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[Research article]

Fabrication and evaluation of a stable flurbiprofen hydrogel

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ABSTRACT

The purpose of the study was to prepare a stable 6% Flurbiprofen hydrogel. Oral Flurbiprofen generates several side effects; hence hydrogel was prepared to reduce these side effects in the present study. Gastrointestinal side effects such as bleeding, ulceration, and perforation of the stomach or intestines are commonly seen when the drug is administered orally. In this research, a hydrogel was formulated whereby flurbiprofen was the active ingredient, using a thickening agent (Carbopol) and distilled water (solvent). The finished formulation gives a white color hydrogel. Stability studies were performed at different accelerated conditions, i.e. 2-40^{o}C (Cool room), 250C (Room temperature) and 400C (Oven) for 28 days to predict the stability of formulations. Different parameters, namely pH, liquefaction, color, phase separation and effect of centrifugation (Simulating gravity) were determined during stability studies. There were no changes in liquefaction, color, phase separation and centrifugation in the formulation stored at 2-40^{o}C (Cool room), 250^{o}C (Room temperature) and 400^{o}C (Oven) up to 28 days. Based on one-way ANOVA test, the changes in pH values of the sample was not significant at different levels of time and temperature ($p > 0.05$). The mean pH value of the sample at different storage conditions was not far from the initial value of the studies, which is pH 5.5. The drug content of Flurbiprofen hydrogel was found to be 76.3% of Flurbiprofen. The Hydrogel released 79.46% of the drug content by 8 hours. Overall, this indicates that the formulation was stable and can be used for the topical dosage form.

Keywords: Hydrogel, Flurbiprofen, Carbopol, Distilled water and Stability.

INTRODUCTION

Flurbiprofen, a nonsteroidal anti-inflammatory drug, is frequently prescribed to treat gout, musculoskeletal disorders, rheumatic diseases, post-operative pain, dysmenorrhoea and migraine. Oral administration of Flurbiprofen is associated with severe gastrointestinal adverse events including abdominal discomfort, constipation, diarrhea, dyspepsia, nausea and vomiting (Rang HP *et al*., 2007). Moreover, it requires frequent dosing due to its short elimination half-life of 3.9 hrs. (Heyneman CA *et al*., 2000).

Transdermal route of drug delivery has received increasing attention due to the advantages of avoidance of hepatic first-pass metabolism thereby reducing the dose, easier and convenient administration for patients, possibility of immediate withdrawal of treatment, and potential of long-term controlled release with steady-state

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plasma drug levels and ultimately improving the patient's compliance (Barry BW, 2007).

Topical drug delivery offers several advantages over conventional dosage forms. The topical administration is to be absorbed by the drug molecule to be pass through the biological membrane is a limiting factor of lipid solubility and molecular size (Aiazuddinm, 2010). The topically used gels have several characteristics like sol-gel transition, non greasy, easily washable, stable and inert (Klich, 1992; Patel *et al*., 2011). Permeability coefficient of the drug is higher in case of gel due to its higher lipid solubility (Aly and Naddaf 2006). Other formulation does not provide long term stability, therefore delivery of drug through gels are the best option to overcome the stability of the formulation.

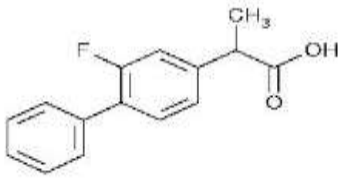

Figure 1 Chemical structure of Flurbiprofen

Currently the great attention is devoted to the hydrogel as they are easily applicable, absorbed and do not leave feeling of greasiness. These are mostly hydrogel of Carbopol, which are transparent have an attractive appearance and develop pleasant cool feeling.

Hence, the objective of this study was to prepare a stable 6% Flurbiprofen hydrogel. Hydrogel of Flurbiprofen was prepared using Carbopol 940. The evaluation methods used in this study were stability testing, organoleptic characteristics, centrifugation, measuring the pH value of the hydrogel, drug content and in vitro drug release study.

MATERIALS AND METHODS

Materials

Flurbiprofen, Carbopol 940, ethanol 96%, Triethanolamine, Phosphate buffer solution and Distilled water. (All chemicals were obtained from the Pharmacy Laboratory of Management & Science University).

Apparatus/ Equipments

Digital weighing scale, digital pH meter, magnetic stirrer, centrifuge, spectrophotometer, oven, cool room, beakers, spatula, glass rod, measuring cylinder, dropper bottle, reagent bottle, urine containers, centrifuge tube, cuvettes, weighing tray, disposable pipette, pipette, volumetric flask, conical flask, aluminium foil, Float-A-Lyzer® G2 and floatation ring.

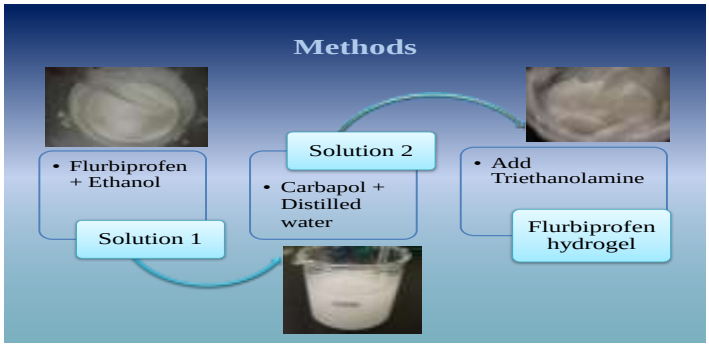

Figure 2 Flurbiprofen hydrogel formulations

Methods for preparation of drug formulation

Table 1 shows the composition for the preparation of Flurbiprofen hydrogel containing different amount of Carbopol 940. The powder of pure Flurbiprofen was used for the preparation of Flurbiprofen hydrogel. Carbopol 940 was gradually added into distilled water and steered by a

magnetic stirrer until a homogenous mixture appeared. Then, hydrogel base was added Flurbiprofen which was dissolved in ethanol 96%. Finally, the mixture was neutralized by adding drop by drop of Triethanolamine (Fig. 2). pH of Flurbiprofen hydrogel was adjusted by using Triethanolamine. Flurbiprofen hydrogel was ready when it forms into a white semisolid. The sample was stored at the temperature of 2-4^{0}C (Cool room), 25^{0}C (Room temperature) and 40^{0}C (Oven).

Table 1 Composition of Flurbiprofen hydrogel containing different amount of Carbopol 940.

Formulation code	Flurbiprofen (g)	Ethanol 96% (g)	Carbopol 940 (g)	Water (g)
F_1	2.5	5	0.5	Up to 50 g
F_2	2.5	5	1	Up to 50 g
F_3	2.5	4	0.5	Up to 50 g
F_4	2.5	4	1	Up to 50 g
F_5	3	5	0.5	Up to 50 g
F_6	3	5	0.75	Up to 50 g
F_7	3	5	1	Up to 50 g
F_8	3	4	0.5	Up to 50 g
F_9	3	4	0.75	Up to 50 g
F_{10}	**3**	**4**	**1**	**Up to 50 g**
F_{11}	3	3	1	Up to 50 g

EVALUATION OF PREPARED FLURBIPROFEN HYDROGEL

Stability test

Stability tests were performed at different storage conditions. The tests were performed on samples kept at 2-4^{0}C (Cool room), 25^{0}C (Room temperature) and 40^{0}C (Oven). The samples kept at different storage conditions were observed for a period of 28 days. Samples were observed with respect to any changes in liquefaction, color and phase separation.

Organoleptic characteristics

Flurbiprofen hydrogel was investigated organoleptically such as liquefaction, color and phase separation. Organoleptic characteristics of Flurbiprofen hydrogel kept at different storage conditions were noted at various intervals such as 0 h, 1 h, 1 day, 3 days, 7 days, 14 days, 21 days and 28 days for 28 days.

Centrifugation tests

Centrifugation tests were performed for the Flurbiprofen hydrogel immediately after preparation by using a centrifuge. The same test was repeated for the Flurbiprofen hydrogel after 1 h, 1 day, 3 days, 7 days, 14 days, 21 days and 28 days for 28 days of preparation. Centrifugation conditions were 25^{0}C and 5000 rpm by placing 10 g of sample in the tube.

pH determination

The pH value of the prepared Flurbiprofen hydrogel kept at different storage conditions were determined by a digital pH-meter. pH measurements were repeated for Flurbiprofen hydrogel after 0 h, 1 h, 1 day, 3 days, 7 days, 14 days, 21 days and 28 days for 28 days of preparation.

Drug Content

A specific quantity (100 mg) of Flurbiprofen hydrogel was taken and dissolved in 100ml of phosphate buffer (pH 6.8). The volumetric flask containing hydrogel solution was stirred by using a magnetic stirrer in order to get complete solubility of drugs. This solution was estimated spectrophotometrically at 255 nm using phosphate buffer (pH 6.8) as blank. The drug content of Flurbiprofen was calculated using a calibration curve (Fig. 4).

In-vitro drug release study

To test the pattern of release of drug from formulations, in-vitro diffusion study was carried out. The developed formulation was subjected to in-vitro diffusion through Spectra/Pro® Float-A-Lyzer G2, with molecular weight cut off 3500-5000 D. The receptor compartment was filled with saline phosphate buffer (0.2 M, pH 7.4). The whole

assembly was maintained at 37±1° and the receptor solution was stirred with a magnetic stirrer at 100 rpm throughout the experiments. 5 ml sample was withdrawn at intervals of 1, 2, 3, 4, 5, 6, 7 and 8 hours, the volume of each sample withdraw was replaced by the same volume of fresh buffer to maintain constant volume. The samples were analyzed spectrophotometrically at 255 nm for Flurbiprofen content. The amount of drug release determined spectrophotometrically at 255 nm versus a calibration curve in the same phosphate buffer.

Statistical analysis

The data obtained from different formulations were analyzed by one-way analysis of variance (ANOVA) procedure using the Statistical Package for the Social Science (SPSS) program (SPSS Statistics 22.0). When there was a statistically significant difference, a post-hoc Tukey test was then conducted to detect the differences among the pairs. A statistically significant difference was considered at $p < 0.05$.

RESULTS AND DISCUSSION

Organoleptic characteristics

Organoleptic characteristics of the formulated Flurbiprofen hydrogel are presented in Table 2.

Centrifugation test

Results of the centrifugation tests for the Flurbiprofen hydrogel kept at different storage conditions are given in Table 2. No phase separation was seen after centrifugation in any of the samples at 0 h, 1 h, 1 day, 3 days, 7 days, 14 days, 21 days and 28 days in 2-4^{0}C (Cool room), 25^{0}C (Room temperature) and 40^{0}C (Oven).

Table 2 Organoleptic characteristics and centrifugation test results of Flurbiprofen hydrogel at various storage conditions.

Time	Liquefaction			Color			Phase Separation			Centrifugation		
Hrs/Wks	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
0 Hr	-	-	-	W	W	W	-	-	-	-	-	-
1 Hr	-	-	-	W	W	W	-	-	-	-	-	-
24 Hrs	-	-	-	W	W	W	-	-	-	-	-	-
72 Hrs	-	-	-	W	W	W	-	-	-	-	-	-
7 days	-	-	-	W	W	W	-	-	-	-	-	-
14 days	-	-	-	W	W	W	-	-	-	-	-	-
21 days	-	-	-	W	W	W	-	-	-	-	-	-
28 days	-	-	-	W	W	W	-	-	-	-	-	-

Where: A= 2-4^{0}C (Cool room); B= 25^{0}C (Room temperature); C=40^{0}C (Oven); **-** = No change; W= White.

Color

Freshly prepared Flurbiprofen hydrogel was white in color and it maintains the same color up to 28 days. Results show no changes in color at 0 h, 1 h, 1 day, 3 days, 7 days, 14 days, 21 days and 28 days in 2-4^{0}C (Cool room), 25^{0}C (Room temperature) and 40^{0}C (Oven). This shows that Flurbiprofen hydrogel was stable at different storage conditions up to 28 days.

Liquefaction

No liquefaction was observed in the Flurbiprofen hydrogel at all storage conditions. This shows that Flurbiprofen hydrogel was stable at different storage conditions up to 28 days.

Phase separation

In the case of Flurbiprofen hydrogel, no phase separation was observed in any of the samples. This indicates that Flurbiprofen hydrogel was stable in all storage conditions for 28 days.

pH value

pH values of the Flurbiprofen hydrogel kept at different storage conditions are shown in Table 3 and Figure 3. pH values of skin range between 5 and 6, and 5.5 are considered to be the average pH of the skin. Therefore, the formulations intended for dermal application should have a pH value around this range. In this work, the pH of the freshly prepared Flurbiprofen hydrogel formulation was 5.50, which is very close to the pH of the skin. pH values of the samples kept at 2-4^{0}C (Cool room), 25^{0}C (Room temperature) and 40^{0}C (Oven) were found to be slightly varied up to 28 days.

pH value of the sample stored at 2-4^{0}C (Cool room) increased to 6.0 at the end of the 28th day. pH value of the sample stored at 25^{0}C (Room temperature) increased to 5.7 at the end of the 28th day. While the pH value of the sample stored at 40^{0}C (Oven) maintained at 5.5 at the end of the 28th day. Data obtained was evaluated statistically using one-way ANOVA test. It was found by the one-way ANOVA test at the 5% significance level that the changes in pH values of the sample was not significant at different levels of time and temperature ($p > 0.05$). The pH values of the sample stored in three different temperatures were compared with the control group which is pH 5.5. It means that three storage conditions of the samples were not significantly variants from the control group. The mean of the sample stored at 2-4^{0}C (Cool room) was 5.5. Meanwhile, the mean of the sample stored at 25^{0}C (Room temperature) was 5.3. In addition, the mean of the sample stored at 40^{0}C (Oven) was also 5.3. It shows that the mean of the sample stored at different storage conditions were having an average of a value not far from pH 5.5.

Table 3 pH values of sample kept at different storage conditions

Time	pH		
Hrs/days	**A**	**B**	**C**
0 Hr	5.5	5.5	5.5
1 Hr	5.4	5.2	5.2
24 Hrs	5.3	5.1	5.1
72 Hrs	5.5	5.3	5.4
7 days	5.4	5.1	5.2
14 days	5.5	5.3	5.4
21 days	5.6	5.2	5.3
28 days	6.0	5.7	5.5

Where: A= 2-4^{0}C (Cool room); B= 25^{0}C (Room temperature); C= 40^{0}C (Oven); Hr = hour

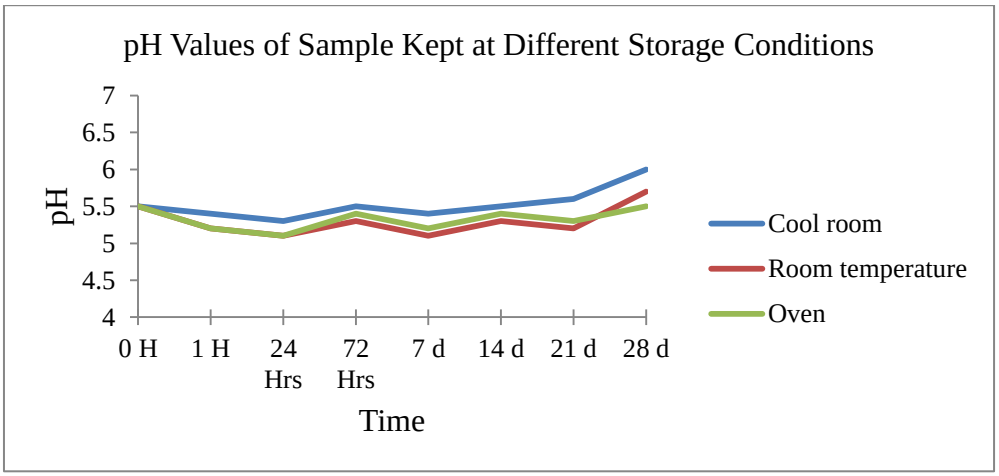

Figure 3 pH values of sample kept at different storage conditions

Standard calibration curve

Flurbiprofen was estimated spectrophotometrically at 255 nm. From stock solution, dilutions were prepared for giving the concentration of each solution ranging from 0-20 µg/ml. Absorbance of each solution was measured at 255 nm against phosphate buffer pH 6.8 as a blank (Fig. 4).

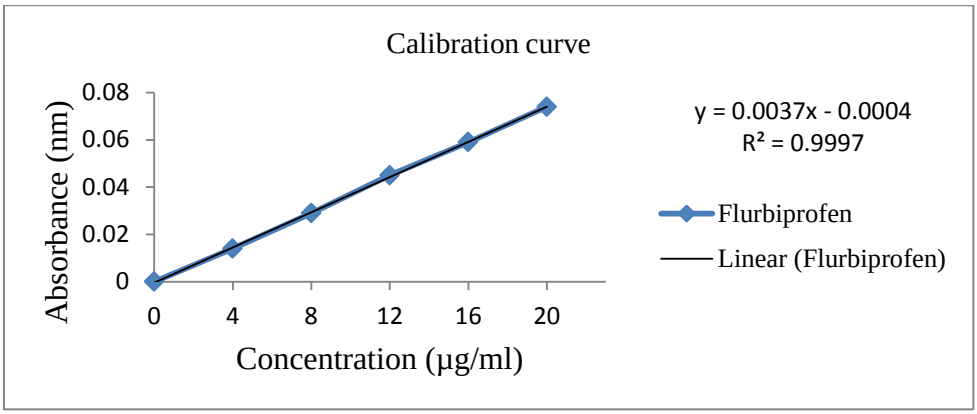

Figure 4 Calibration curve

Drug content

Drug content of Flurbiprofen hydrogel is found to be 76.3% by using a calibration curve.

In-vitro drug release study

The data obtained from release studies were shown in Figure 5. A graph was plotted between the percentages of drug released versus time. The Hydrogel released 79.46% of the drug content by 8 hours.

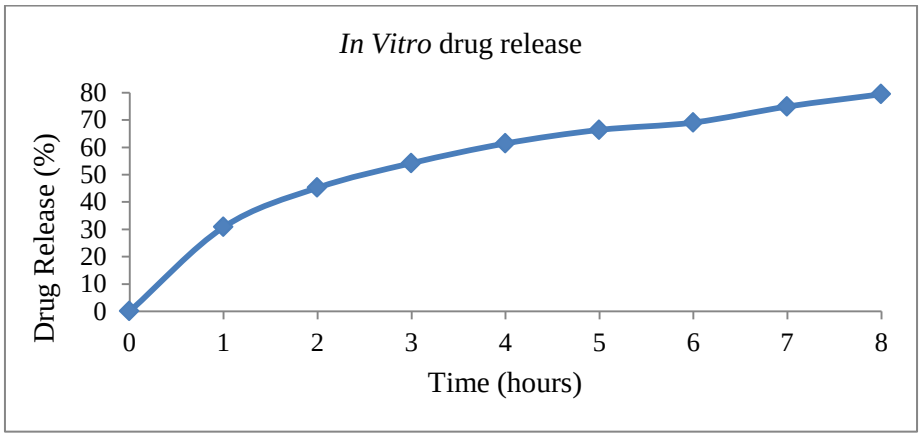

Figure 5 In Vitro release of Flurbiprofen hydrogel

CONCLUSION

Flurbiprofen hydrogel was prepared and successfully formulated into topical preparation using Carbopol 940. This formulation approach can be used to improve the limitation of oral Flurbiprofen. The formulation has demonstrated that it is stable at the liquefaction, color, phase separation, centrifugation and pH for a period of up to 28 days at three different storage conditions. The drug content of Flurbiprofen hydrogel was found to be 76.3%. The Hydrogel released 79.46% of the drug content by 8 hours. The objective of the study on developing a stable 6% Flurbiprofen hydrogel formulation has been achieved.

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