IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 1, Issue 1 (May. – June. 2012), PP 70-73
www.iosrjournals.org

Formulation and Evaluation of Topical Gels of Carbopol 940

R. P. S. Rathore*, and Dr. R. K. Nema
B. N. College of Pharmacy, Udaipur 313002 (Raj.)
E-mail: rajendrapalrathore@yahoo.com

Abstract
Topical gels of Ketoprofen were prepared by using varying concentrations of Carbopol 940. The prepared gels were evaluated for various parameters as clarity, colour homogeneity, presence of particles and fibers, spread ability, extrudability, pH., viscosity, irritation, swelling & synergesis, drug content and in-vitro release studies. The in-vitro release study was performed using a modified K.C. diffusion cell across sortious cellulose acetate membrane. The release was diffusion controlled and followed zero-order kinetics.

Keywords: *Topical gels, Ketoprofen*

I. INTRODUCTION

A large number of dermatological and transcutaneous formulations commercially available and their administration typically involves rubbing a dose onto the skin resulting in the formation of a thin film.[1] Topical NSAIDs have several advantages over their systemically administered counterparts, they are simple to apply and deliver high drug concentrations locally into affected tissues, while producing only limited side effects.[2,3] Organogels of ketoprofen were prepared using Carbopol 940 as a gelling agent.[4]

Ketoprofen a potent nonsteroidal anti-inflammatory drug (NSAID). Following oral administration ketoprofen is first absorbed into the circulating blood and then delivered to the inflamed sites for its therapeutic action. However, oral doses often cause gastric irritation and unwanted systemic side effects due to dose dumping effects. A significant reduction in the gastric irritation was observed by this route, while similar pharmacological activities were achieved.[5]

II. MATERIALS AND METHODS

Materials
Ketoprofen was obtained as a gift sample from BEC Chemicals (Roha) Maharasthara. Carbopol 940 was obtained as a gift sample. All other chemicals and reagents used were of analytical grade.

Preparation of Topical Gels of Carbopol
The topical gels were prepared using dispersion method in which Carbopol 940, in 0.5%,1%,1.5% were dispersed in water respectively.[6] The other additives used were ethanol a solvent for drug as it is insoluble in water, glycerin a humectant, SLS a permeation enhancer, methyl-paraben, propyl -paraben as an antimicrobial agent. The gels were prepared by dispersing the specified quantity of polymer in distilled water with constant stirring at 900-1000 rpm.[7] Polymers or gelling agents were added slowly in parts to distilled water in the beaker with constant stirring and maintaining the speed of stirring. The maintenance of speed was important to avoid air entrapment and proper dispersion of gelling agent. The optimum speed was selected for formulating the gels because higher speeds lead to vortexing which leads to air entrapment an undesirable property. Weighed amount of ketoprofen was dissolved in ethanol, measured amount of glycerin, methyl-paraben and propyl-paraben were mixed with stirring, and finally this mixture was added to the beaker containing distilled water and polymer before complete gelling took place. After complete dispersion the solutions were kept in dark for 24 h. for complete swelling of the polymers. The preparations were air cooled for sometime for setting and then packed in wide mouth plastic jars covered with screw capped plastic lid after covering the mouth with an aluminium foil. The prepared formulations were evaluated visually for there consistency parameters ie. the beaker in which the gels were kept were tilted if the gels were freely flowing then a higher concentration of polymer were used. The formulations were also kept at 40ºc if any synergesis effect was seen it confirms that the polymer concentration should be increased in that formulation. The concentration of polymers having good consistency parameters were used for preparing the other formulations.

Concentration of methyl-paraben and propyl- paraben was kept constant in all the formulations. Triethanolamine was finally added to the polymeric dispersion for achieving the gels, this is done to neturalize the pH of the carbopol which is necessary for gelling.

Evaluation of Gels:
Ketoprofen gels were visually inspected for clarity, colour homogeneity, presence of particles and fibers. The other parameters were evaluated as follows:

Rheological Properties:

Spreadability:

A modified apparatus suggested by *Multimer et al.,* (1956)[8] was used for determining spreadability. The spreadability was measured using a modified apparatus which consisted of two glass slides. The lower one was fixed to a wooden plate and the upper one was attached by a hook to a balance. The spreadability was determined by using the formula: S=ml/t, where S, is spreadability, m is weight in the pan tied to upper slide and t is the time taken to travel a specific distance. The measurement of spreadability of each formulation was in triplicate and the average values are presented.

Extrudability:

A simple method was adopted for determining the extrudability. The weight in grams required to extrude 1 cm ribbon of gel in 10 seconds from the collapsible tube was the extrudability of the gel.[9] The measurement of extrudability of each formulation was in triplicate and the average values are presented.

Viscosity:

The viscosity of gels was determined by using a Brookfield viscometer. Gels were filled in a jar and the spindle was lowered taking care that spindle does not touch bottom of the jar. The spindle was rotated and the corresponding dial reading was noted.[10] The measurement of viscosity of each formulation was in triplicate and the average values are presented.

Measurement of pH.:

The pH. of the gels was determined by a digital pH. meter at constant temperature. The pH. meter was calibrated by using a buffer solution of pH. 7.0 & 9.2 and then the electrode were washed with distilled water. One gram of gel was dissolved in 100 ml of distilled water and stored at 4^{o}C for two hours. The measurement of pH. of each formulation was in triplicate and the average values are presented.

Drug Content:

1 gm. of the prepared gel was mixed with 100ml. of methanol AR. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 255 nm.[11] Drug content was calculated by linear regression analysis of the calibration curve.

Synergesis & swelling of gels

Freeze thaw cycling tests can be used to see whether separation or synergesis will occur. Synergetic effects were seen in gels with low polymer concentration at 40 ºC no synergesis or bleeding was seen in any other formulation at 4 ºC and 25 ºC. Synergesis leads to extrusion of the liquid entrapped in the polymeric network of the gels (hydrogel) and are converted to xero gels which lead to loss of drug which is entrapped in the network.[12,] The synergesis in the formulation implies that the gels should be stored at temperature below 40 ºC. The swelling was conducted in buffer solution of pH 7.4 at room temperature. Results show that the swelling % of the gels increases as the polymer concentration increases in formulation FC1, FC2, FC3, this may be due to the property of the polymer to retain more amount of water. Further change in swelling % may be attributed to the composition of the gels.

5.3.2.6 Skin irritation studies

Dorsal hairs at the back of the rats were clipped off one day prior to the commencement of the study. Animals showing normal skin texture after clipping were housed individually in cages with copography meshes to avoid contact with the bedding so as to prevent the wiping of the gels. One side of each animal was used for intact study. Clipping was done carefully to avoid bleeding of stratum corneum. About 50 mg of test sample was applied over one square centimeter area of intact and abraded skin. Animals were immobilized in a restrainer for 24 h. Skin responses were evaluated according to the visual analog scale used in the Draize technique. For this study the Draize test was used because it is simple, reliable and reproducible. Variations around this basic

method have formed the regulatory classification of skin corrosion and skin irritation worldwide. Skin reactions are graded separately for erythema/eschar scale each on a 0–4 grading scale**.** Grading had a reading of zero which shows that there is no irritation or erythema caused by the gels (table 5.5 - table 5.8). For erythema/eschar: 0 = no erythema; 1 = very slight erythema, barely perceptible; 2 = well-defined erythema; 3 = moderate to severe erythema; 4 = severe erythema (beet redness) to slight eschar formation (injuries in depth).The absence of irritation by the gels might be due to the appropriate pH of the formulations and the characteristics of the polymers and the additives which make them suitable candidates for topical application.[13]

In -Vitro drug release:

The release of Ketoprofen from gels were studied at 37 ºC using a modified K.C cell. The sortious cellulose acetate membrane was clamped between the two compartments. The receptor compartment was filled with 75 ml of medium (phosphate buffer 7.4). The medium was stirred by external driven Teflon coated magnetic beads. The temperature in the diffusion cell was maintained at 37 ºC by the hot water circulating in the surrounding water jacket. 1 gm of gel was placed on the membrane in an area restricted by a Teflon ring ensuring no air between gel and membrane surface. For the next 6 hours, 2 ml. aliquots of sample were withdrawn at intervals of 1, 2, 3, 4, 5 & 6 hours. The sample removed was immediately replaced with an equal volume of fresh phosphate buffer.[14] Studies were performed in triplicate runs and the mean values were used for the analysis of the data.

III. Result and Discussion:

All the formulated gels of ketoprofen were evaluated for various physiochemical parameters as spreadability, extrudability, pH, viscosity, drug content, and cumulative drug release. Ketoprofen gels were visually inspected for clarity; colour homogeneity, presence of particles & fiber's and the results were found to be satisfactory. Viscosity is an important parameter for characterizing the gels as it affects the spreadability, extrudability & release of drug. The viscosity of gels was increasing in the order of F3>F2>F1. The spreadability of the formulations was good which was essential for easy application. The spreadability of F1>F2>F3. The extrusion of the gels from the tubes is important during application. All the formulated gels had good extrudability. The pH. of the formulations was between 6.6 to 7.2. The results revealed that the drug content of all the formulations was found to be within100 ± 12 % indicating the suitability of the adopted method.

Invitro release of Ketoprofen from all the prepared gel formulations is illustriated in Fig.1. The cumulative percent of drug released within 6 hrs. for the prepared gels were 52.8, 47.1, 40.1 percent respectively. It confirms the controlled release behavior of the formulations, the release was in the order FC1>FC2>FC3.

IV. Conclusion

In the present study it can be concluded from the physiochemical and *in -vitro* release studies that FC1 is the pharmaceutically most suitable and acceptable formulation as compared to the other formulations. Thus it can be concluded that drug diffusion proportionally increases F1>F2>F1 .Further it also has aesthetic appeal superior to other formulations, an important aspect for patient compliance.

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Table 1:Observation table of quantities physical parameters of Carbopol gels.

Code	Drug Content (%) *	Viscosity (cps)	Extrudability (sec.) *	Spread ability (gm.cm/sec.) *	pH *	Irritation	Swelling (%) *	Syneresis (40ºc)
FC1	98.6±8.8	59950	20.2±1.8	10.63±0.9	7.2±0.2	-	32.1±2.1	-
FC2	98.2±8.9	77700	30.3±2.5	8.82±0.8	6.5±0.3	-	38.6±2.8	-
FC3	98±9.2	111316	35.6±2.8	7.83±0.6	6.6±0.6	-	43.4±3.1	-

* Average of three readings (-) no irritation & syneresis (+) irritation & syneresis

Table 2: *In-vitro* release of ketoprofen from gels FC1, FC2 and FC3.

Sqrt. Time (min.)	% Cumulative drug released		
	FC1	FC2	FC3
5.477226	5.2	6.1	4.1
7.745967	11.1	13.1	8.7
9.486833	17.5	19.3	16.2
10.95445	24.1	23.8	21.8
12.24745	30.5	28.4	25.6
13.41641	36.2	31.9	28.8
14.49138	39.3	33.1	30.1
15.49193	42.6	35.3	32.9
16.43168	44.2	38.2	34.8
17.32051	46.5	41.8	36.2
18.1659	49.2	45.1	38.4
18.97367	52.8	47.1	40.1

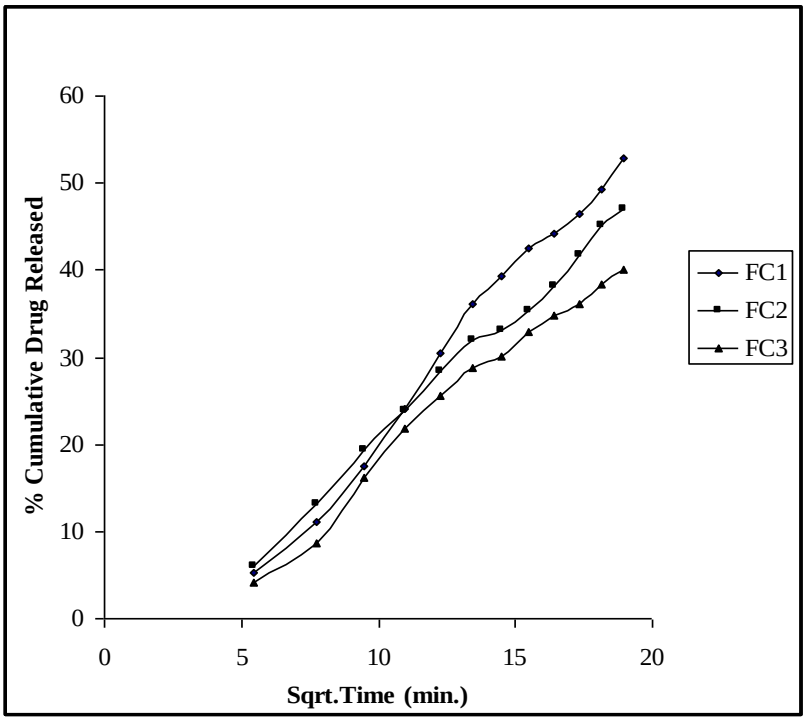

Figure 1: *In-vitro* release of ketoprofen from gels FC1, FC2 and FC3.