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RESEARCH PAPER

Formulation and evaluation of transdermal gel of norfloxacin for the topical action

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ABSTRACT

The lipophilic nature of majority of newly developed drugs has resulting in poor bioavailability, and pharmacokinetic variations. The goal of this evaluation is to evaluate and report the current potential and future scope of gel formulation for becoming an effective delivery system for poorly water-soluble drugs. Gel consist two different systems in which drug containing nanoemulsion is incorporated into a gel base. Topical gel are transparent or translucent semisolid formulation and used for the localized drug delivery anywhere in the body through rectal, vaginal, ophthalmic and skin as topical route. Gel formulation provides better application property and stability in comparision of ointment and cream. Gel has emerged as one of the most interesting topical delivery system as it has dual release control system i.e. Hydrogel and nanoemulsion. Gel having rapidly penetrates and delivers active substance deeper and quicker. The use of gels can be considered well in analgesics and antifungal drugs. In recent year there has been great interest in the use of novel polymer with complex function such as emulsifiers and thickeners. The gelling capacity of this compound allows the formulation of stable emulsion and creams by decreasing surface and interfacial tension at the same time increasing the viscosity of aqueous phase. In spite of many advantage of gels a major limitation is in the delivery of hydrophobic drug. So to overcome this limitation an emulsion based approach is being used to that even a hydrophobic moiety can enjoy the unique property of gel.

Keywords: - *Transdermal Gel, Polymer, Antifungal, Topical*

INTRODUCTION

In pharmaceutical industry developing a controlled dosage form has become increasingly important. Therefore various forms of Novel drug delivery system such as Transdermal drug delivery systems, controlled release system, Transmucosal delivery system etc. has been developed [1-5]. Transdermal delivery has been emerged as a novel tool over injectables and oral routes as it increases the patient compliance and avoids the first pass hepatic metabolism [6-7]. In transdermal drug delivery system the drug is delivered in a controlled rate into systemic circulation through the skin. The intact skin is used as a port to administer a drug in transdermal gels but skin act as a barrier to ingress

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the material, it only allows a small material to penetrate over a period of time into systemic circulation [8-10]. The one way to deliver a sufficient amount of drug transdermally is in which the drug agent is applied to skin in a patch and another one is by incorporating a drug in a gel. From both patches and Transdermal gels medicament is delivered in a controlled diffusion mechanism [11-15].

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism, etc. However, drugs should possess several physio-chemical prerequisites such as shorter half-life, small molecular size, low dose etc. [16-18] to be a suitable candidate for Transdermal drug delivery system (TDDS) due to formidable barrier action of keratinized cells present in stratum corneum (SC) of skin. Many chemical and physical approaches have been applied to increase the efficacy of the material transfer across the intact skin which expands the range of drugs delivered [19-22]. These involve chemical and physical methods, based on two strategies: increasing skin permeability and providing driving force acting on the drug which can bypass stratum corneum [23-25]. Though chemical enhancers have achieved limited success in increasing the transdermal transport, they can be employed together with physical methods to give synergistic action which would improve the efficacy, safety and convenience of use and open up the benefits of the transdermal drug delivery technology to a much broader range of therapeutic areas [26-30].

A transdermal gel is local medication that is applied to and absorbed directly through the skin. Transdermal delivery can provide both local and systemic effects.

Factor affecting on Transdermal gel [31-35]

- pH of myofibrillar protein: These are strongly pH dependent. The myofibrillar protein, pH 5.3 required at the isoelectric point. The pH is affected on gel formulation for the myosin reached for these pH values are required pH6.
- Muscles types: Generally in human body there are three types of muscles visceral, cardiac and skeletal muscles. We study about red and white muscles there is required stronger gel formulation for the white muscles than the red muscles because the red muscles are thin as compare to the white muscles. Red muscles are lazy contraction. In the red muscles the heavy amount of myoglobin are responsible for red color. In the white muscles minimum amount of myoglobin are present. In the white muscles lactic acid are accumulated.
- Protein concentration: For the formulation of gel necessary or required the critical protein concentration. The amount of protein concentration is increase due to the increasing of hardness of gel.

- Temperature: Temperature is important factor for the gel formulation. Due to application at the pH 6 temperature required 60°C to 70°C for the inducing gelation of myosin. Temperature is also affected on the storage condition of the gel.
- Skin condition: Skin is the barrier layer of our body which protects us from external environment. For the therapeutic effect of gel should be need the cross the skin layer. Skin is consisting of three layer epidermis, dermis and hypodermis. Epidermis is responsible for the thin and thick skin. Thick skin has five layers asstratumcorneum, stratum spinosum, stratum granulosum, stratum lucidum and stratum basal, and in the thin layer absence of stratum lucidum.

METHOD OF PREPARATION OF NORFLOXACIN GEL

1% w/w NORFLOXACIN Transdermal gels were prepared by using different Concentrations of polymers such as Carbopol 940P and other polymers. The formulation data for the preparation of NORFLOXACIN Transdermal gels using Carbopol 940P. Accurately weighed amount of Polymers (Carbopol940P and other polymers) in four different ratios was placed in known amount of distilled water (Six different formulations were prepared using varying concentrations of Carbopol 940 P and other polymers). After complete dispersion, the polymer solution was kept in dark for 24 hours for complete swelling. Accurately weighed amount of NORFLOXACIN was dissolved in a specified quantity of suitable solvent. The drug solution was added slowly to the aqueous dispersion of polymer with the help of high speed stirrer (500 rpm) taking precaution that air did not entrap. Finally, the remaining ingredients were added to obtain a homogeneous dispersion of gel [36-40].

EVALUATION PARAMETERS OF NORFLOXACINGEL [40-53]

Physical appearance: The prepared Gel is checked visually for their color, homogeneity, consistency and phase separation.

pH Evaluation: pH evaluation is the important criteria especially for the topical formulation. The pH of gel should be between 5.8 – 6 to mimic the skin condition. If the pH of the prepared gel is acidic or basic, it may cause irritation to the patient. PH of the prepared gel was measured using digital pH meter by dipping the glass electrode into an gel. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Spreadability: Spreadability of gel is measured in terms of diameter of gel circle produced when gel is placed between two glass plates of definite weight. A weighed quantity (350 mg) of gel is taken on one glass plate and another glass plate is dropped from a distance of 5 cm. The diameter of the circle of spread gel is measured.

Extrudability Study [tube test]: It is calculated by the force required to extrude the gel from the tube. The method applied for determination of applied shear in the region of the rheogram corresponding to

a shear rate exceeding the yield value and exhibiting consequent plug flow. In this study gel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of gel in 10 seconds. For better extrudability, more quantity is extruded. For the measurement of extrudability, it is done in triplicate and the average values are calculated. The extrudability is then calculated by using the following formula.

Extrudability = weight applied to extrude gel from tube (in gm) / Area (in cm2).

Rheological Studies: Viscosity of gel is determined at 25°C using a cone and plate viscometer with spindle 52 and connected to a thermostatically controlled circulating water bath.

Swelling Index: It is determined by taking 1g of gel in a porous aluminum foil and mixed with 0.1N NaOH kept in a 50ml beaker. Then samples are withdrawn at different time intervals and kept for drying and it is reweighed. Swelling index is calculated as follows:

Swelling Index = {Wt Wo/Wo}100 Where,

(SW) % = Equilibrium percent swelling,

Wt = Weight of swollen gel after time 't' Wo = weight of gel at zero time

Drug Content Determination

Gel is mixed in a suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. From the standard equation by putting the absorbance value concentration and drug content can be obtained.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

Bioadhesive strength measurement

The modified method was used for the measurement of bioadhesive strength. The apparatus consist of two arm balance, both the ends are tied to glass plates using strings. One side contains single glass plate for keeping weight. The right and left pans were balanced by adding extra weight on the left hand pan. The balance was kept in this position for 5 mints.

Procedure: Accurately weighed 1g of gel was placed between these two slides containing hair less fresh rat skin pieces, extra weight from the left pan was removed to sandwitch the two pieces of glass and some pressure was applied to remove the presence of air. The balance was kept in the position for 5 min. weight was added slowly at 200mg/min to the left hand pan until the two glass slides got detached from each others. The weight required to detach the gel from the glass surface gives the measure of bioadhesive strength by using a formula,

Bioadhesive strength=weight required (in g) / area(cm2)

Skin Irritation Test (Patch Test): For this study gel is applied on the shaven skin of rat and its adverse effect like change in color, change in skin morphology are evaluated up to 24 hours. About 8

rats can be used for the study. Test passes if no irritation shown. If it fails the test is repeated with another 2 rats.

Microbiological assay: Microbiological assay was performed by using ditch plate technique. Previously prepared Sabouraud's agar dried plates were used. 3 grams of the gellified emulsion are placed in a ditch cut in plate. Freshly prepared culture loops are streaked across agar at a anglefrm the edge of the plate. After incubation for 18-24hrs at 25◦c, the fungal growth was observed and the percentage inhibition was measured as follows

% inhibition = L2 /L1× 100

In-vitro Release Studies: The in vitro drug release studies were carried out using a modified franz diffusion (FD) cell the formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer PH 7.4 was used as a donor and receptor compartment of the cell was maintained at 37c by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar bank set was run simultaneously as a control. sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amount of fresh dissolution media. Samples were analysed spectrophotometrically at 318nm and cumulative %drug release was calculated.

RESULTS AND DISCUSSIONS

The goal of the present investigation was to define Transdermal gels of NORFLOXACIN. Add up to twelve diverse NORFLOXACIN transdermal gels with various polymer proportions were readied. So as to choose the upgraded definition, different assessment parameters were checked and subjected to in-vitro dispersion examines and their discharge motor examination were watched. The improved detailing was additionally considered for ex-vivo saturation utilizing rodent stomach skin. Preformulation ponders Characterization of NORFLOXACIN:

The accompanying tests were performed by British Pharmacopeia.

Description: A white or relatively white powder Solubility: Methanol and Ethanol Melting Point: 296.149˚C from these tests it was affirmed that the example follows the monograph.

Similarity ponders the contradiction between the medication and excipients were considered by FTIR spectroscopy. The outcomes demonstrate that there was no substance inconsistency amongst tranquilize and excipients utilized as a part of the definition. The outcomes are appeared in [Fig 01-05]

Evaluation of Transdermal gels:

Clarity: Carbopol 940P gels were found to be sparkling and transparent, HPMC K4M gels were found to be translucent. All gels were free from presence of particles.

Homogeneity: All developed gels (F1-F12) showed good homogeneity with absence of lumps. The developed preparations were much clear and transparent.

Spreadability: The estimation of spreadability demonstrates that the gel is effectively spreadable by little measure of shear. In definitions F1 to F4, Spreadability of Carbopol 940P gel was in the range 18.75-27.39 g.cm/sec. In plans F5 to F8, Spreadability of HPMCK4M gel was in the range 20.06-24.27 g.cm/sec. In details F9 to F12, Spreadability of Na CMC was in the scope of 19.07-24.57 g.cm/sec, demonstrating Spreadability of Carbopol 940P containing NORFLOXACIN gel i.e. F4 was great i.e. 27.39 g. cm/sec when contrasted with HPMC K4M gel and Na CMC gel.

Extrudability: The expulsion of the gel from the tube is a critical amid its application and in tolerant acknowledgment. Gels with high consistency may not expel from tube while, low gooey gels may stream rapidly, and thus appropriate consistency is required keeping in mind the end goal to expel the gel from the tube. Extrudability of Carbopol 940P gel i.e. F4 detailing was observed to be Excellent when contrasted with different definitions.

Surface pH: The pH estimation of every single created definition of Carbopol gels (F1-F4) were in the scope of 5.71-6.27, HPMC gels (F5-F8) were in the scope of 6.45-6.82 and Na CMC gels (F9-F12) were in the scope of 5.65-6.91 which is well inside the points of confinement of skin pH i.e. 5.6-7.5. Subsequently, it was reasoned that every one of the plans couldn't deliver any neighborhood aggravation to the skin.

Viscosity Measurement: The Viscosity of the plans i.e. F1-F4 containing medication and Carbopol 940P were in the scope of 1,92,000-3,10,000 cps, while the plans i.e F5-F8 containing medication and HPMC K4M were in the scope of 1,36,000 – 1,47,000 cps, though details i.e F9-F12 containing medication and Sodium CMC were in the scope of 1,52,000-1,80,000 cps. From the outcomes it was discovered that the detailing F1 indicated most extreme thickness i.e. 3,20,000 cps and plan F8 indicated least thickness i.e. 1,36,000 cps.

Drug Content: The rate medicate substance of all readied gel definitions i.e. F1 to F12 were observed to be in the scope of 97.21±0.18 to 101.46±0.26%. The rate medicate substance of plans was observed to be inside as far as possible. Thus strategies received for gels plans were discovered appropriate.

In-vitro drug diffusion studies:

In-vitro tranquilize discharge investigation of various gel plans i.e. F1 to F12 were helped out through dialysis sac (cellophane film) and are plotted. The rate sedate discharge for the plans containing drug and carbopol 940P i.e. F1 to F4 were observed to be in the scope of 82.88% to 98.68% of every 6 hours. Among these details, plan F4 containing drug and carbopol 940P in the ratio1:2 indicated high level of medication discharge i.e. 98.68% out of 6 hours. The outcomes demonstrate that expansion in

the convergence of Carbopol 940p, builds the medication discharge. The rate tranquilizes discharge for the details containing medication and HPMC K4M i.e. F5-F8 were in the scope of 79.59 – 87.72% of every 6 hours. Among these, detailing F8 containing medication and HPMCK4M in the proportion 1:4 demonstrated most astounding level of medication discharge i.e. 87.72% out of 6 hours. From the above it was watched that expansion in the grouping of HPMC K4M, builds the medication discharge.

The rate sedate discharge for the plans containing medication and Na CMC i.e. F9-F12 were observed to be in the scope of 83.77 – 90.38% of every 6 hours. Among these, the plan F10 containing medication and Na-CMC in the proportion 1:1.5 demonstrated most noteworthy rate sedate arrival of medication discharge i.e. 90.38% out of 6 hours. From the above it was watched that expansion in the convergence of Na CMC builds the medication discharge. The examination of in-vitro sedate discharge thinks about was directed for the plans F4, F8 and F10. The outcomes are appeared in [Fig 07-10]. From the above outcome it is watched that the detailing F4 containing medication and Carbopol 940P in the proportion 1:2 demonstrated most elevated rate tranquilize discharge i.e. 98.68% out of 6 hours.

Drug release kinetics: In-vitro medicate discharge information of F1 to F12 were fitted to zero request, first request, Higuchi and Korsmeyer-Peppas conditions to discover the example of medication discharge. The outcomes are appeared in [Table 04]. In-vitro sedate discharge information for every one of the definitions F1 to F12 were subjected to discharge motor examination as indicated by Zero request,

First request, Higuchi and Korsemeyer-Peppas condition to find out the instrument of medication discharge. Among the zero-request and first-arrange, the R2 esteems were observed to be higher in zero-arrange. Along these lines, every one of the plans took after zero-arrange energy. Be that as it may, in the event of component of medication discharge, amongst Higuchi and Korsemeyer- Peppas condition, the R2 esteem were observed to be higher in Korsemeyer-Peppas condition and discharge example "n" esteem under 1 i.e. ($n > 0.5$).

This demonstrates every one of the details took after non-Fickian dissemination. Henceforth it was presumed that every one of the definitions took after zero-arrange medicate discharge with non-Fickian dispersion.

Ex-vivo permeation studies: It was presumed that the detailing F4 containing drug, carbopol 940P in the proportion 1:2, demonstrated great spreadability, extrudability and invitro medicate discharge. Based on above outcomes detailing F4 was contemplated for ex-vivo pervasion utilizing rodent stomach skin. The improved definition was broke down by HPLC strategy at 285nm for 6hrs discharge through rodent stomach skin. The motion was computed.

The aftereffects of medication pervasion from streamlined plan through the rodent stomach skin uncovered that NORFLOXACIN was discharged from the upgraded definition and pervade through the rodent stomach film and could penetrate through the human stomach layer. The medication penetration from F4 was gradual and 0.89gm of NORFLOXACIN could saturate through the skin film with a transition of 0.071 gm hr-1 cm-2.

Skin irritation test: In light of in-vitro dissemination think about plan F4 containing medication and Carbopol 940P in the proportion 1:2 was improved. Furthur, Skin bothering test was performed with streamlined definition F4 in white rabbits isolated in 3 gatherings. It was discovered that the gel F4 causes no bothering or erythema.

Stability Studies: Quickened steadiness examines was directed in best plan F4, as indicated by ICH rules i.e. 25˚±2˚C/60±5%RH for initial 30 days and 40˚±2˚C/75±5%RH upto 90 days. The outcomes show that there was no such a great amount of progress in appearance, pH, medicate content and in-vitro tranquilize discharge thinks about.

Table 1: Clarity, Homogeneity, Spreadability, Extrudability Parameters

Formulation code	Clarity	Homogeneity	Spreadability	Extrudability
F1	+	Satisfactory	18.70	+
F2	++	Good	19.88	++
F3	++	Good	22.50	++
F4	+++	Excellent	27.35	+++
F5	++	Good	20.01	++
F6	+++	Good	21.10	+++
F7	++	Excellent	23.60	++
F8	++	Excellent	22.21	++
F9	++	Good	19.38	++
F10	+++	Excellent	21.82	+++
F11	++	Good	24.51	++
F12	+++	Good	23.32	+++

Table 2: pH, Viscosity and Drug Content (%)

Formulation code	pH	Viscosity(cps)	Drug content(%)
F1	5.69±0.07	3,10,000	98.50±0.19
F2	5.81±0.16	1,90,000	97.23±0.12
F3	6.15±0.03	2,42,000	98.89±0.23
F4	6.24±0.04	3,14,000	101.01±0.21
F5	6.69±0.01	1,40,000	101.42±0.24
F6	6.41±0.08	1,44,000	98.95±0.22
F7	6.79±0.06	1,35,000	98.81±0.33
F8	6.65±0.02	1,34,000	99.90±0.14
F9	6.95±0.01	1,50,000	97.90±0.30
F10	6.68±0.08	1,58,000	98.04±0.48

F11	5.92±0.11	1,69,000	97.28±0.35
F12	5.70±0.13	1,75,000	99.10±0.15

Table 3: Drug release kinetics of all the formulations (F1 - F12)

Formulation code	Zero order	First order	Korsmeyer	Peppas	Higuchi
	R^2	R^2	R^2	R^2	R^2
F1	0.988	0.890	0.998	0.781	0.952
F2	0.992	0.874	0.999	0.782	0.954
F3	0.990	0.872	0.992	0.778	0.953
F4	0.994	0.940	0.996	0.785	0.954
F5	0.992	0.924	0.994	0.786	0.952
F6	0.989	0.906	0.996	0.786	0.953
F7	0.985	0.967	0.942	0.786	0.929
F8	0.989	0.965	0.975	0.808	0.940
F9	0.990	0.926	0.985	0.784	0.940
F10	0.985	0.979	0.982	0.775	0.949
F11	0.990	0.968	0.974	0.788	0.942
F12	0.988	0.972	0.964	0.792	0.938

Table 4: Stability studies of formulation F4

Formulation	Days	Temperature & Relative Humidity	Appearance	pH	Drug content	*In-vitro* drug release
F4	0	25º±2ºC/60±5% RH	Clear	6.24	101.2	98.64
F4	15	25º±2ºC/60±5% RH	Clear	6.22	101.0	98.58
F4	30	25º±2ºC/60±5% RH	Clear	6.18	99.7	98.52
F4	60	40º±2ºC/75±5% RH	Clear	6.17	99.6	98.36
F4	90	40º±2ºC/75±5% RH	Clear	6.16	99.4	98.22

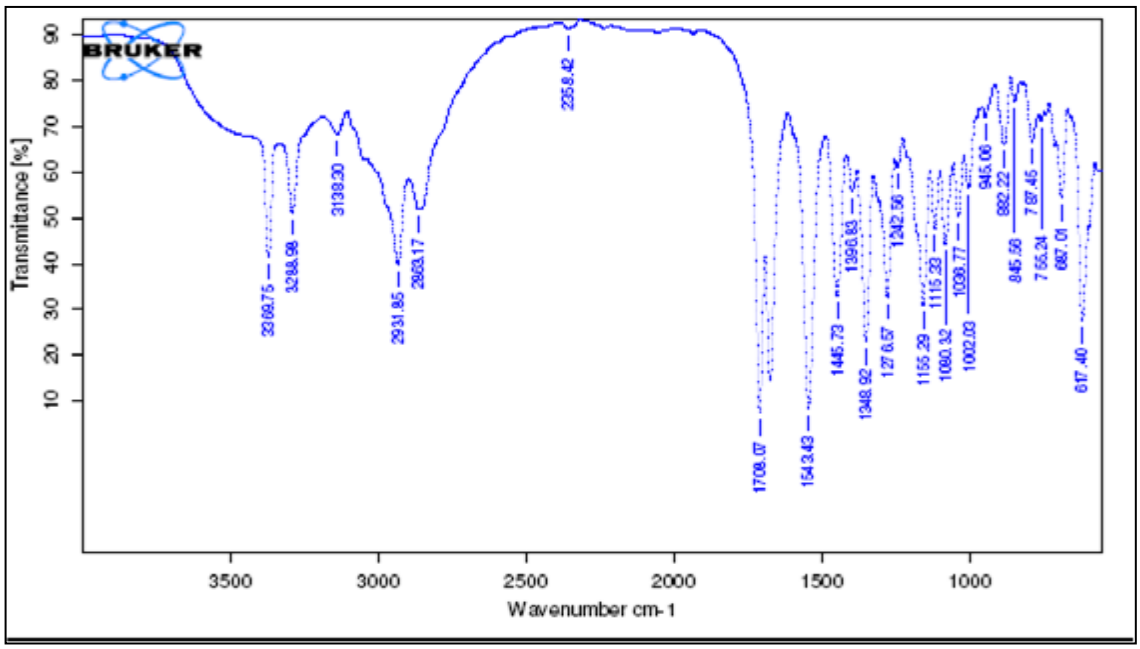

Fig 1: FTIR Spectra of NORFLOXACIN

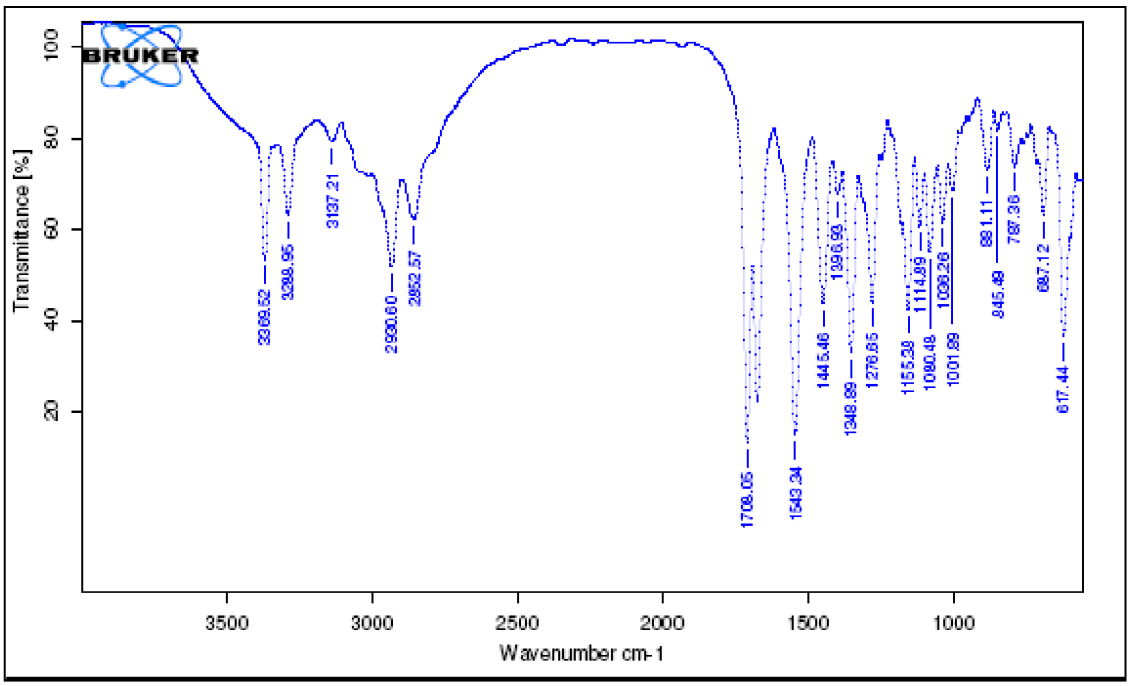

Fig 2: FTIR of Carbopol 940P

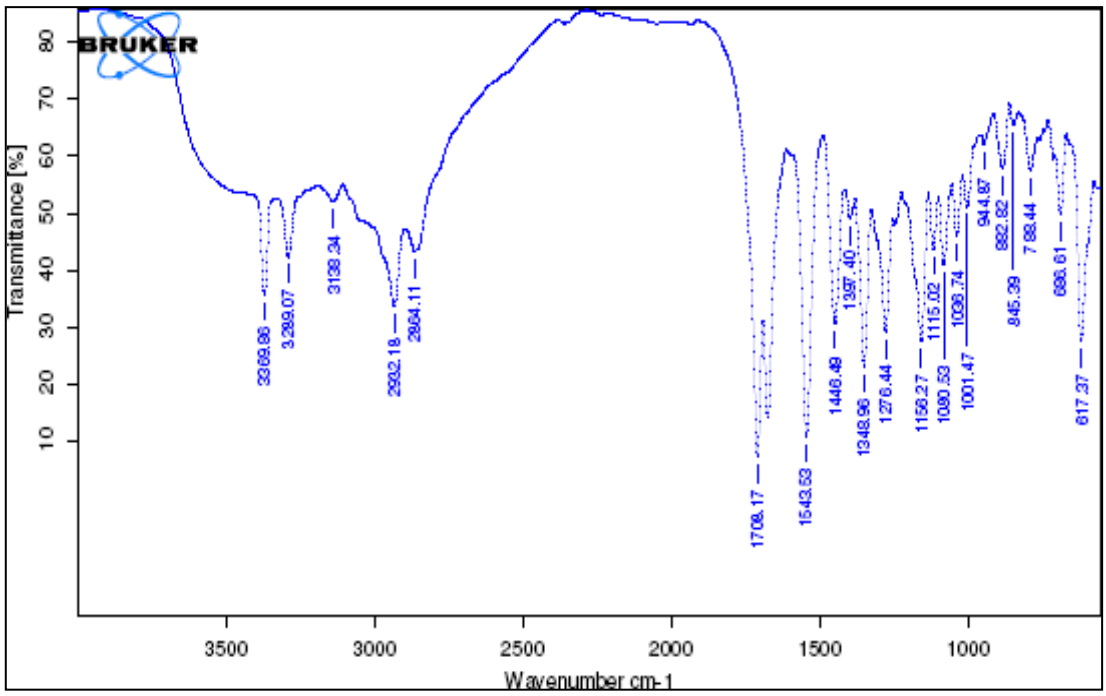

Fig 3: FTIR Spectra of HPMCK4M

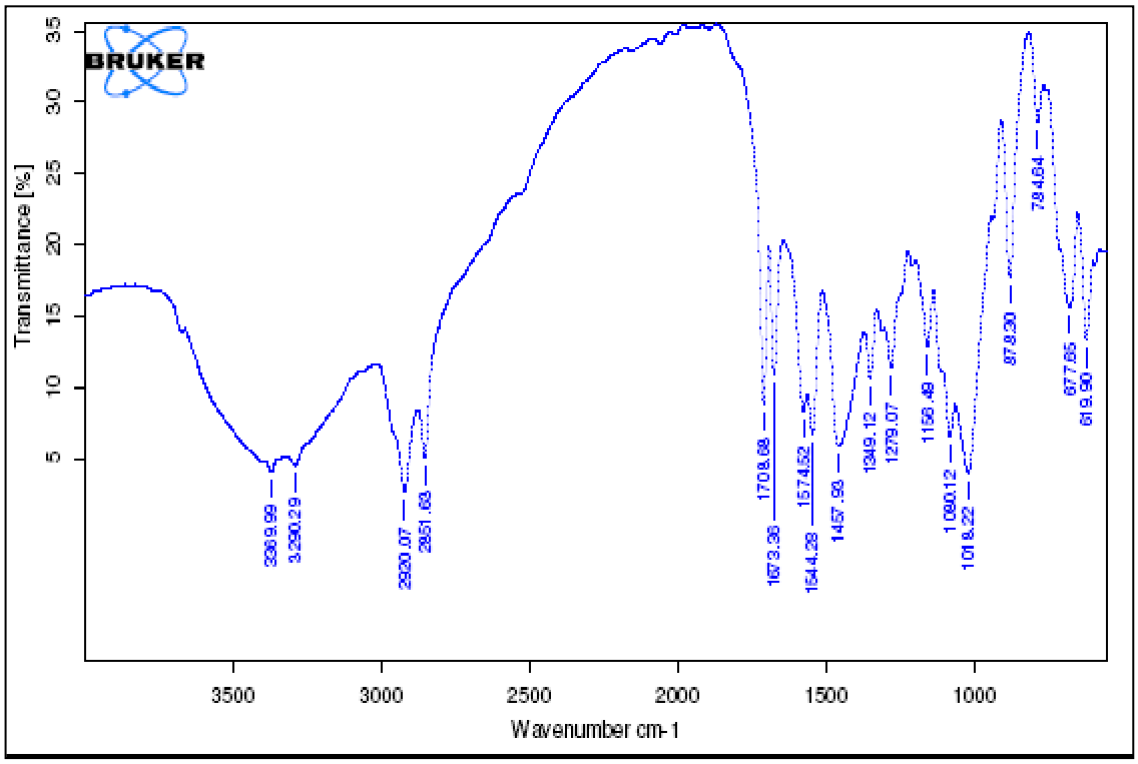

Fig 4: FTIR Spectra of Sodium CMC

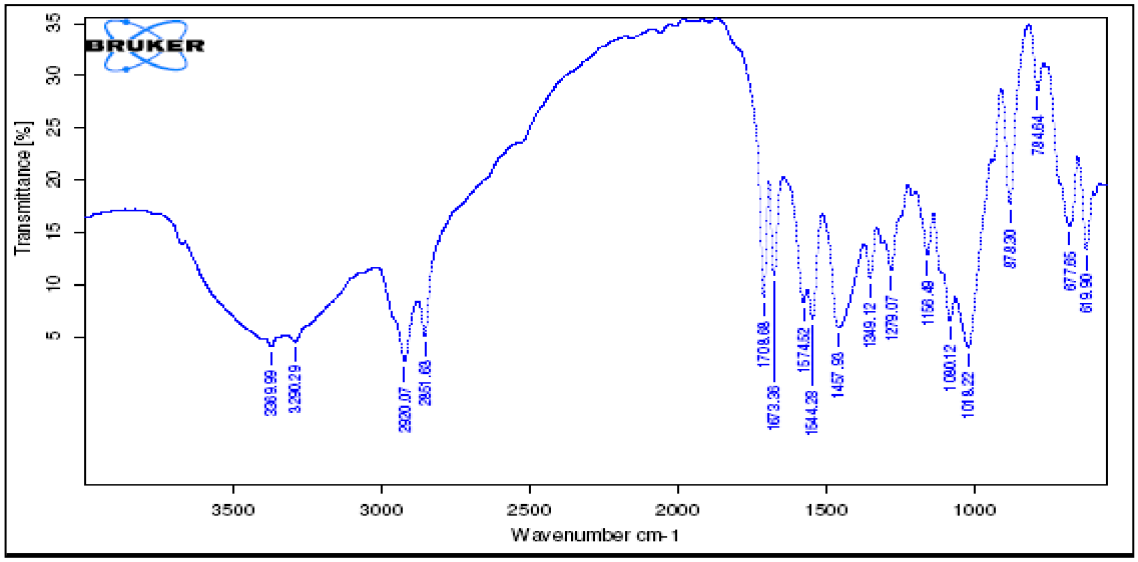

Fig 5: FTIR Spectra of NORFLOXACIN+ Carbopol 940P + HPMCK4M + Sodium CMC

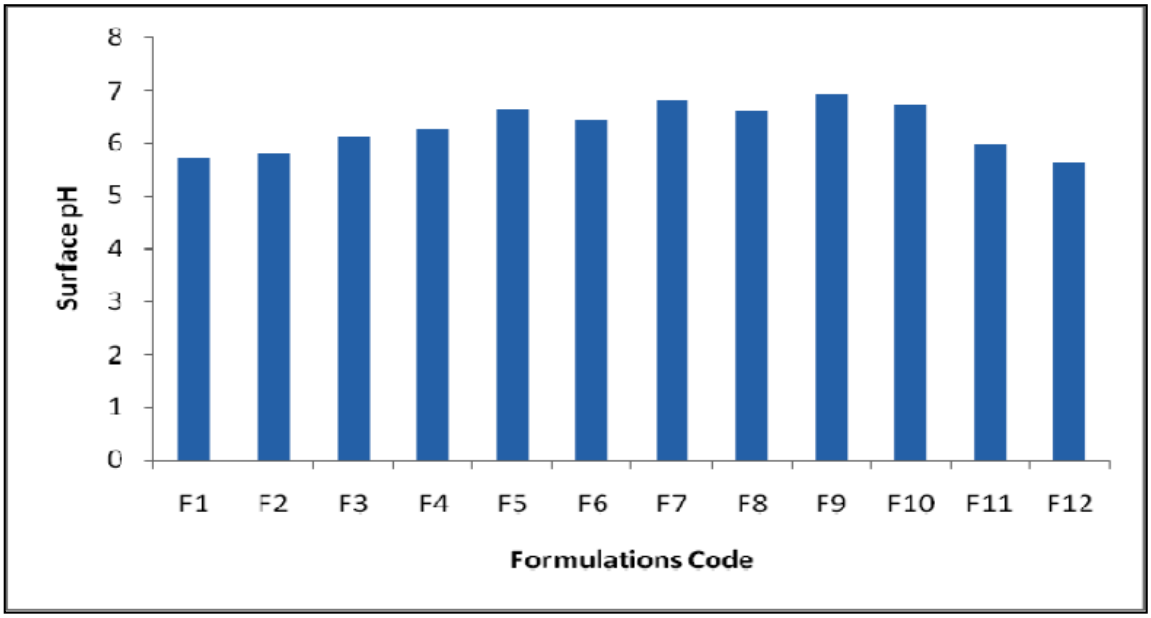

Fig 6: Surface pH of all the formulations (F1 to F12)

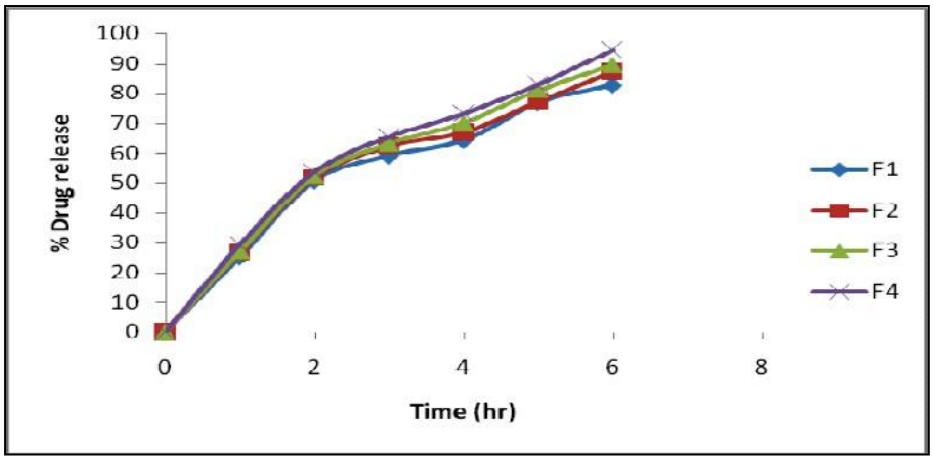

Fig 7: In-vitro drug release profile of formulations F1 to F4

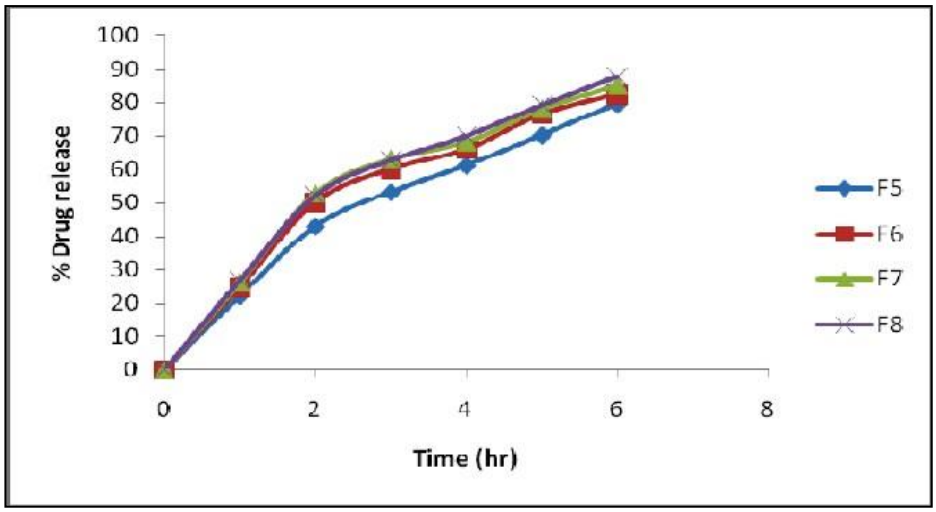

Fig 8: In vitro drug release profile of formulations F5 to F8

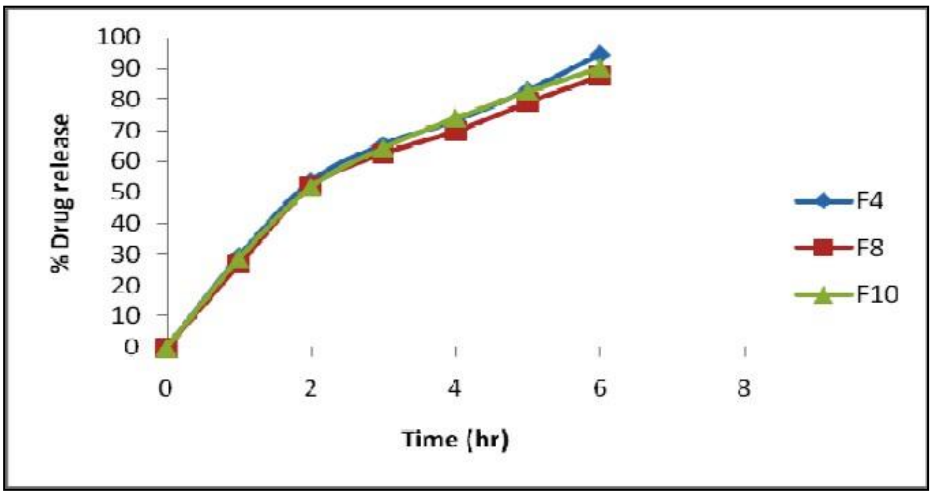

Fig 9: In-vitro drug release profile of formulations F9 to F12

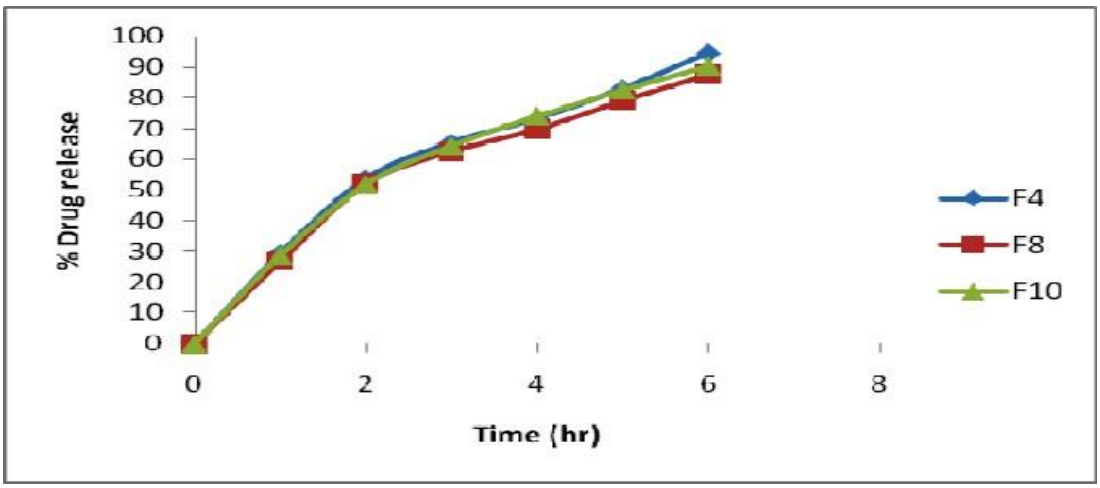

Fig 10: Comparison of In-vitro drug release profile of formulations F4, F8 and F10

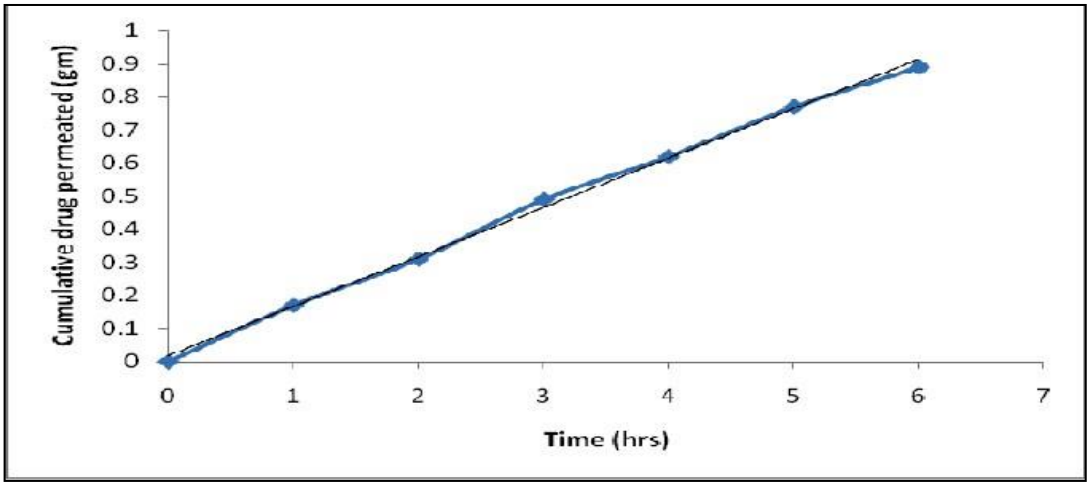

Fig 11: Ex-vivo permeation of optimized formulation F4

SUMMARY AND CONCLUSION:

It was observed that Carbopol 940P gel containing NORFLOXACIN in 1:2 ratio (F4) produced better spreadability and consistency as compared to other formulations. The developed F4 gel showed good homogeneity, suitable pH, no skin irritation and good stability. The maximum percentage of drug release was found to be 98.68% in 6 hours in formulation F4. The drug permeation from optimized formulation i.e. F4 was slow and steady and 0.89 gm of NORFLOXACIN could permeated through rat abdominal skin membrane with a flux 0.071 gm hr-1 cm-2 and could possibly permeate through human abdominal membrane. The Carbopol 940P forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system.

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