Development, Characterization and Evaluation of Drug Delivery Systems (Polymeric Matrix Film and Niosomes) of Aceclofenac

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Abstract: **The aim of the study is Development, Characterization and Evaluation of drug delivery systems (Polymeric matrix film and niosomes) of Aceclofenac. Polymeric matrix film formulations and niosomes formulations were prepared by solvent evaporation technique and modified ether injection technique respectively. These formulations were characterized using different parameters including % Cumulative drug release. Formulations showing best results were compared for % cumulative drug release through dialysis membrane and excised rat skin and release rate data were fitted into different kinetic models.**

Keywords: **Drug delivery systems, Polymeric matrix film, Niosomes, Niosomal gel, Aceclofenac.**

I. INTRODUCTION

Development of new drugs is difficult, expensive and rather time consuming process, therefore, safety and efficacy of existing drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring and, most importantly, delivering drugs at controlled rates at targeted sites[1,2].

Nowadays, lipid and non-ionic surfactant based drug delivery systems have drawn much attention from researchers as potential carriers of various bioactive molecules that could be used for therapeutic applications. Some of the examples of these lipid and non-ionic surfactant based drug delivery systems are Trandermal patches, Niosome gels, Liposomes, Nanosomes, Hydrogels, etc[3] .

A. Polymeric Matrix Films

Transdermal drug delivery systems (TDDS) are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation[4]. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. Different types of Transdermal films used for drug delivery are Single layer drug in adhesive, Multi layer drug in adhesive, reservoir systems, vapour patch, matrix systems, microreservoir systems, etc.

B. Niosomes

Niosomes are non-ionic surfactant based liposomes. Niosomes have more penetrating ability than emulsions. Niosomes are a better alternative to liposomes; these are vesicles containing non-phospholipid constituents. Niosomes are lamellar structures that are microscopic in size. They consist of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media[5]. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer.

C. Aceclofenac

Aceclofenac, a phenyl acetic acid derivative, is a drug of choice in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Researchers have attempted development of oral drug delivery systems for aceclofenac[6]. The chronic oral administration of aceclofenac tends to cause severe gastric irritation[7]. So, different drug delivery

systems to deliver Aceclofenac into body are very common for therapeutic application.

Based on this, the objective of this research was to develop, characterize and evaluate the different drug delivery systems (Polymer matrix film and Niosomes) of Aceclofenac.

II. MATERIAL & METHODS

Aceclofenac was obtained from Sarthak Biotech, Karnal, Haryana. All other chemicals, reagents and solvents used were of analytical grade and used directly as supplied by the manufacturer.

A. Preparation and Characterization of Aceclofenac loaded Polymeric Matrix Films

1. Preparation of Aceclofenac loaded Polymeric Matrix Films

Polymeric films containing Aceclofenac were prepared by the solvent evaporation technique. The drug reservoir was prepared by dissolving Polyvinly pyrolidine (PVP) and Ethylycellulose (EC) in Chloroform. The ratio of the polymers was varied for all the formulations keeping the total weight fixed at 350 mg. The films (FF1 to FF4) were kept in desiccator until further studied. The proportion of PVP and EC for the preparation of polymeric matrix film is given in Table 1.

TABLE 1
FORMULATION OF ACECLOFENAC LOADED POLYMERIC MATRIX FILM

Ingredient	FF 1	FF 2	FF 3	FF4
ACF (mg)	50	50	50	50
PVP (mg)	100	75	50	25
EC (mg)	200	225	250	275
Dibutylphthalate (%)	15	15	15	15
Choloroform (ml)	5	5	5	5

2. Characterization of Aceclofenac loaded Polymeric Matrix Films

Characterization of polymer matrix films was done using following parameters: thickness[8], weight variation[8], moisture content[8], moisture uptake[8], flatness[9], folding endurance[8], drug content determination and[10] % cumulative drug release (%CDR).

B. Preparation and Characterization of Niosomes containing Aceclofenac

1. Preparation of Niosomes containing Aceclofenac

Niosomes containing aceclofenac were prepared by modified ether injection technique using nonionic surfactant (span 60) and cholesterol at different concentrations. The proportion of surfactant and cholesterol for the preparations of niosomes is given in Table 2.

TABLE 2
FORMULATION OF ACECLOFENAC NIOSOMES

S.No.	Ingredients	NF1	NF2	NF3
1	Cholesterol	200	200	200
2	Span60	200	300	400
3	Aceclofenac	200	200	200
4	Methanol	2ml	2ml	2ml
5	Diethyl ether	8ml	8ml	8ml
6	Phosphate buffer 7.4	15ml	15ml	15ml

2. Preparation of niosomal gel (Niosome Formulation selected)

Carbopol 940 (as a gelling agent at 1% w/w concentration) was dispersed in distilled water. The dispersion was allowed to hydrate overnight. The niosomal formulation selected i.e. Batch NF3, equivalent to 1% w/w of aceclofenac was centrifuged at 20,000 r/min and 4˚C temp for 30 min to obtain the pellets. Niosomes pellets equivalent to 0.95g drug were incorporated instead of drug (Batch NF3) to

aqueous dispersion of carbopol. The resultant dispersion after uniform mixing was neutralized and made viscous by the addition of polyethylene glycol 400, isopropyl alcohol, propylene glycol triethanolamine (5% w/v) to obtain a translucent gel.

3. Characterization of Niosomes containing Aceclofenac

Characterization of niosomes was done using following parameters: % yield, Microscopy, vesicle size distribution, zeta potential measurement, scanning electron microscopy, percentage drug entrapment, drug content determination and % cumulative drug release.

C. In vitro drug release study through Dialysis membrane and Ex vivo drug release study

Formulation from polymeric matrix film and niosomes showing best results were compared for % cumulative drug release through dialysis membrane and excised rat skin and release rate data were fitted into different kinetic models.

III. RESULT AND DISCUSSION

A. Characterization of Polymeric Matrix Film loaded with Aceclofenac

All the formulations (polymeric matrix film loaded with Aceclofenac) were evaluated for thickness, weight, variation, moisture content, moisture uptake, flatness, drug content and % cumulative drug release by *in vitro* drug release study. The *in vitro* drug release studies shows that as the concentration of the ethyl cellulose increases the release of the drug from the films decreases from 90.10% to 77.66%. Table 3 shows parameters for characterization of different formulations of polymatrix film loaded with aceclofenac.

The Polymeric matrix film FF1 had the least thickness (0.21mm), lesser moisture content, moisture uptake with optimum folding endurance and maximum % CDR (90%) among all the four formulation studied. Hence, Formulation FF1 was selected for comparative *in vitro* drug release studies through dialysis membrane and *ex vivo* drug release study through rat skin.

TABLE 3
CHARACTERIZATION OF POLYMATRIX FILM LOADED WITH ACECLOFENAC

Parameters	**FF1**	**FF2**	**FF3**	**FF4**
Thickness(mm)	0.21±0.01	0.31±0.03	0.28±0.02	0.29±0.02
Weight Variation (mg)	44.3±0.1	42.3±0.3	40.83±0.2	40.87±0.1
Moisture content	1.128±0.02	0.983±0.04	0.808±0.02	1.110±0.01
Moisture uptake	0.82±0.02	0.72±0.03	2.21±0.01	0.91±0.01
Flatness	100	100	100	100
Folding Endurance	92±2	163±4	69±3	55±3
Drug content	98.4±0.03%	99.2±0.04%	99.8±0.01%	99.6±0.01%
% CDR	90.01	86.22	82.56	77.66

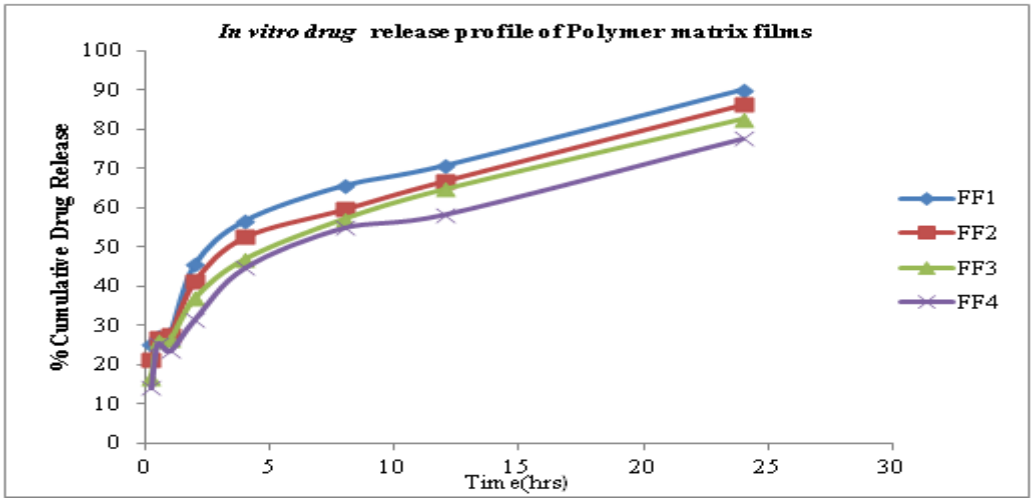

Fig. 1 *In vitro* Drug release profiles of formulations (FF1-FF4)

B. Characterization of Formulated Niosomes (Niosomes loaded with Aceclofenac)

All the formulations were evaluated for percentage yield, particle size, entrapment efficiency, and *in vitro* drug release.

Table 4 shows parameters for characterization of different formulations of noisome containing aceclofenac.

The formulation NF3 showed maximum entrapment efficiency, drug content, smaller particle size, zeta potential and maximum %CDR among all the three niosomal formulations. Hence it is formulated to gel and selected for further studies.

1. Particle Size and Zeta Potential

Particle size lies in between 200-500 nm. Size Distribution of different batches of Niosomes is summarized in Fig. 2-7.

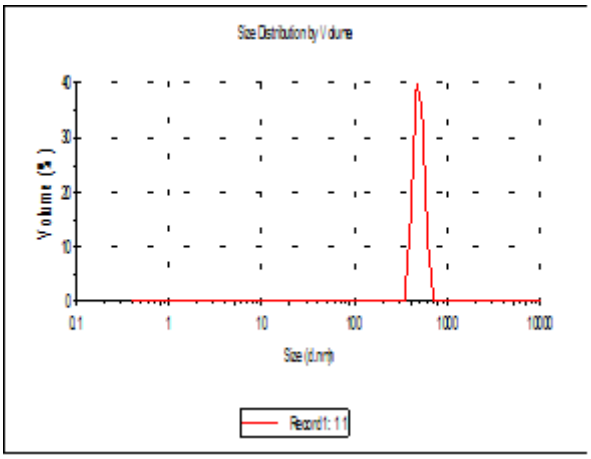

Fig. 2 PSA of Batch NF1

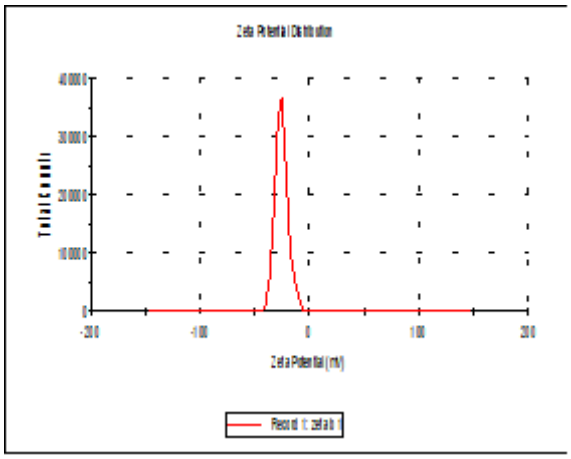

Fig. 3 Zeta potential of Batch NF1

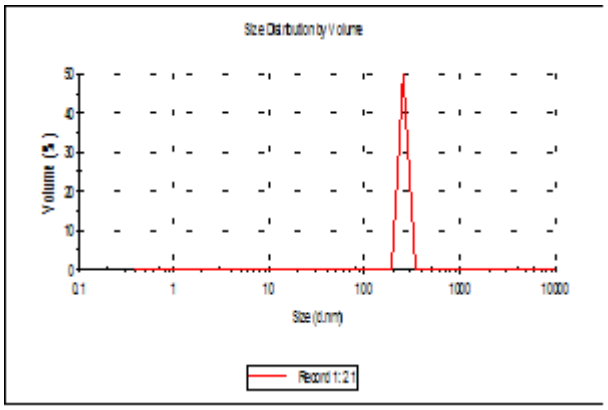

Fig. 4 PSA of Batch NF2

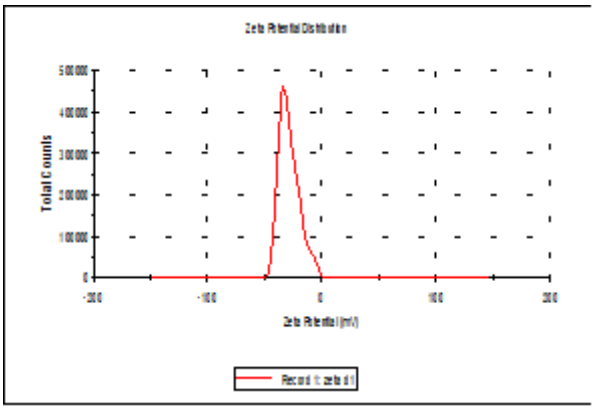

Fig. 5 Zeta potential of Batch NF2

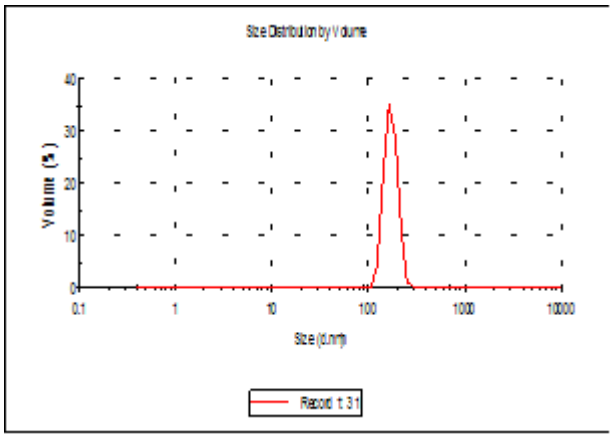

Fig. 6 PSA of Batch NF3

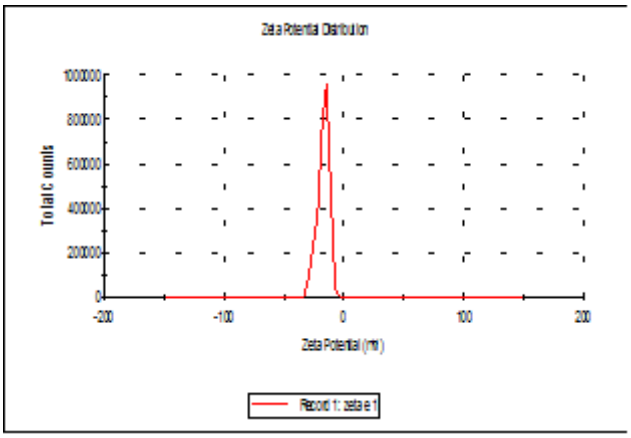

Fig.7 Zeta potential of Batch NF3

2. *Scanning Electron Microscope:* Scanning electron micrographs (A, B) of lyophilised niosomes NF3 was shown in Fig. 8 & 9.

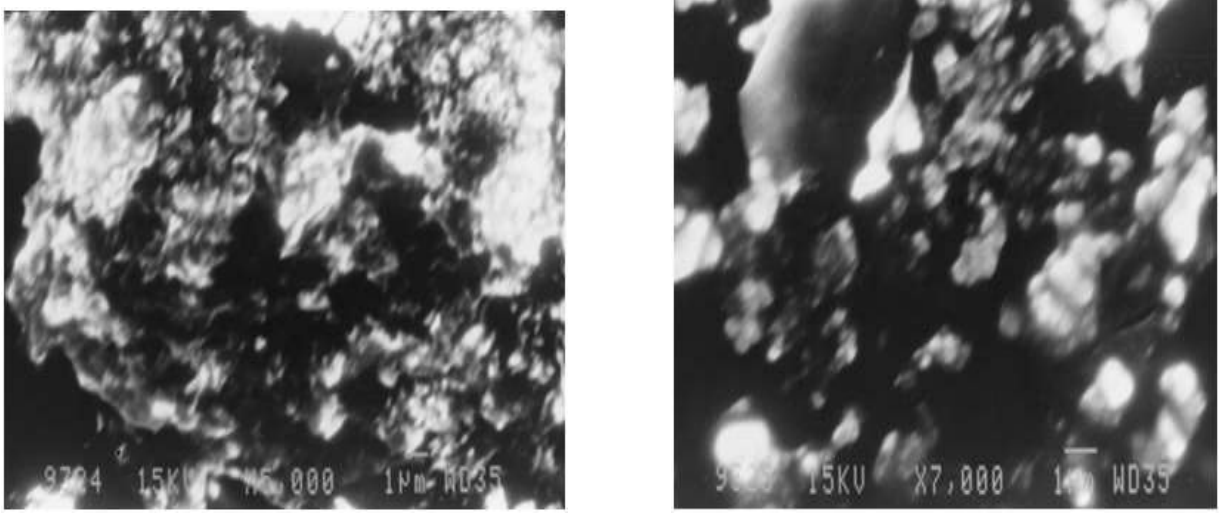

Fig. 8,9 Scanning electron micrographs of lyophilised niosomes NF3

TABLE 4CHARACTERIZATION OF NIOSOMES CONTAINING ACECLOFENAC

Characteristics	NF1	NF2	NF3
Particle Size(d nm)	438.3±0.02	330.0±0.05	225.9±0.02
Zeta Potential (mV)	-27	-30	-25
Percentage Yield (%)	79.2±0.2	82.2±0.3	88.6±0.2
Drug Content	67.8 ±0.02%	69.3 ±0.01%	72.3 ± 0.04%
Drug Entrapment	85.2 ±0.15%	87.2±0.13%	88.4±0.35%
% CDR	37.15%	57.14%	64.81%

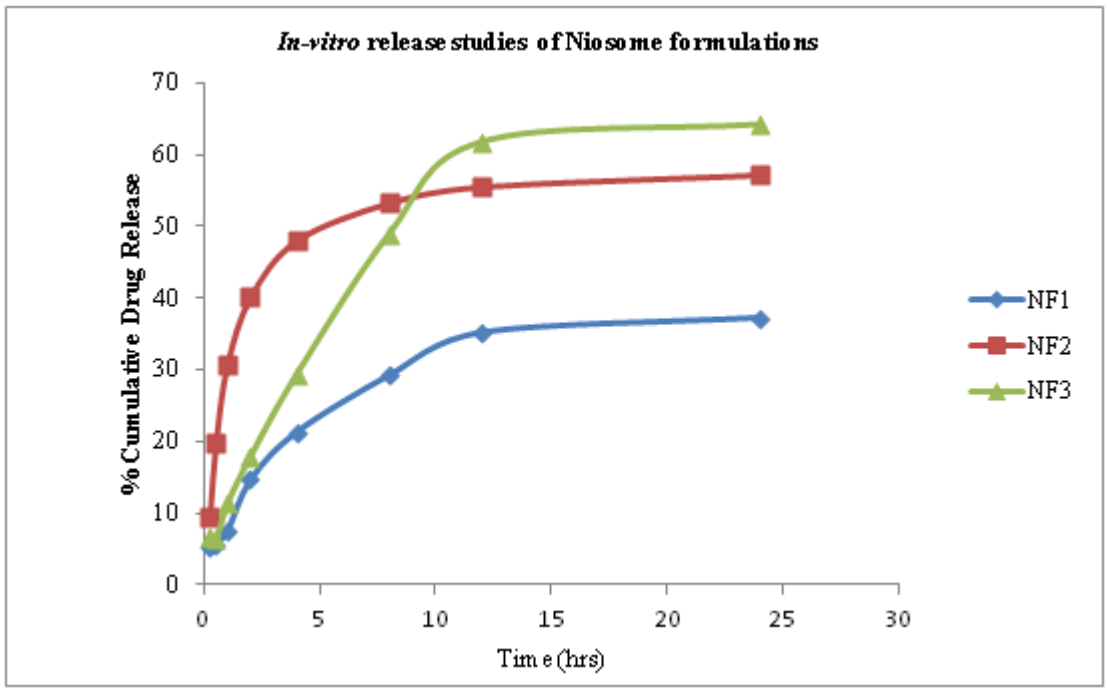

Fig. 10: *In vitro* Drug release profiles of formulations (NF1-NF3)

C. Ex-vivo Release Studies of Selected Formulations and Pure Aceclofenac

Ex vivo release study was performed using rat skin and % cumulative drug release (%CDR) through rat skin was compared for selected formulations FF1 (polymeric matrix film) and NF3 (niosomal gel prepared) and pure aceclofenac (control).

The release rate of the drug from the different formulation was observed to be lowest from the niosomal gel and maximum (82.34%) from the polymeric matrix film.

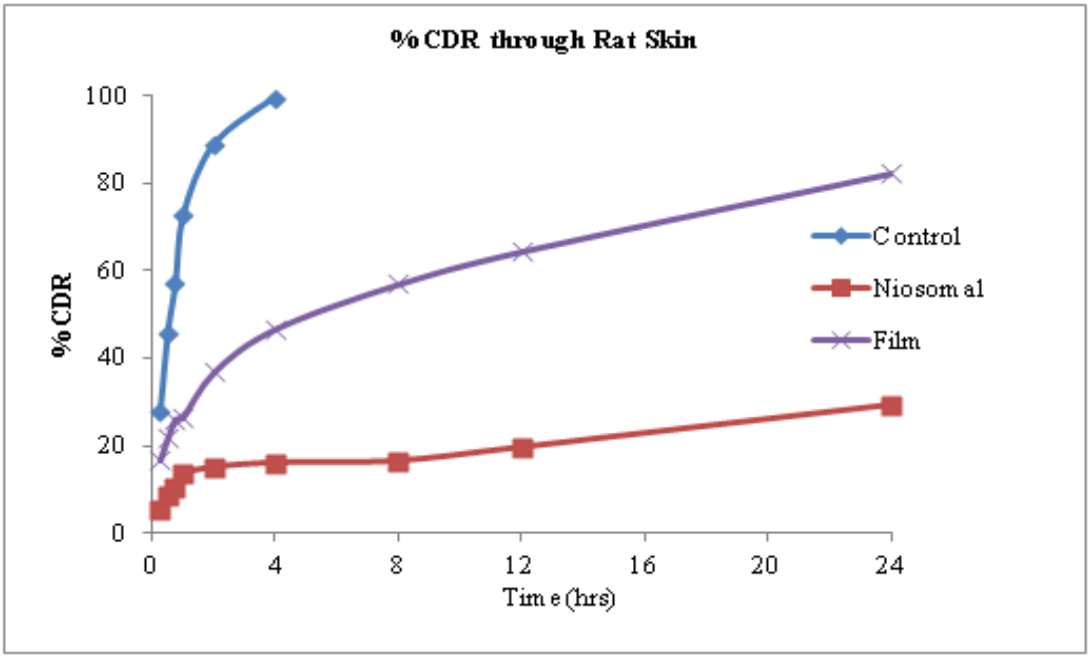

Fig. 11: Graphical representation of % CDR through rat skin

D. In Vitro Release Studies of Formulations Selected and Pure Aceclofenac (Control) using Dialysis Membrane

The polymeric matrix film (FF1) and niosomal gel (prepared from formulation NF3) were compared for % cumulative drug release through dialysis membrane and release rate data were fitted into different kinetic models.

Pure drug ACF and the two formulations were subjected to *in-vitro* release studies. These studies were carried out in phosphate buffer pH 7.4. The results obtained were plotted in four modes of data treatment as follows:

- ✓ Cumulative percentage drug release v/s Time (Zero order rate kinetics)[11]
- ✓ Log cumulative percentage drug retained v/s Time(First order kinetics)[12]
- ✓ Higuchi classical diffusion equation (Higuchi matrix) in which cumulative percentage release was plotted against square root of time.[13]
- ✓ Log of cumulative percentage drug released v/s Log time (Peppas exponential equation).

Fig. 12 shows plots of % CDR as a function of time. Cumulative % drug release of pure drug formulation found to be 92.79% at 4 hours and the selected formulations (Film, niosomal gel) was found to be 53.61% and 48.65% at 4 hours. % CDR after 12 hours was 66.86 and 50.95 respectively.

When compared with pure drug the release of formulation was prolonged over a period of 24 hours or more. The values of *in vitro* release were attempted to fit into various mathematical models. Plots of Zero order, First order, Higuchi and Peppas are depicted in Fig. 12, 13, 14 and 15.

The regression coefficients of formulations (Film, niosomal gel) of zero order were found to be 0.9206 &0.7670 respectively. The regression coefficients of formulations (Film, niosomal gel) of First order were found to be -0.9835 & -0.8213 respectively.

These results indicated that these plots were not linear. So, the release of drug from formulation might not have followed zero order or first order kinetics.

Fig. 14 shows graphical representation of % CDR as a function of square root. This Higuchi plot's regression coefficient values were 0.9801 and 0.871. The linearity suggests that the release from formulations was diffusion controlled.

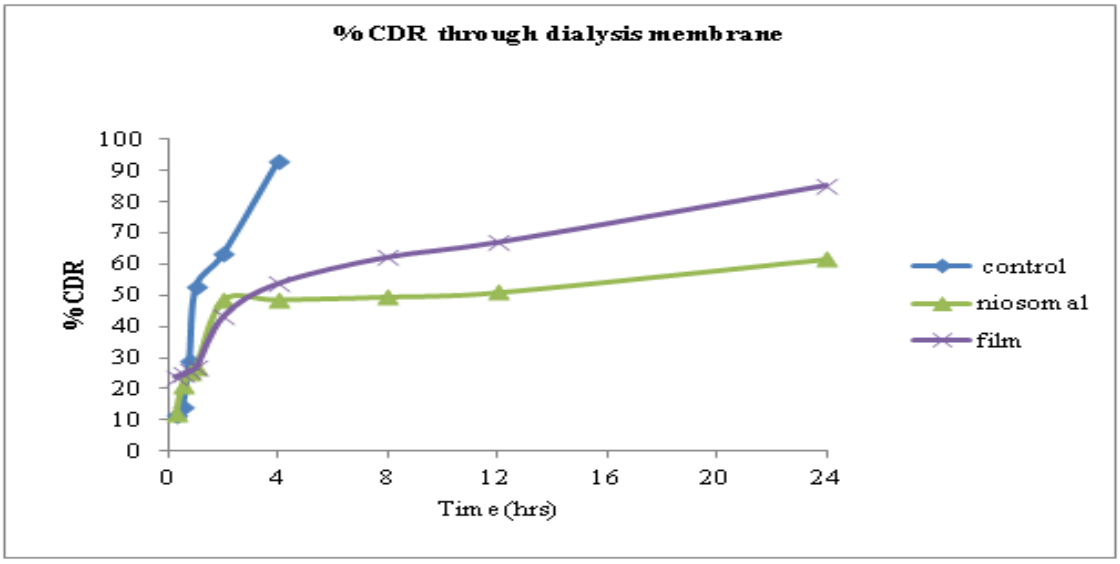

Fig.12: Graphical representation of drug release profile of selected formulations and control (pure Aceclofenac)

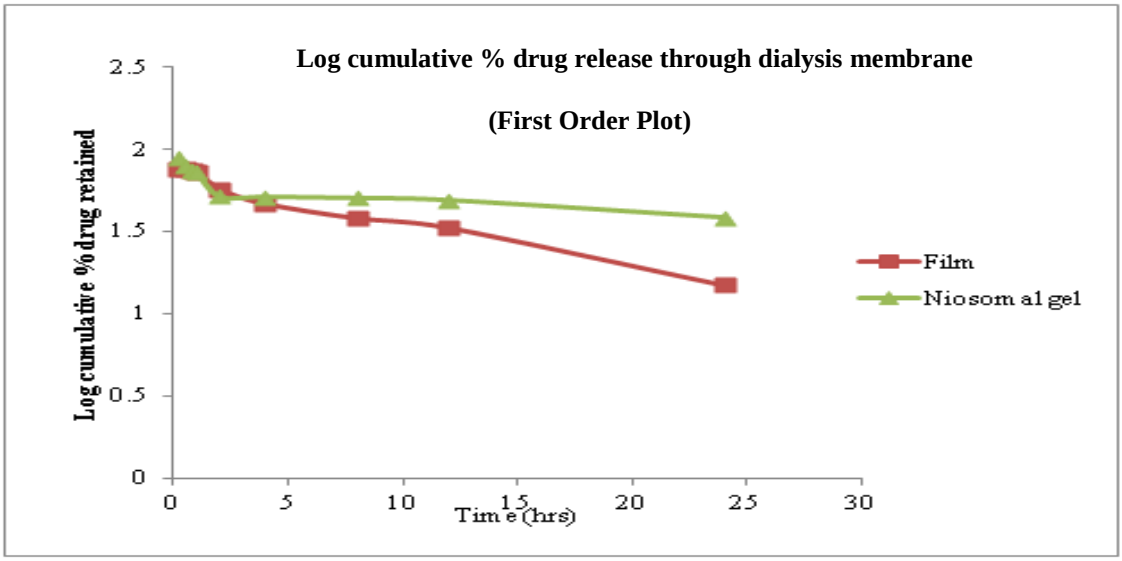

Fig. 13: Graphical representation of drug release profile of selected formulations (First Order Plot)

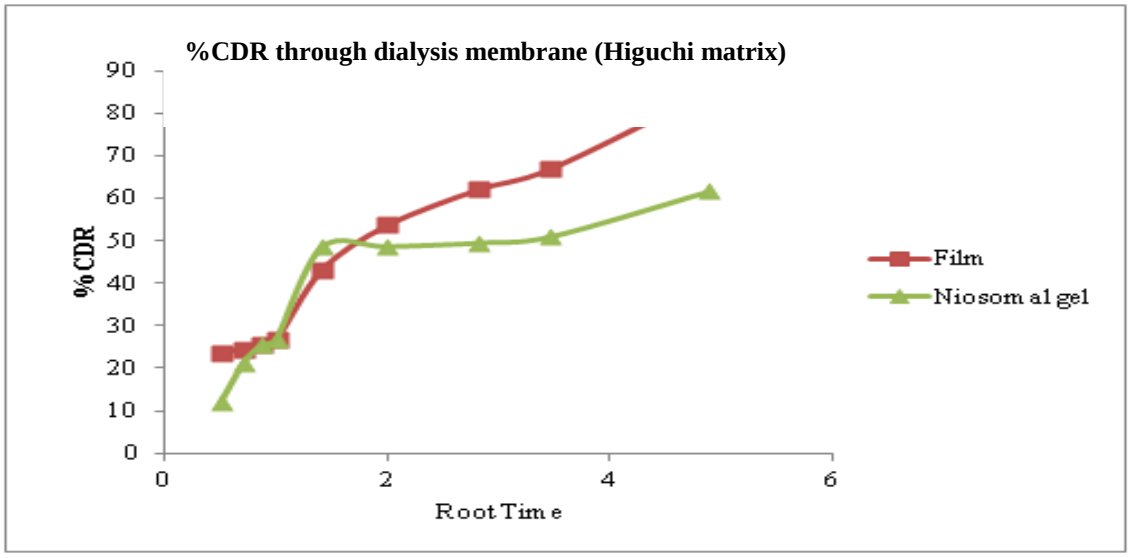

Fig. 14 Graphical representation of drug release profile of selected formulations (Higuchi Matrix)

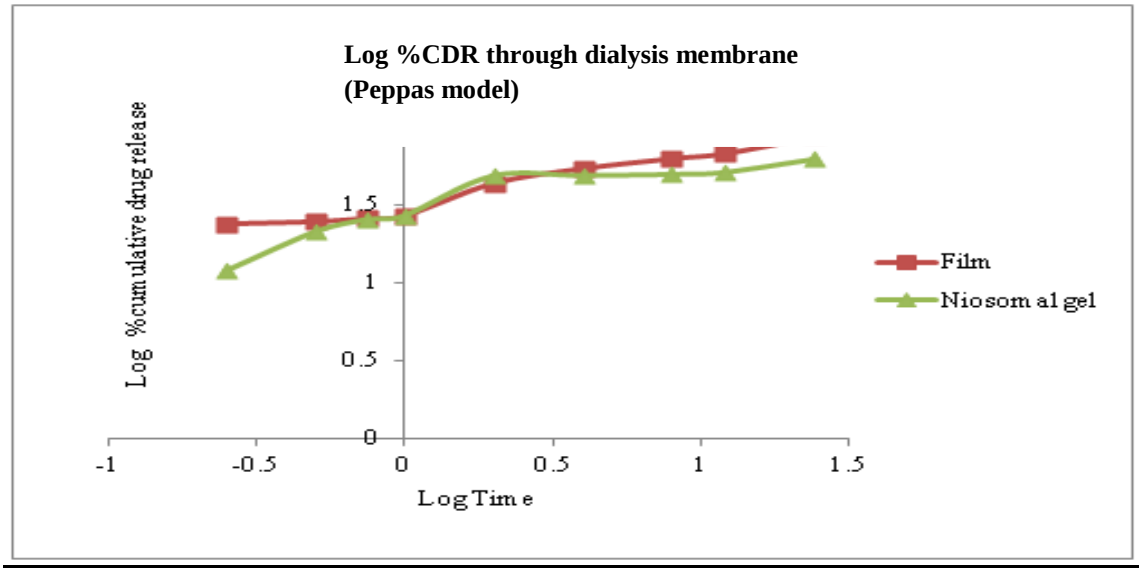

Fig. 15 Graphical representation of drug release profile of selected formulations (Peppas model)

IV. CONCLUSION

Different formulations of Aceclofenac i.e. polymeric matrix film and niosomes were formulated in the present study and compared for their formulation characteristics and *in vitro* and *ex vivo* drug release profile.

From the present experimental work it can be concluded that:

- As the hydrophilic polymer (PVP) concentration increased in the matrix film the drug release also increased.
- The non-ionic surfactant (span 60) along with cholesterol is a suitable carrier for preparing the ACF niosomes.
- As the non ionic surfactant (span 60) concentration increased the drug entrapment efficiency of the formulation also increased.
- Particle size analysis showed the niosomes sizes were in the range (225.9±0.02 to 438.3±0.02 nm).

- The niosomal formulation NF-3 showed high entrapment efficiency, good particle size and % CDR.

- The formulation with best results among film and niosomes (FF1 and NF3 respectively) were selected and subjected to further *in vitro* release studies through dialysis membrane and *ex vivo* release studies through rat skin (Niosomal gel of NF3 formulation).

- It was found that the film formulations released 70 to 80 % of the total drug within 24 hours of studies. The drug release kinetics for film formulation was found to be fit in higuchi model hence it is diffusion controlled.

- The aceclofenac would release at a slower and sustained rate from the niosomal gel. Hence, the niosomal gel showed better performance in the formulations used for diseases which required prolonged action of the drug (arthritis, osteoarthritis). The release of drug from niosomal gel found to follows Peppas kinetics model

  The order of drug permeation in different formulation was found to be more for Polymer matrix film than Niosomal gel. This revealed that prolonged drug release was observed during *in-vitro* diffusion study across the rat skin from the niosomal gel as compared to the film which may be due to slower diffusion of the drug into the skin and creation of reservoir effect for drug in the skin. The other component of the niosomes, that is, cholesterol and surfactant also deposit along with the drug into the skin thereby increasing drug retention capacity into the skin. Therefore NF3 formulation was found to have the potential for improving the transdermal delivery of aceclofenac.

  A successful polymeric matrix film and niosomes may be developed following long term pharmacokinetics and pharmacodynamic studies in laboratory animals and humans.

V. ACKNOWLEDGEMENT

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