Research Article

Formulation and In-Vitro Evaluation of Ciprofloxacin Loaded Topical Emulgel

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ABSTRACT

Topical drug delivery systems have been used for centuries for the treatment of local skin disorders. One side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. On the other hand, topical delivery system increases the contact time and mean resident time of drug. The aim of the work is to develop & characterize an emulgel formulation of ciprofloxacin. Ciprofloxacin gellified emulsion formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed,then the pH was adjusted to 6 - 6.5 using Tri Ethanol Amine (TEA). Evaluation of the ciprofloxacin emulgel was carried out for Physical appearance, pH values , Spreadability, Rheological study, Drug content determination, In vitro release study, Skin irritation test, Accelerated stability studies and fitting of results into different kinetic equations was also carried out. It was observed that all the formulations were liquefied and diluted at the end of the experiments, indicating water diffusion through the membrane. In general, it was observed that the better release of the drug was seen from all formulations. The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics and drug release was by both diffusion and erosion. The accelerated stability studies were performed according to ICH guidelines for 3 months and the results were found to be stable in varying temperature. The results demonstrate that the release of the drug is dependent on viscosity of the polymer used.

Keywords: Ciprofloxacin, Carbopol, Emulgel.

INTRODUCTION

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The emulsion gels are hydrogels containing randomly distributed oil microdroplets. Topical drug delivery systems have been used for centuries for the treatment of local skin disorders, one side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. On the other hand, topical delivery system increases the contact time and mean resident time of drug at the applied site leading to an increase in local drug concentration while the pharmacological activity of Emulgel formulations may not change as rapidly as the solution form[1].

Drug absorption through the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient. For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and, as such, are formulated to provide prolonged local contact, with minimal systemic drug absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, skin emollients, and protectants. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying

time are other advantage of The topical drug delivery system is generally used where the others system of drug administration fails. Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body whilst preventing the ingress of noxious chemicals or microorganisms. It is also the largest organ of the human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m^2. Whilst such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self repairing barrier designed to keep 'the insides in and the outside out'.[3]

The aim of the work is to develop & characterize an emulgel formulation of ciprofloxacin. It was also proposed to investigate the influence of oil, surfactant & gelling agent concentration on the invitro release profile of drugs.

The main objective of utilising the topical drug delivery system is to bypass first pass metabolism. The study is also carried out for the avoidance of the risks and inconvenience of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes and gastric emptying time.

EXPERIMENT

Materials used

Ciprofloxacin sample was obtained from Micro Labs, Hosur and Ethanol, Tween20, Liquid paraffin, Propylene glycol were obtained from Loba chemie.

Methods

FORMULATION OF CIPROFLOXACIN EMULGEL:

Ciprofloxacin gellified emulsion formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed,then the pH are adjusted to 6 to 6.5 using Tri Ethanol Amine (TEA). The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propyl paraben was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70º- 80º C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature.

Evaluation of the Ciprofloxcin Emulgel [2, 3, 4, 5]

Physical appearance

The prepared ciprofloxacin emulgel formulations were inspected visually for their color, homogeneity, consistency and pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter.

Spreadability

One of the criteria for a Gellified Emulsion to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spread on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula.

S = M. L / T

Where M = wt. tied to upper slide
L = length of glass slides
T = time taken to separate the slides.

Extrudability study

In conducting the test, a closed collapsible tube containing above 20 grams of gel was pressed firmly at the crimped end and a clam was applied to prevent any rollback. The cap was removed and the microencapsulated gel was extrudes until the pressure was dissipated.

Rheological study

The viscosity of different Gellified emulsion formulations were determined at 37˚c using a brook field viscometer.

Drug content determination:
Drug concentration in Gellified emulsion was measured by spectrophotometer. Ciprofloxacin content in Gellified emulsion was measured by dissolving known quantity of gellified emulsion in solvent (methanol) by sonication. Absorbance was measured after suitable dissolution at 271 nm in UV/ visible spectrophotometer.

In vitro release study
Franz diffusion cell (with effective diffusion area 3.14cm² and 15.5ml cell volume) was used for the drug release studies. Gellified emulsion (200mg) was applied on to the surface of egg membrane .The egg membrane was clamped between donor and receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.01ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV visible spectrophotometer at 271 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time.

Skin irritation test
A 0.5 gm sample of the test formulation was then applied to each site (two sides per rabbit) By introduction under a double guaze layer to an area of skin approximately 1″ × 1″ (2.54 × 2.54 cm) square. After the Gellified emulsion was applied on the skin of rabbit, the animals were returned to the cages .After a 24 hrs exposure, the Gellified emulsion was removed. The test sites were wiped with tap water to remove any remaining residue.

Accelerated stability studies of Gellified Emulsion
Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°C, 45 ± 2°C and 60 ± 2°C for a period of 3 months. The samples were analyzed for drug content every two weeks by UV-Visible spectrophotometer at 271 nm. Stability study was also carried out by measuring the change in pH of gel at regular interval of time.

Fitting of results into Different kinetic Equation [6,7]
The results of in vitro release profile obtained for all the formulations were plotted in models of data treatment as follows:-
1. Zero - order kinetic model - cumulative % drug released Vs time.
2. First - order kinetic model - Log cumulative percent drug remaining Vs time.
3. Higuchi's model - cumulative percent drug released Vs square root of time.
4. Korsmeyer equation / peppa's model - Log cumulative percent drug released Vs log time.

RESULTS
Physical appearance
The prepared ciprofloxacin Gellified Emulsion formulations were white viscous creamy preparation with a smooth and considered acceptable to avoid the risk of irritation upon application to the skin.
Rheological studies
The measurement of viscosity of the prepared Gellified emulsion was done with Brookfield viscometer (Brookfield DV-E viscometer). The Gellified Emulsion were rotated at 10 (min.) and 100 (max.) rotations per minute with spindle 6. At each speed, the corresponding dial reading was noted. The viscosity of the formulations was obtained as indicated in figure – 1.
Drug content determination
1g of the prepared Gellified Emulsion was mixed with 100 ml of suitable solvent (methanol). Aliquots of different concentration were prepared by suitable dilution after sonication and filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve. The drug content of all Gellified formulations is given in figure-2.

In vitro Drug release

The in vitro release profiles of ciprofloxacin from its various Gellified Emulsion formulations are represented in figure. It was observed that all the formulation had become liquefied and diluted at the end of the experiments, indicating water diffusion through the membrane. In general, it can be observed from figures that the better release of the drug from all Gellified Emulsion formulation. From results of in vitro diffusion studies using Franz diffusion cell, it can be concluded that F2 had better sustained release than the other formulations. In order to understand the complex mechanism of drug release from the emulgel, the in vitro ciprofloxacin release data were fitted to Korsmeyer-peppa's release model and interpretation of release exponent values (n) enlightens us in understanding the release mechanism from the dosage form. The release exponent values thus obtained were from 0.50 to 0.79.Based on these values we can say that the formulation exhibited non-fickian transport.The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear (r>0.9291). The formulations showed higher R^2 values for zero order plot indicating that drug release followed zero order kinetics and drug release from these emulgels were by both diffusion and erosion.

Skin Irritation Test

The primary irritation index of the sample was calculated to be 0.00; No irritation was observed on the skin of the rabbit.

Accelerated stability studies

The accelerated stability studies were performed according to ICH guidelines for 3 months and the results were found to be stable in varying temperature.

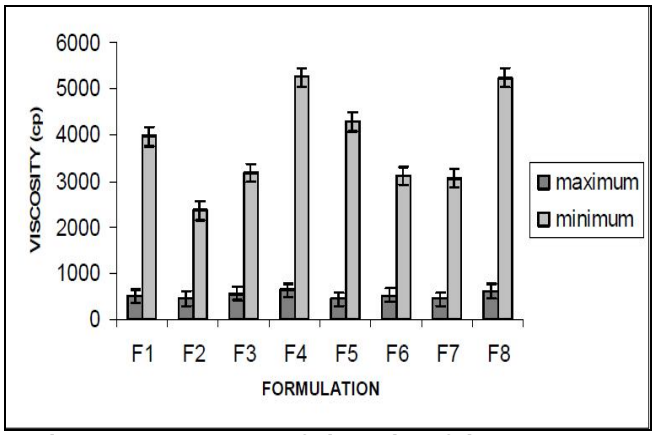

Fig. 1: Measurement of viscosity of the prepared gellified emulsion

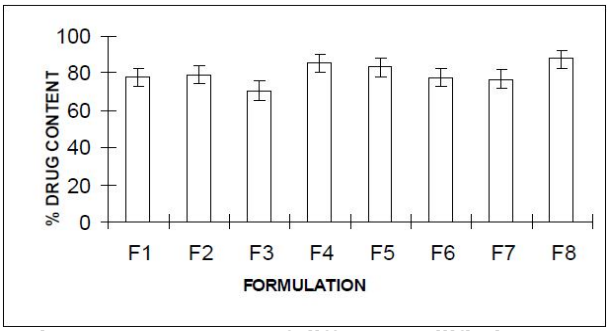

Fig. 2: Drug content of different gellified formulations

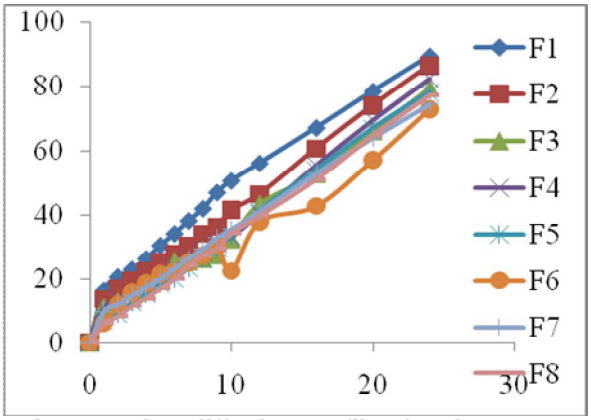

Fig. 3: In vitro diffusion profile of various formulations

Table I: Composition of various emulgel formulations

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Ciprofloxacin	1	1	1	1	1	1	1	1
Ethanol	2	2	2	2	2	2	2	2
Tween 20	1.5	1.5	1.5	2.5	2.5	2.5	2.5	2.5
Liquid paraffin	4	4	2	2	4	4	4	4
Propylene glycol	5	5	5	5	5	5	5	5
Carbopol 934	0.25	0.50	0.25	1	1.25	1.5	1.75	2.00
water	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10ml	10ml

Table II: In vitro diffusion profile of various formulations

Time (hrs)	Cumulative % of Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.37	13.70	11.30	10.91	6.810	6.084	9.826	6.055
2	20.63	16.78	13.01	13.67	9.225	12.03	11.99	8.301
3	23.02	19.49	16.19	15.84	12.66	15.65	14.75	11.59
4	26.34	22.43	18.44	18.25	15.43	18.54	17.34	14.04
5	30.51	25.48	20.66	20.44	18.60	21.44	19.96	17.05
6	34.19	27.79	25.57	23.38	20.02	22.14	23.11	19.98
7	38.21	30.42	25.44	26.38	23.43	25.22	26.48	24.07
8	42.04	34.22	26.22	28.48	26.38	27.31	29.31	27.35
9	47.10	36.31	27.42	30.99	29.60	30.39	32.90	29.45
10	50.75	41.53	32.37	33.11	33.58	22.36	35.47	34.32
12	56.24	46.58	43.50	40.32	41.46	37.85	41.12	39.79
16	67.21	60.80	52.81	55.48	54.14	42.73	52.92	51.25
20	78.52	74.10	66.08	69.38	67.03	57.10	63.98	64.90
24	89.47	86.52	79.52	82.21	78.18	72.85	74.29	77.38

Table III: Kinetic Profile of various formulations

F. code	Zero-order			First-order		Higuchi		Korse Meyer Peppa's		Possible mechanism Of drug release
	n	R^2	Release Rate constant	n	R^2	n	R^2	n	R^2	
F1	3.4789	0.9526	3.4789	0.0351	0.9505	18.168	0.9918	0.5277	0.9923	Zero-order, Non-fickian
F2	3.3586	0.9897	3.3586	0.0304	0.9362	17.128	0.9473	0.6022	0.9516	Zero-order, Non-fickian
F3	3.0687	0.9871	3.0687	0.0243	0.9358	15.551	0.917	0.635	0.9266	Zero-order, Non-fickian
F4	3.1859	0.9913	3.1859	0.0264	0.9259	16.132	0.9183	0.652	0.9405	Zero-order, Non-fickian
F5	3.2134	0.9977	3.2134	0.0249	0.9559	16.46	0.9318	0.7954	0.9776	Zero-order, Non-fickian
F6	2.7647	0.9821	2.7647	0.0196	0.9503	14.313	0.9547	0.7121	0.9866	Zero-order, Non-fickian
F7	2.7557	0.9951	2.7557	0.0189	0.9637	14.217	0.9465	0.8063	0.9938	Zero-order, Non-fickian
F8	2.8091	0.9987	2.8091	0.0189	0.9708	14.528	0.9416	0.9443	0.9969	Zero-order, Non-fickian

CONCLUSION

The present study reports for the development of ciprofloxacin emulgel for topical release of the drug. The results demonstrate that the release of the drug is dependent on viscosity of the polymer used. It can be conclusively stated that the ciprofloxacin emulgel formulation appears to be the promising system for the topical delivery of ciprofloxacin to avoid the disturbances of the conventional routes of administration.

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