % while from marketed gel it was 22.20 ± 0.750 %. Drug permeated from marketed gel was low as compared to nanogel due to carrier system that reduces the permeation of drug through skin.

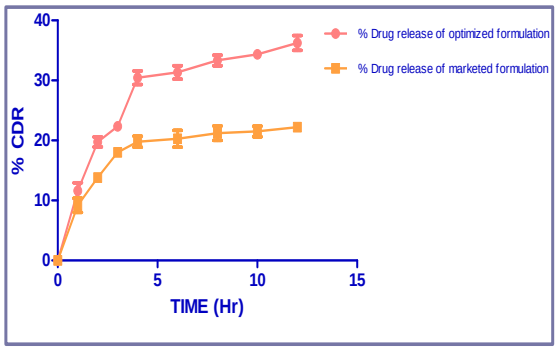

Fig. 13: Cumulative % drug permeation through skin vs time plot for both formulations.

3.3.9 Skin retention studies of nanogel

Amount of drug retained in skin after 12 hrs was 54.23 ± 1.234% and 32.12 ±1.552 % from optimized nanogel and marketed gel. High drug retention in case of nanogel may be due to formation of drug reservoir in basal epidermis due to deposition of nanogel there.

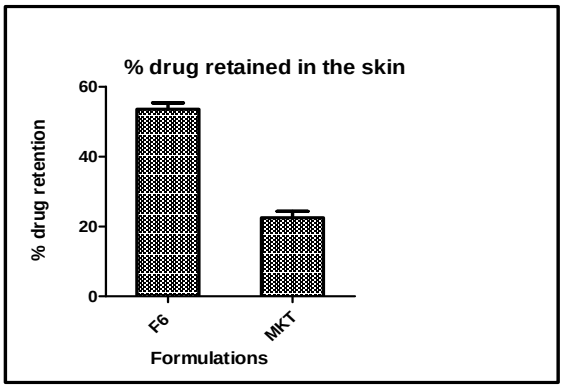

Fig.14: Percent drug retention of gel formulations in skin

3.3.10Pharmacodynamic studies The paw volume was noted at 0, 0.5,1, 1.5, 2, 3, 5 ,6 and 8 hours from the induction of the edema. Volume of inflamed paw goes on decreasing as time increases that shows drug acting on inflammation cause by Carrageenan. Optimized nanogel showed significant reduction in paw volume as compared with the control as well as mkt formulation. The formulation showed not only decreased the inflammation to the larger extent, but also sustained this level for the period of measurement.

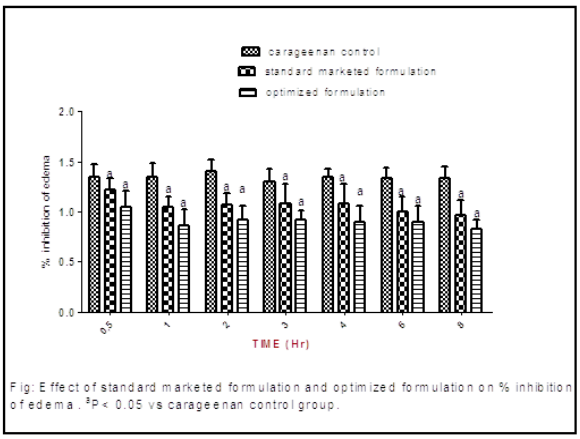

Fig. 15: effect of standard marketed formulation and optimized formulation on%inhibition of edema.[a]p<0.05 vs carageenan control group

3.3.11 Stability studies

The stability studies were carried out for optimized formulation that is on F 6 nanogel. The samples were stored at at refrigerated temperature (5±3^{0}C) , room temperature (25± 2°c) and at accelerated stability studies (40°±2°c) for 3 months (Climatic zone IV condition for accelerated testing) RH for three months to access their stability. After 1, 2 and 3 months samples were withdrawn and retested for particle size and total drug content studies. The formulation did not show any significant change in both parameters. It indicates that this formulation was able to retain its stability up to 3 months. Stability data had showed in Table-4.

Table 4: Effect of storage on particle size and Drug content of formulations at different intervals of time for 3 months.

Particle size and Drug content						
Temp	**Initial particle size and Drug content of optimized formulation**	**15 Days**	**30 Days**	**45 Days**	**60 Days**	**90 Days**
At room temp (25± 2°c)	228.4± 0.32	246.3 ± 2.42	250.0 ± 2.43	258.3 ± 1.45	269.0 ± 0.43	296.2 ± 0.23
	97.05 ± 0.903	96.48 ± 0.149	95.30 ± 0.189	93.53 ± 0.750	92.53 ± 0.550	90.13 ± 0.445
Refrigerated temperature (5±3^{0}C)	228.4 ± 0.32	234.2 ± 1.54	245.0 ± 1.33	261.2 ± 2.22	250.0 ± 1.54	240.0 ± 1.33
	97.05 ± 0.903	94.53 ± 0.750	93.53 ± 0.750	92.13 ± 0.345	91.53 ± 0.234	89.53 ± 0.234
Accelerated temp(40°±2°c)	228.4 ± 0.32	235.6 ± 1.63	237.0 ± 1.43	234.3 ± 0.23	240.2 ± 1.22	233.1 ± 1.65
	97.05 ± 0.903	96.34 ± 0.140	95.48 ± 0.141	93.48 ± 0.260	92.18 ± 0.139	90.48 ± 0.146

4.0 CONCLUSION

Nanogel formulation represents an effective and better carrier system for transdermal preparation which showed the promising alternative than conventional gel and worked as an enhancer of percutaneous penetration.The stability studies for 3 months showed that the formulations were stable at all three conditions and showed substantial increase in the efficacy in animal studiesThis shows that nanogel displays more effective and having good permeation in epidermis and dermis as compared to marketed conventional gel and has more effective retention which shows drug delivery in a controlled manner at the site of application.

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