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FORMULATION AND DEVELOPMENT OF FLURBIPROFEN CONTAINING FILM FORMING GEL

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ABSTRACT

The purpose of present research work was to develop a Film Forming gel formulation of flurbiprofen using carbopol 934 as a gelling agent for topical delivery with the aim to avoid hepatic first pass metabolism, improve stability of emulsion, reduce dosage regimen and enhance residence time in the treatment of Rheumatoid arthritis. Film Forming gels have emerged as one of the most interesting topical drug delivery systems as it has dual release control i.e. Film and gel. The developed gels were evaluated for their physicochemical properties like color, homogeneity, consistency, spreadability, pH value, rheological behaviour, drug content, drug release and stability. All the prepared film forming gels showed satisfactory physicochemical properties like color, homogeneity, consistency, spreadability, and pH value. The drug release was found to be higher for optimized formulation as compared to the other prepared formulations. The highest drug content was observed with F2, i.e; 98.66%. The drug releases from all the gels were found to follow diffusion-controlled mechanism. Stability studies indicated that the physical appearance, rheological properties, spreadability, drug content in all the prepared gels remained unchanged upon storage for 3 months.

KEYWORDS: Flurbiprofen, Carbapol 934, Rheumatoid arthritis, Film formation, gel formulation.

INTRODUCTION

Film Forming gels which on application forms a thin, transparent film on skin surface, which are gelled by mixing with a gelling agent. They have a high patient acceptability since they possess the previously mentioned advantages of both film and gels. Therefore, they have

been recently used as vehicles to deliver various drugs to the skin. Film Forming gel is stable one and better vehicle for hydrophobic or water insoluble drugs. Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID). Flurbiprofen works by reducing hormones that cause inflammation and pain in the body. Flurbiprofen inhibits the activity of both COX-1 and -2. Flurbiproen is increasingly administered by topical route may increase the bioavailability. Flurbiproen is insoluble in water so because of its hydrophobicity, cosolvent can used. Gel is having good absorption property along with greaseless, easily spreadability, easily removable, nonstaining and emollient but major limitation is delivering hydrophobic drug. The aim of present work was to develop a film forming gel. formulation of Flurbiprofen by using carbopol as a gelling agent. Emulgel has dual release mechanism due to emulsion & gel.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disorder that can affect more than just your joints. In some people, the condition also can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels.

An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks your own body's tissues. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity. The inflammation associated with rheumatoid arthritis is what can damage other parts of the body as well. While new types of medications have improved treatment options dramatically, severe rheumatoid arthritis can still cause physical disabilities.

Sustained release delivery systems with features of both semisolid formulations and patches may be employed here. The concept of film forming formulations is very recent. Film forming formulations may be solutions, gels or emulsions. Film forming formulations are defined as non-solid dosage forms that produce a substantial film in situ after application on the skin or any other body surface. Such compositions can either be liquids or semisolids with a film forming polymer as basic material for the matrix. The formed film is sufficiently substantial to provide a sustained drug release to the skin.

Very few examples of film forming gel formulations have been reported in literature. BeeGentleTM and GELNIQUE are commercially available film forming gel formulations.

In this study a dermal gel containing Flurbiprofen was prepared using the film forming polymer, Carbopol and gelling agent, Hydroxypropyl methyl cellulose (HPMC). HPMC also played the role of a secondary film forming polymer. Polyethylen Glycol (PEG) was used as a plasticizer.

MATERIAL AND METHOD

Flurbiprofen (FDC Pvt. Ltd, Mumbai), Carbapol 934 (CDH(P)Ltd. Mumbai), Polyethyline Glycol (SD fine chem. Ltd.), Hydroxypropyl methyl cellulose (SD fine chem. Ltd.),Glycerol (MERCK specialitiesPvt Ltd) Isopropyl alcohol (Macleods Pharmaceuticals, Baddi).Tween 80 (SD fine chem. Ltd)

Formulation of Flurbiprofen Film forming gel

Appropriate quantity of carbopol 934was soaked in water for a period of 2 hours. Carbopol was then neutralized with triethanolamine (TEA) with stirring. Then specified amount of drug was dissolved in appropriate and preweighted amounts of polyethylene glycol, Glycerol and IPA. Solvent blend was transferred to carbopol container and agitated for additional 20 min. The dispersion was then allowed to hydrate and swell for 60 min, finally adjusted the pH with 98% TEA until the desired pH value was approximately reached (6.8-7). During pH adjustment, the mixture was stirred gently with a spatula until homogeneous gel was formed.andfinaly there is addition of tween 80 and methyl and propyl paraben in adequate amount with constant stirring. All the samples were allowed to equilibrate for at least 24 hours at room temperature prior to performing rheological measurements.

METHOD OF PREPARATION

STEP1: Formulation of gel base.

STEP2: Formulation of Drug phase.

STEP3: Incorporation of Drug phase into gel base with continuous stirring

The flow chart of Film forming gel preparation is shown in figure 1.

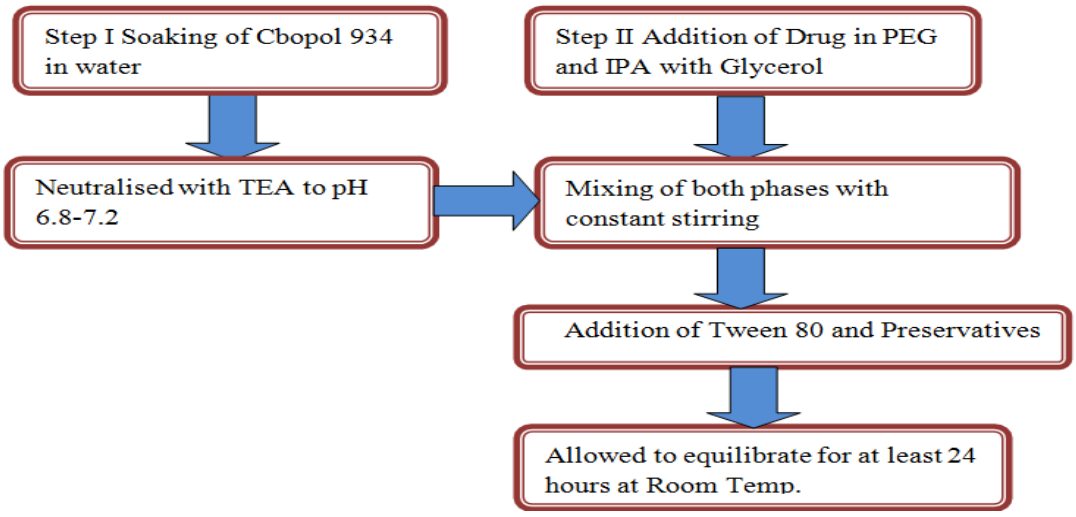


Fig.No.1: flow chart of Film forming gel preparation.

RESULT AND DISCUSSION

Formulation Design

Ingredients	Formulation			
	F1	F2	F3	F4
Flurbiprofen (%w/v)	1.0	1.0	1.0	1.0
Carbapol 934 (%w/v)	1.0	1.0	1.0	1.0
HydroxyPropylMethylCellulose(%w/v)	0.5	0.5	1.0	1.0
Polyethylene Glycol (%w/v)	1.0	1.0	1.0	1.0
Isopropyle alcohol(%w/v)	1.0	1.0	1.0	1.0
Glycerol (%w/v)	0.25	0.25	0.5	0.5
Tween 80(%w/v)	00	0.25	0.4	0.5
Propyl parben(%w/v)	0.01	0.01	0.01	0.01
Trethanolamine(%w/v)	q.s	q.s	q.s	q.s
Purified Water(ml)	100	100	100	100

Analytical Profile

The sample of Flurbiprofen procured for study was identified by Infrared spectrum.

Compatibility studies

From the spectra of pure drug and the combination of drug with excipients, it was observed that the entire characteristic peaks of were present in the combination spectrum, thus indicating compatibility of the drug and excipients. On the basis of IR spectra of the pure drug and in combination with the excipients are shown the compatibility.

1) IR Spectra of Flurbiprofen (Plain drug)

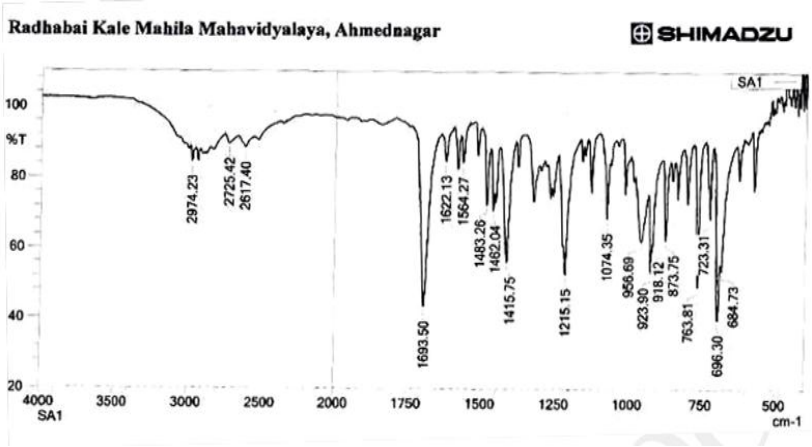
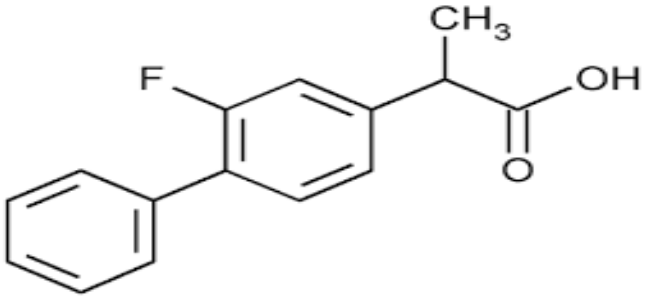


Fig. No.2 IR spectrum of (2RS)-2-(2-Fluorobiphenyl-4-yl) propanoic acid.



Flurbiprofen

2) IR Spectra of Formulation (FIFOGE)

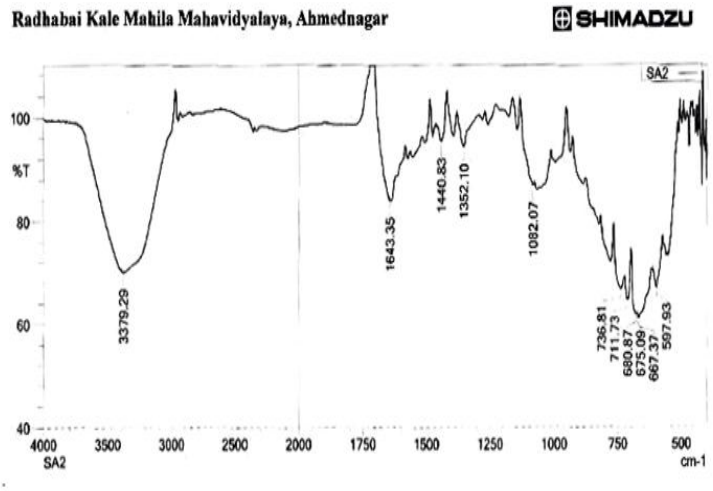


Fig. No.3 IR spectrum of Flurbiprofen with Polymer.

Determination of analytical wavelength

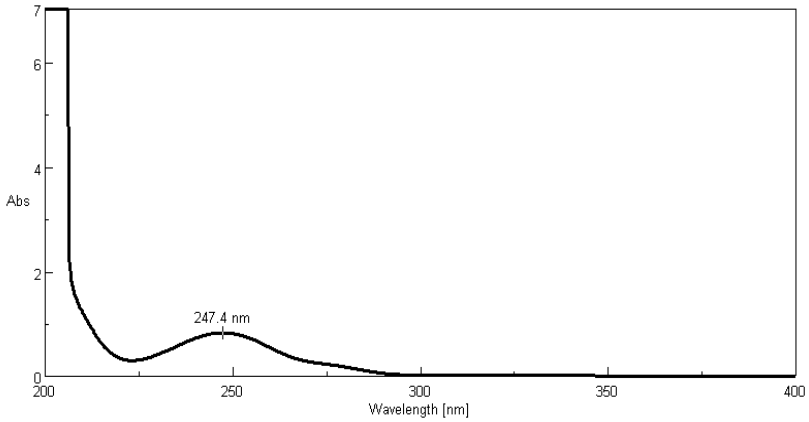


Figure 4: U.V. Spectrum of Flurbiprofen.

Calibration Curve of Flurbiprofen: The standard calibration curve of Flurbiprofen was obtained by plotting Absorbance vs. Concentration. Table shows the absorbance values of Flurbiprofen. The standard curve is shown in figure. The standard calibration curve shows correlation coefficient of 0.998. The curve was found to be linear in the concentration range of 5-30g/ml (Beer's range) at 247.4nm. The calculations of drug content, in vitro dissolution study were based on this calibration curve.

Table. No. 2: Analytical data for calibration curve of Flurbiprofen.

Sr. No.	Concentration	Absorbance
1.	5	0.1212
2.	10	0.5951
3.	15	1.0862
4.	20	1.6467
5.	25	2.2632
6	30	2.8053

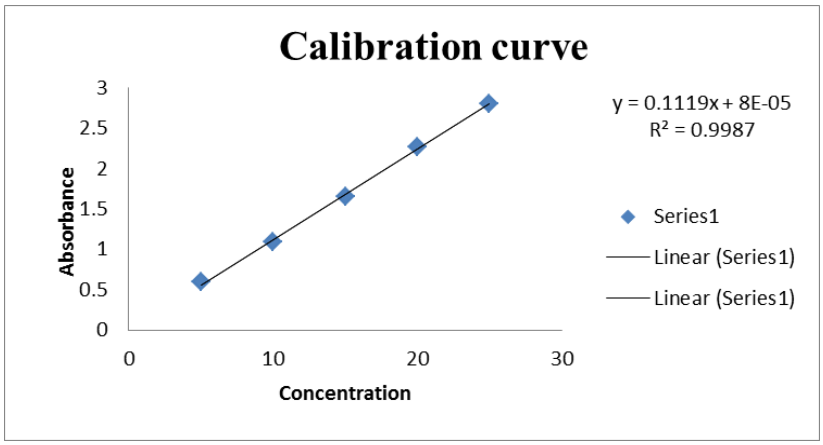


Fig. No. 5: Calibration curve of Flurbiprofen in Phosphate buffer (Ph 7.4) and 37 °C.

Melting point determination

Melting point of Flurbiprofen was found to be 115˚C as reported in literature, thus indicating purity of sample.

Evaluation of gels

Physicochemical properties: Formulations were subjected to evaluation of physical parameters like appearance, pH Spreadability consistency, Homogeneity,

Table. no.3: Each values of evaluation parameters of developed FIFOG.

Batch No.	pH	Spreadability (g.cm/sec)	Consistency (60 sec)	Homogeneity
F1	6.8	6.0	5mm	Good
F2	6.8	6.5	5mm	Good
F3	6.8	7.0	5mm	Good
F4	6.8	6.5	5mm	Good

Drug Content: The content uniformity was performed for all the four formulations and results are shown in (Table No 4). Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the gel was found between 96.62 to 98.66% of Flurbiprofen.

Table. no.4: Percentage Drug contents of developed FIFOG.

Formulation No.	F1	F2	F3	F4
%Drug content	96.62 ±0.305	98.66 ±0.532	97.83 ±0.550	98.15 ±0.372

Rheological studies: Viscosity was measured by using Brookfield Viscometer LVDV II+ model. Gels were placed under the viscometer to determine the viscosity of the formulation. Gels were placed under the viscometer using S 64 spindle to determine the viscosity of the formulation. The viscosity was determined at 10 RPM and the corresponding viscosity and torque were noted in Table no.5.

Table. 5: Viscosity details of Formulation.

Sr. No.	Percentage Torque at 10 Rpm	Viscosity (cps)
F1	29.1	19961
F2	29.9	19900
F3	29.7	19994
F4	28.9	20012

Swelling Index and Extrudability study: Increasing Drug: polymer ratio resulted in less swellability which can be justified by thickness increase and less water accessibility. The

results for Extrudability are shown in the (Table 6). Carbopol gave good extrudability. The Extrudability of the gel was found between 15.95 to 19.97% of Flurbiprofen.

Table. 6: Swelling Index And Extrudability details of Formulation.

Formulation No.	F1	F2	F3	F4
Swelling index (%)	17.5	18.9	28.5	26.7
Extrudability	15.95	16.49	16.54	16.97

***In–vitro* Drug Diffusion Study:** From these data we have found that the prepared FIFOG releases drug over a period of 2 hrs. Table 7 shows the data for the in-vitro drug diffusion study of prepared topical gel. Figure 4 shows the graphical representation of in-vitro drug diffusion study of topical gel. Formulations with more Tween 80 i.e. Permeation enhancer had more Diffusion, gel containing Carbopol 934 and 0.5% tween show better spreadability, viscosity and consistency as compared to other formulations. The F4 (Carbopol 934 gel with 0.5% tween) show good pH, homogeneity and *in vitro* release.

Table. 7: *In vitro* Drug Diffusion Study (Cumulative %Release).

Time(min)	Formulation code			
	F1	F2	F3	F4
0	0	0	0	0
10	6.29	7.66	8.28	8.9
20	15.1	16.8	19.72	21.88
30	27	31.09	31.72	37.83
60	44.27	49.84	50.34	58.13
90	64.06	70.14	74.48	81.91
120	87.48	93.61	100.54	107.06

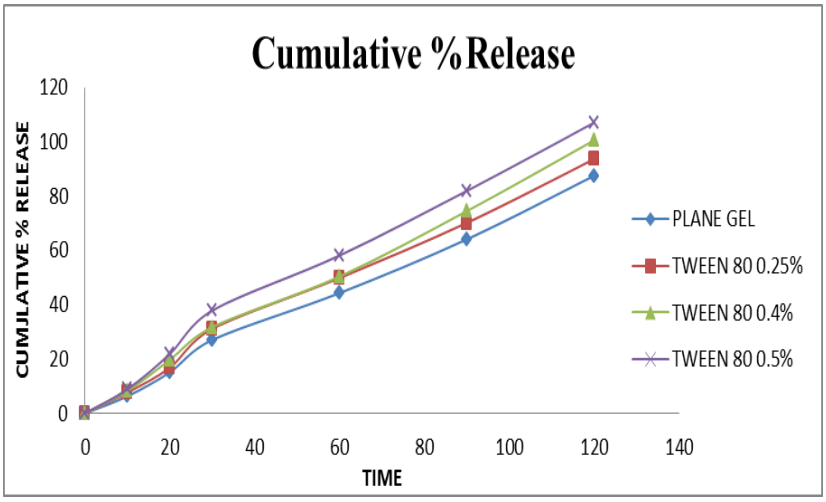


Fig. No. 6: *In–vitro* Drug Diffusion Study of Film forming Gel of Flurbiprofen.

Accelerated Stability Studies of the Optimized Formulation

The samples (in triplicate) of best formulation kept sealed and exposed to controlled temperature (40±2 °C) and relative humidity (75±5%) for a period of 45 days in stability chambers (Thermo lab Scientific Equipment Pvt. Ltd.). After 30 and 45 days, samples were taken out and analyzed for the following tests.

Table. 8: Stability study of various kind prepared gel.

Batches	Months	Appearance	pH	Drug Content (%)
F1	0	Clear	6.8	96.62
	1	Clear	6.8	96.50
	3	Clear	6.8	96.30
F2	0	Clear	6.8	98.66
	1	Clear	6.8	98.57
	3	Clear	6.7	98.52
F3	0	Clear	6.8	97.83
	1	Clear	6.7	97.78
	3	Clear	6.7	97.75
F4	0	Clear	6.8	98.15
	1	Clear	6.8	98.00
	3	Clear	6.8	98.01

CONCLUSION

Film forming gel proves to effective dosage form for the topical delivery of NSAIDs in the initial stages, as it can bypass the side effects related to the NSAIDs like gastric ulceration and bleeding and can provide effective topical release of the NSAID. Also it remains adhered to the effected part for a longer period without getting rubbed off. It provides sustained effect and better pain relief than the conventional gels and frequent reapplication is not required. From the results it can be concluded that Flurbiprofen was successfully formulated as Film forming gel using carbopol 934 and HPMC. FIFOGE concept can change the treatment therapy of various diseases and provide a broad platform for young scientist and researchers in this field of film forming gels.

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