Formulation And In-Vitro Diffusion Studies For Controlled Release Of Nsaid's

Mr. Ashish Balasaheb Jadhav[1]*, Mrs. Priti Rajendra Kale[2], Mr. Vipul Vilas Trivedi[3], Dr. Sudarshan Narayan Nagrale[4], Mr. Amit Vilas Pondkule[5]

[1]* Department of Pharmaceutical Quality Assurance Dattakala College of Pharmacy, Swami Chincholi, Dist-Pune, Maharshtra, India. Email-ashishjadhav973@gmail.com
[2]Department of Pharmaceutical Quality Assurance Dattakala College of Pharmacy, Swami Chincholi, Dist-Pune, Maharashtra, India**.** Email- kalep.dkcop@dattakala.edu.in
[3]Department of Pharmaceutical Chemistry Dattakala College of Pharmacy, Swami Chincholi, Dist-Pune, Maharshtra, India. Email- vipulvtrivedi@gmail.com
[4]Department of Pharmaceutical Chemistry Dattakala College of Pharmacy, Swami Chincholi, Dist-Pune, Maharshtra, India. Email- sudarshannagrale@gmail.com
[5]Department of Pharmaceutics Anusaya College of Pharmacy, Swami Chincholi, Dist-Pune, Maharshtra, India Email-pondkulemit@gmail.com

***Corresponding Author:** Mr. Ashish Balasaheb Jadhav
* Department of Pharmaceutical Quality Assurance Dattakala College of Pharmacy, Swami Chincholi, Dist-Pune, Maharshtra, India. Email-ashishjadhav973@gmail.com

Abstract
Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis, Aceclofenac is one of them. It is a newer derivative of Diclofenac with low gastrointestinal complications. The short biological half-life (3- 4h) and dosing frequency more than one per day make Aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, an once-daily sustained release formulation of Aceclofenac is desirable. In the present study an attempt was made to formulate and evaluate the Nanogel containing Aceclofenac drug. Aceclofenac Nanogel is prepared by solvent diffusion method (high speed homogenization) using Carbopol 934 and Xanthan gum as polymers. Total seven formulations were prepared and all were characterized for FTIR studies confirmed that the drug and polymer are compatible with each other during preparation. The average particle size ranges from 233 nm to273 nm and the M1 formulation shows -70.9 mV zeta potential. Viscosity studies show all the formulation in the range of 3310 to 3600 cps, and having good viscous property. The drug content studies of formulations were from 81.00 to 92.00%. From the stability studies data, it was found that there was no such difference in drug content and In-vitro drug release. It shows that the prepared nanogel formulations are stable. Formulation M1 shows good results for the invitro diffusion studies for controlled release.

Keywords: Aceclofenac, Nanogel, Xanthan gum, Carbapol-934.

INTRODUCTION:

Nanogels are sub-micrometer-sized cross-linked polymers made up of hydrophilic polymers. They are water soluble, but their properties differ from those of linear macromolecules of the same molecular weight. Nanogels are a new term for hydrogel nanoparticles [1]. The term "Nanogel" was first used in papers to describe a hydrophilic polymer network made by chemically crosslinking poly (ethylene glycol) and poly (ethyleneimine) to deliver antisense oligo nucleotides [2]. Nanogels are chemically or physically cross-linked, swollen small particles and they are made up of flexible hydrophilic or amphiphilic polymer networks. And these polymer networks can be anionic or cationic because they behave as a carrier molecule for drugs and designed in which a way that they can easily absorb

biologically active compounds by the formulation of biomolecular interactions like o bonds, hydrophobic or hydrogen bonding. And also, they are designed in such a way that the nanogels can easily encapsulate diverse class of biomolecules by optimizing the molecular composition, size and morphology, to make sure the controlled release of drug molecule in vivo.

When nanogels dispersed in the aqueous media, their swollen networks become soft and are allowed to encapsulate a required volume of water. Nanogels, during the first decade of its development, have been proved to be a potential structure for systemic drug release, conniving multifunctional nano carriers like theragnostic and controlled drug release at the target site. The pores in nanogels can be filled with small molecules or macromolecules and usually the size of nanogels in the one to hundreds nanometer in diameter. The nanogels contains some properties like Swelling, degradation, and chemical functionality are all things that can be controlled. Nanogels are being studied not only for drug delivery but also for making miscellaneous agents such as quantum dots, dyes, and other diagnostic agents over a longer period of time. The main advantages of nanogels have arisen as a result of the specific delivery system expectation. Nanogels are used in the field of gene therapy because gene delivery within cellular organelles for gene silencing and system is now possible. By varying the solvent quality and branching the volume fraction in nanogel, the three-dimensional structure can be maintained. Nanogels are promising drug carriers because of their high entrapment efficiency, increased stability, and environ-mental responsiveness, which are unheard of in common pharmaceutical nano-carriers [3].

Nanogel-based formulations have been shown to be a useful scaffold in nano medicine, with applications including biosensors, artificial muscles, biomaterials, biochemical separation, cell culture systems, biocatalysts, photonics, biomimetics, drug delivery, anticancer therapy, and more. The nanogels, on the other hand, were studied over a longer period of time in relation to synthetic procedure trends [4].

MATERIALS AND METHODS:

Aceclofenac were obtained from Micro lab Bangalore. Xanthan gum were received from Himedia laboratories Mumbai. Carbapol-934 were received Central drug house new Delhi. Ethanol were obtained Bio-scientific Lab. Propylene glycol is obtained Finar chemicals Ahmedabad. Triethanolamine were received from Central drug house new Delhi.

Nanogel is prepared from modified Emulsion Solvent Diffusion method

Step 1: In the first step accurately weighed quantity of drug is dissolved in ethanol and propylene glycol with stirring (organic phase). Step 2: In the second step aqueous phase is prepared by using carbopol-934 dissolved in water with continuous stirring and heat for a 20min in a magnetic stirring. And the drug phase is sonicated under ultrasonic bath so nicator for 10min.

Step 3: In this step drug phase is added drop by drop into aqueous phase during high-speed homogenization for 30min at 6000rpm to from emulsion The emulsion is converted into nanodroplet by homogenizer results in O/W emulsion formed.

Step 4: In this step O/w emulsion is homogenized for 1 hour at 8000rpm and triethanolamine is added with continues stirring to from nanogel.

Table No.1 Formulation of Aceclofenac Nanogels Different concentrations of polymer and same concentration of drug.

Formulation code	M1	M2	M3	M4	M5	M6	M7
Aceclofenac (ml)	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Xanthan gum (mg)	100	100	100	100	400	300	200
Carbapol-934 (mg)	100	200	300	400	100	100	100
Ethanol (ml)	10	10	10	10	10	10	10
Propylene glycol (ml)	4	4	4	4	4	4	4
Triethanolamine (ml)	4	4	4	4	4	4	4
Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs

FTIR Study:
Infrared absorption spectroscopy (IR) of Aceclofenac and Nanogel formulations (F1 to F7) were done using Bruker FTIR (ATR) spectroscopy to ascertain compatibility in all the formulations [5].

Scanning Electron Microscopy (SEM):
Scanning electron microscopy was used to examine the shape and surface morphology of the Nanogel prepared with optimised parameters.

Particle size:
The Nanogel was found to be in the nanometer range after particle size analysis. The homogenization time and Carbopol 934 concentration had an impact on the size of the nanoparticles.

Zeta potential:
Manipal University tested the stability of the formulated Nanogel. measuring the Nanogel's zeta potential (it was within the desired range of mV).

Homogeneity:
After the nanogels had been set in the container, visual inspection was used to check for homogeneity. They were examined for the appearance of aggregates and the presence of any.

pH:
A digital pH metre was used to determine the pH of various nanogel formulations.

Spread ability:
A wooden block and a glass slide apparatus were used to determine it. Weights of about 20g were added to the pan, and the time it took for the upper slide (movable) to completely separate from the fixed slides was recorded.

The formula for calculating spread ability was then used:
Where, S=Spread ability, M=Weight tide to upper slide, L=Length of glass slide T=Time taken to separate the slide completely from each other.
Extrudability The formulations were filled in to collapsible aluminium tubes. The tubes were pressed to extrube the 0.5 cm ribbon of the gel in 10 second and the extrudability of formulations was checked.

Drug content studies the weight equivalent to 100mg of gel was taken and transferred to a 100ml standard flask.25ml of ethanol and 25 ml of 7.4 pH phosphate buffer is added and shaken for about half an hour and the volume was made up to 100ml with 7.4 pH phosphate buffer. The above solution was filtered and 5 ml of filtrate was taken and diluted to 100ml with 7.5 pH phosphate buffer.
The absorbance of the resulting solution was measured at 245nm and the content of Aceclofenac was calculated.

Viscosity:
The viscosity of the formulations (gel) is determined at 25°C by using Brookfield viscometer with spindle no. S-96 at 1 rpm and viscosity was measured in cps. The measurement of each formulation was done in triplicate and average values are calculated.

In –vitro diffusion study:
Cellophane membrane is used for this study in Frantz Diffusion Cell.100mg of nanogel is placed in donor compartment with which is filled phosphate buffer 7.4. The membrane was mounted between the compartments of the Frantz Diffusion Cell. Reservoir compartment was filled with phosphate buffer 7.4. Then the study was carried out at 37±10°C and speed was adjusted to 100 to 120rpm and it is carried out for 10 hours .5ml of sample was withdrawn from reservoir compartment by the help of hypodermic syringes at half an hour interval for 2 hours, then one –hour interval for 10 hours and finally 6hrs to next 10 hrs. And absorbance is measured spectrophotometrically at 286nm Each time the reservoir compartment was replenished with the 5 ml fresh volume of phosphate buffer 7.4pH solution to maintain constant volume.

Stability studies: The optimized formulation is tested for 45 days in accordance with ICH guidelines at a temperature of 402°C and a relative humidity of 75%. By following the

procedure outlined above, the optimized formulation was examined for changes in drug content and in-vitro diffusion studies.

RESULTS AND DISCUSSION

FTIR studies:

From the FTIR spectra it has been noticed that there is no molecular shifting in functional group as though of pure drug specified in pharmacopeia hence there is compatibility between the drug and polymer. The individual FTIR spectra of pure drug Aceclofenac and polymer Carbapol-934 and xanthan gum and also a combination spectrum of the drug and polymer and formulation F1 are shown in the Figure No.1 & 2 and it was observed that the drug was compatible with polymer in physical mixture.

IR Spectra's of Pure Drug: Wave number observed peak in cm^{-1} 3300, 2946, 2899, 2750, 1650, 1400 Substituted Functional groups -OH Stretching -N-H Tertiary amine Stretching Aromatic stretching Aliphatic Stretching Carbonyl stretching and Alkaline stretching

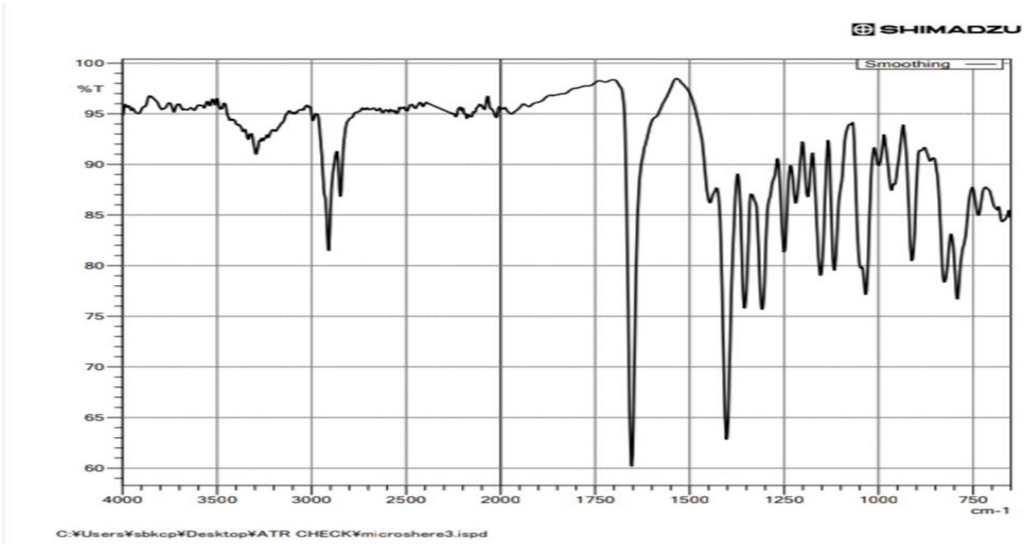

Figure No: 1. IR spectra of pure drug peak

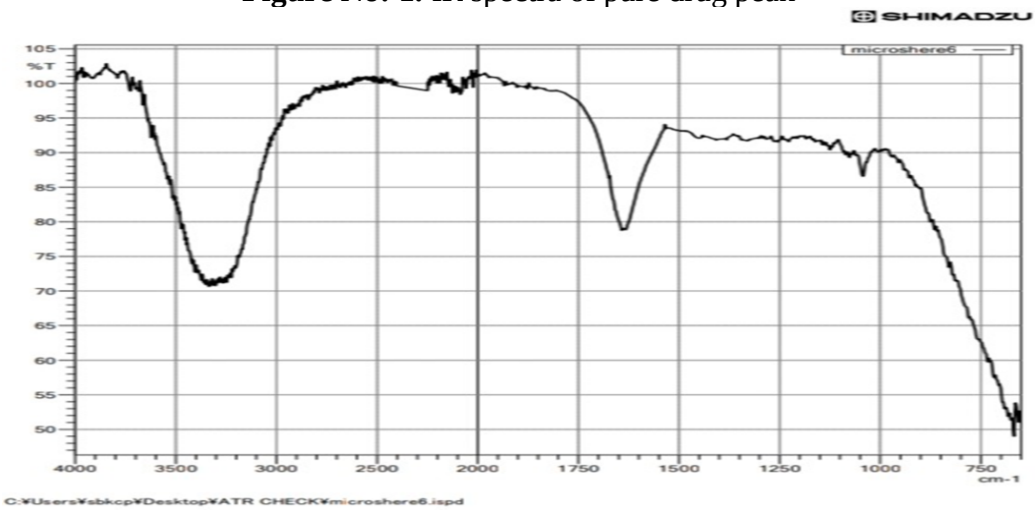

Figure No.2: I R Spectra of Nanogel Formulation M1

IR Spectra's of M1 Formulation: Wave number observed peak in cm $^{-1}$ 3300, 2946, 2893, 2753, 1650 and 1050 and Substituted Functional Groups -OH Stretching -N-H Tertiary amine, stretching, Aromatic stretching, Aliphatic stretching, Carbonyl Stretching and Alkaline stretching.

Particle size analysis:

The particle size determination of the nanogel were carried out by using melvern instrument

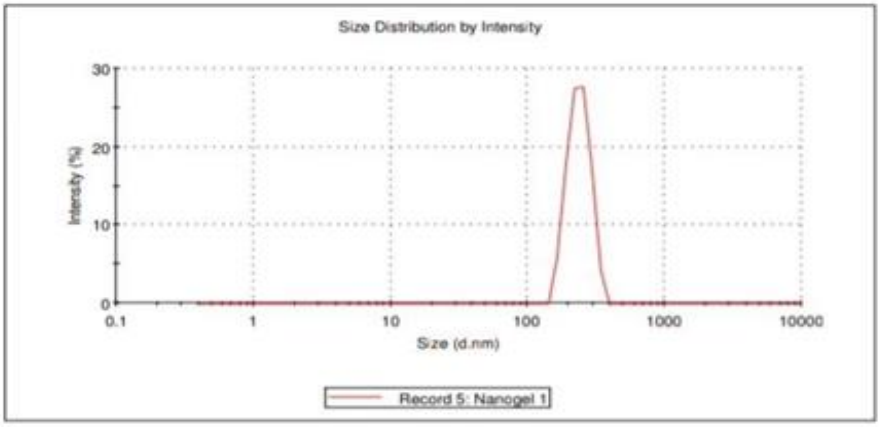

Figure No:3 particle size distribution by intensity

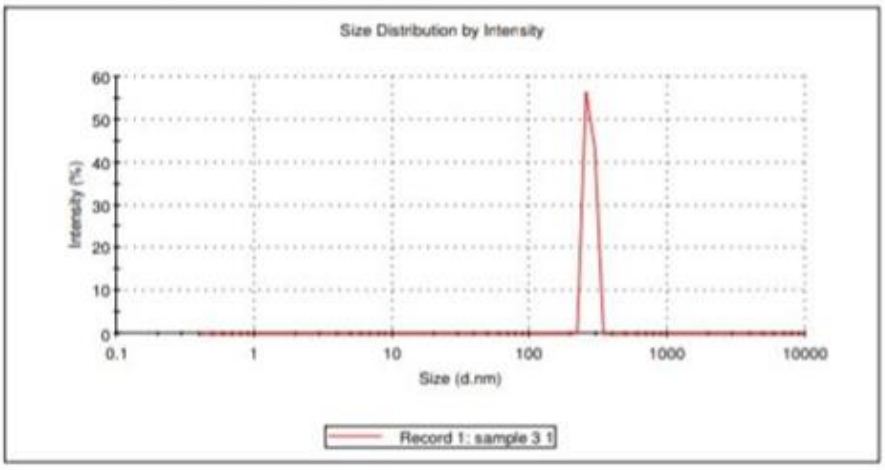

Figure No: 4. Particle size distribution by intensity

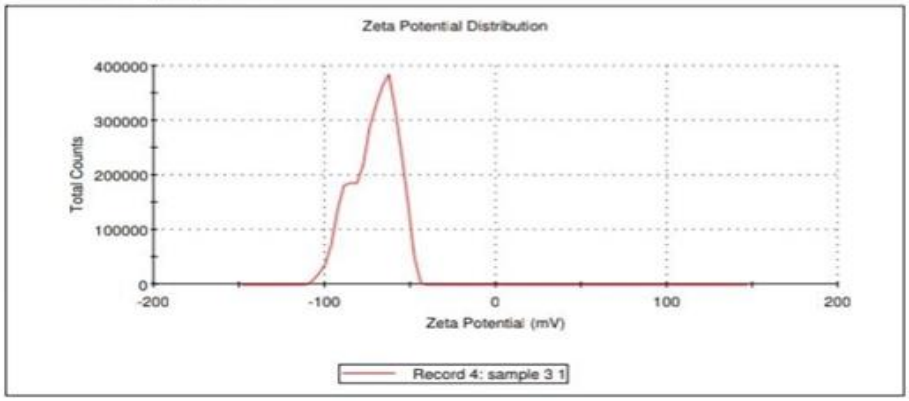

Figure No: 5. Zeta potential

Table No 7. Particle size analysis of Nanogel containing Aceclofenac.

Formulation code	Particle size(nm)
M1	272.8
M2	251.4
M3	265.5
M4	245.4
M5	233.4
M6	241
M7	239.4

Homogeneity:

All the gel formulation (M1-M7) showed better homogeneity with absence of lumps and the gels were found to be transparent and were free from presence of particles, uniformity of gel, aggregates, foreign matter and phase separation and the results are

shown in table No.2.

Determination of pH:
The pH of different formulation from M1 to M7 was showed in Table No. 2. The pH varies from one formulation to another according to their polymer ratios with drug.

Spread ability:
Spread ability diameter for different formula tions M1-M showed good spread ability i.e gels are easily spreadable. The results are shown in Table No.2.

Extrudability:
For a good gel formulation, it should extrude easily from the container. The extrudability of all formulations was found to be good. The result shown Table No.2

Drug content:
The drug content of all the formulation from M1 to M7 is shown in Table No.2.

There is no much difference in the drug content of each formulations.so, the effect of polymers ratios is less considerable here.

Viscosity:
All the formulation of Nanogel were subjected to Brookfield viscometer used to measure the viscosity (in cps) by dropping a cone attached to a holding rod from distance of 10 cm in such a way that, it should fall on centre of the glass cup filled with Nanogel. The results are shown in Table No. 2.

Table no: 2. Evaluation of formulated batches of Nanogel.

Formulation code	Homogeneity	pH	Spreadibility (cm)	Extrudability	Drug content	Viscosity (cps)
M1	Homogenous	6.8	3.4	++	91.25%	3568
M2	Homogenous	6.5	3.2	+	88.55%	3528
M3	Homogenous	6.2	2.5	++	82.10%	3368
M4	Homogenous	6.4	2.9	++	81.11%	3459
M5	Homogenous	5.9	3.2	+	83.40%	3501
M6	Homogenous	6.3	2.6	++	85.50%	3498
M7	Homogenous	6.1	2.8	+	84.45%	3340

In vitro diffusion studies:
The drug release from the Nanogel was studied by Franz diffusion cell method the in vitro release profiles of Aceclofenac from nanogel are shown in Table No. 3 The cumulative percentage release of Aceclofenac Nanogel were varied depends on the drug polymer ratio for 10 hrs.

Table No: 3. In-vitro drug release kinetics of Nanogel formulation M1 to M7

%Drug Release n=3							
Time (hr)	M1	M2	M3	M4	M5	M6	M7
0	0	0	0	0	0	0	0
0.5	11.756	10.650	15.632	6.2316	9.562	18.0324	13.012
1	16.762	17.762	24.561	18.2356	15.652	26.135	18.321
1.5	24.150	26.6861	30.562	25.1576	28.623	36.5629	27.9685
2	33.423	32.5623	39.154	32.659	35.496	48.2689	31.6892
3	42.640	45.3685	48.268	41.0653	43.213	53.156	45.6042
4	48.650	50.256	52.691	52.68	50.289	65.2305	54.6512
5	57.962	69.3291	64.523	56.1203	63.163	71.9686	65.356
6	63.682	78.263	79.263	68.6329	69.136	83.2653	72.623
7	69.442	82.264	82.652	72.263	75.135	87.135	80.361
8	77.134	87.623	85.785	84.632	86.896	89.445	85.263
9	85.632	88.263	88.253	89.530	90.458	90.563	86.2631
10	94.456	90.123	90.350	93.862	92.694	93.186	89.6503

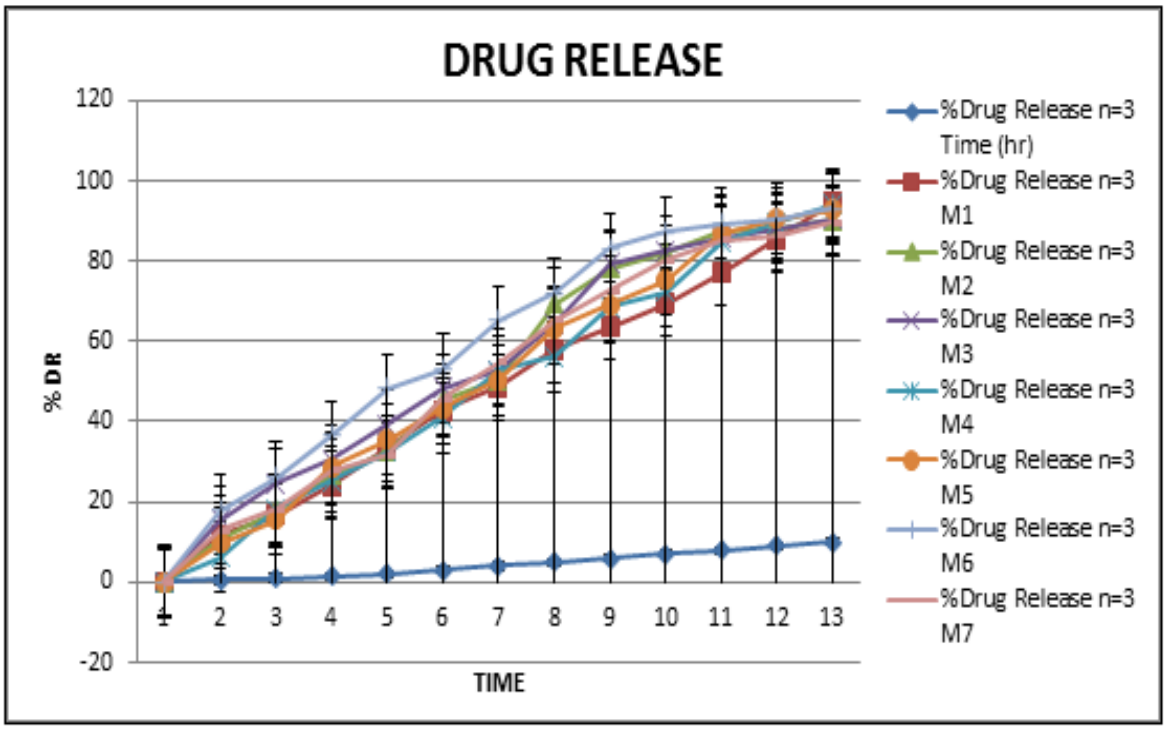

Figure No: 6. % drug release of Nanogel formulation

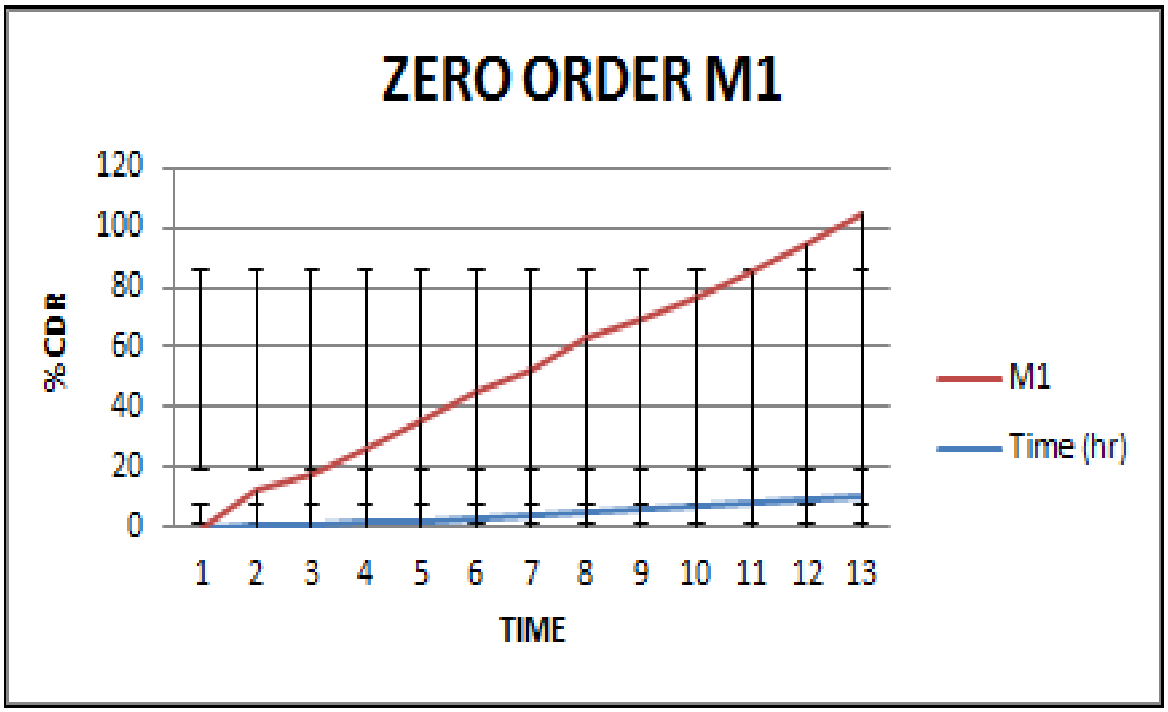

Figure no: 7. Graph of In-vitro drug release of Nanogel formulation M1

Table No: 4. Regression co-efficient value and 'n' value of different Nanogel

Formulation code	Zero order		First order		Higuchi		Peppas	
	n	R^2	n	R^2	N	R^2	N	R^2
M1	8.7075	0.9769	0.1223	0.6028	34.0223	0.9914	0.9897	0.6163

Stability studies:

The stability study was performed as per ICH guidelines. The Optimized formulations of gel were filled in the collapsible tubes and stored at different temperatures and humidity conditions, viz.250 C±20C/60%±5% RH,

30°C±2°C/65%±5%RH, 40°C±2°C/75%±5% RH for a period of 45 days samples were analysed drug content and drug release studies

Table No: 5. Drug content studies.

Formulation code	Drug content	
	Before stability test	After stability test
M1	89.15%	88.20%

Table No: 6. In-vitro diffusion studies

Formulation code	Percentage of drug diffusion	
	Before stability test	After stability test
M1	94.20±0.025	89.15±0.015

The diffusion study of optimized nanogel was studied according to previous procedure and determine the drug diffusion rate.

DISCUSSION

The main aim of this work was to formulate and evaluate the Nanogel containing Aceclofenac drug. Aceclofenac nanogel is prepared by solvent diffusion method (high speed homogenization) using Carbapol 934 and Xanthan gum as polymers and triethanolamine as a gelling agent and propylene glycol used as a humectant to prevent skin from drying. And the nanogel was subjected to the evaluation for homogeneity, readability, extrudability, drug content studies, viscosity, in-vitro diffusion and stabilities studies and characterized for FTIR studies, Surface morphology, and Particle size analysis. FTIR studies confirmed that the drug and polymer are compatible with each other during preparation. The average particle size ranges from 233 nm t0 nm. 273 nm. and the formulated Nanogel shows -70mV of zeta potential Homogeneity and extrudability studies confirmed that the nanogel was homogeneous and easily extrudable. The pH data shows all the formulation is in the range of 6.1 to 6.8 and they are in compatible to skin pH. Viscosity studies show all the formulation in the range of 3310 to 3600 cps, and having good viscous property. The drug content studies of formulations were from 88.00 to 95.00%.The in vitro diffusion study was performed using Franz diffusion cell appartatus. In-vitro diffusion studies of prepared nanogel follow higuchi dissolution kinetics with controlled release mechanism. And by fixing in Higuchi equation, it shows non Fiskian kinetics. From the stability studies data, it was found that there was no such difference in drug content and In-vitro drug release. It shows that the prepared nanogel stable. Formulation M1 shows good results for the invitro diffusion studies for controlled release.

CONCLUSION:

In the present study, an attempt was made to formulate a Nanogel containing non-steroidal anti-inflammatory drug yields a formulation with spherical and smooth surface, nano in size range. The formulated nanogel was opaque, without any lumps, particle and collection. So, all the formulations are homogenous. Install on all the factors the nanogel drug delivery system F1 revel good drug content compare to other. The particle size of the nanogel formulation is optimum and it is less than 1000nm. So, it concluded that the particles are in tiny and nano in size range. All nanogel formulation shows pH in the range of 6.1 to 6.8.and Formulation M1 shows highest pH of 6.8 .Since the pH range of Nanogel were 1 to 7 pH. Found on the readability diameter study it revel the nanogel is having good spread ability. Nanogel formulations shown viscosity range from 3310 to 3600 cps. It concluded that they are stable in nature. Formulation M1 shows highest percentage of drug release compare to other formulations. In-vitro diffusion studies shows M1 formulation shows controlled release pattern of drug from the formulation and the formulation was found to be stable in short term stability studies. Here it is concluded that M1 has an optimized

formulation which revels good morphological features, drug content efficiency and controlled drug release.

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