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Design and Evaluation of Topical Hydrogel Formulation of Aceclofenac for Improved Therapy

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ABSTRACT

Aceclofenac, a non-steroidal anti-inflammatory drug has been used in the treatment of rheumatoid arthritis and osteoarthritis. In order to decrease the gastric ulcerogenic effects, aceclofenac hydrogel have been developed. Topical gel preparations are intended for skin application or to certain mucosal surfaces for local action or transdermal penetration of medicament or for their emollient or protective action. Topical delivery of drugs can be achieved by incorporating drug into the gel matrix for effective delivery of drugs, thus avoiding first pass metabolism and for increased local action in pain management and skin diseases. NSAID's are non-steroidal drugs having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble especially in case of oral administration. In view of adverse drug reaction associated with oral formulations, many NSAID's are increasingly administered by topical route. Hydrophilic polymers like Guar gum and Carbopol 940 of varying concentrations were used in an attempt to develop topical hydrogel formulations of aceclofenac. Evaluation tests for visual appearance, pH, viscosity, spreadability, assay, *in vitro* drug release were carried out. *In vitro* diffusion study was carried out in a Franz diffusion cell using cellophane membrane. No prominent changes in physicochemical properties of formulation were observed after exposure to accelerated conditions of temperature (40 ± 2°C) and humidity conditions (75 ± 5%RH). The gel formulation consisting of 1% w/v Guar gum 1% w/v Carbopol 940 at 1:1 ratio was found to be suitable for topical application based on *in vitro* evaluation. These results suggest the feasibility of the topical gel formulation of aceclofenac.

Keywords: Aceclofenac, Guar gum, Carbopol 940, Topical hydrogel, Franz diffusion cell

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INTRODUCTION

Osteoarthritis (OA) is the most prevalent disease after the age of 65 in about 60% of men and 70% of women[1]. OA is primarily a non-inflammatory degenerative joint disease characterized by progressive loss of articular cartilage, subchondrial bone sclerosis, osteophyte formation, changes in the synovial membrane, and an increased volume of synovial fluid with reduced viscosity and hence, changed lubrication properties. Current treatment options for OA are limited. They include intra-articular (IA) injection of glucocorticoids and hyaluronic acid (HA) preparations or symptomatic treatment with simple non-steroidal anti-inflammatory drugs (NSAIDs)[2]. Due to the localized nature of the disease, the IA injection of glucocorticoids and HA seems to be an attractive approach for OA, but they provide only short-term pain relief and/or often do not provide adequate pain relief and have no patient compliance[2]. On the other hand, Rheumatoid arthritis (RA) is a common chronic systemic inflammatory disease that is primarily characterized by inflammation of the synovium with destruction of cartilage and bone as the disease progresses. More severe disease may be associated with vasculitis, pericarditis, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules and scleritis[3,4]. Since there is no cure, symptomatic treatment is the only choice to reduce the pain and inflammation. Formulations of NSAIDs are the first choice remedies which would fulfill the need of providing significantly long remission of pain with improved patient compliance. Aceclofenac (ACF) is a non-steroidal anti-inflammatory drug (NSAID) and has been indicated orally for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis[5,6]. However, the oral administration of ACF has often resulted in side effects, including gastrointestinal ulcer and anemia due to gastrointestinal bleeding [7]. It requires frequent oral dosing because of its short half-life (3-4 h). Topical administration of ACF would be a possible alternative offering distinct advantages such as elimination of the absorption variable rate, first pass intestinal and hepatic metabolism inherent with oral dosing and delivering the

drug directly to the inflamed site and thereby, producing high local concentrations and avoiding the side effects[8]. Topical administration of therapeutic agents offers many advantages over oral and intravenous administrations. Hydrogel based drug delivery system is a most promising novel approach now-a-days for delivery of drug for extended period of time. Hydrogels are the three-dimensional network polymers that swell in aqueous solutions and in swollen state, these become soft and rubbery, resembling a living tissue and some possess excellent biocompatibility. Hydrogel systems possesses a good stability in surrounding conditions like change in pH, ionic strength, temperature and frequent changes of environment in the GI-tract, which has a variation of environment from the stomach to intestine [9]. Hydrogel from natural polymers, especially polysaccharides have been widely used for their advantages over synthetic polymers such as non-toxic, biocompatible, biodegradable, freely available, able to modify the properties of aqueous environment, capable of thicking, emulsify, stabilize, encapsulate and swell and to form gels films. But they can be modified to overcome some drawbacks, like uncontrolled rate of hydration, microbial contamination, drop in viscosity on storing, etc [10]. In present work, attempt was made to formulate and evaluate topical hydrogel drug delivery systems. Attempts were made to enhance drug absorption and exposure to improve therapy by controlling the rate of drug release from dosage forms. Rate of drug release was modified using cross-linking agents, gelling or thickening agents. The ultimate aim was to improve bioavailability of the drug and to improve the market formulation by the use of combination of hydrophilic polymers.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Yarrow Chemical Ltd, Bombay. Carbopol- 940 (Loba Chemie Pvt. Ltd., Mumbai, India), Guargum (Qualigens Fine Chemicals, Mumbai, India), Benzalkonium chloride (Prime laboratories, Hyderabad), Isopropyl myristate (Alpha Chemika, Maharashtra, India), sodium hydroxide (Prime laboratories, Hyderabad), potassium dihydrogen phosphate (Alpha Chemika, Maharashtra, India) were procured and used in this investigation. All other chemicals used were of analytical grade and were used without any further chemical modification.

Determination of λ_{max} of ACF

Accurately weighed 10 mg of drug was dissolved in 10 ml of 7.4 pH buffer solution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 7.4 pH buffer solution. Prepare suitable dilution to make it to a concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer. A graph of concentration Vs absorbance was plotted.

Formulation of aceclofenac topical hydrogel

Hydrophilic polymers like guar gum and carbopol 940 were selected and 0.1N NaOH solution used as cross linking agent[11,12]. Carbopol 940 is soluble in water while guar gum produces colloidal dispersion in water. 0.1-5% w/v concentrations of polymeric dispersions were made separately and were found to be having good mechanical properties when guar gum and carbopol 940 colloidal dispersions mixed in certain proportions.

The topical hydrogels using different proportions were prepared as follows:

1. Hydrogels were fabricated using different concentrations of polymeric dispersions.

2. Different concentrations of carbopol940 colloidal dispersions were prepared using distilled water.

3. Different concentrations of guar gum colloidal dispersions were prepared using distilled water.

4. After complete dispersion, both the polymer solutions were kept in dark for 24 h for complete swelling.

5. Dispersions of polymers were made using magnetic stirrer (500rpm). After dispersing carbopol940 in distilled water, colloidal dispersion of guar gum was added to it under magnetic stirring. 1% v/v isopropyl myristate and 0.25% w/v benzalkonium chloride were added. Aqueous drug solution was added to the polymeric dispersion after addition of sodium hydroxide solution. Finally, the remaining distilled water was added to obtain a homogeneous dispersion of gel under magnetic stirring. The composition of different formulation was given in Table 1.

Table 1 Different formulas of aceclofenac hydrogel

Ingredients (Mg)	Formulation Code				
	F1	F2	F3	F4	F5
Aceclofenac	100	100	100	100	100
Carbopol-940	0.375	0.5	0.25	0.375	0.5
Guar gum	0.05	0.5	0.375	0.375	0.375
Isopropyl myristate (ml)	1	1	1	1	1
Benzalkonium chloride	0.25	0.25	0.25	0.25	0.25
Purified water (q.s)	100ml	100ml	100ml	100ml	100ml

Evaluation of hydrogel

Physical characteristic

The prepared hydrogel formulations were inspected visually for their pH, colour, homogeneity, consistency, grittiness, texture and phase separation

Determination of pH

The pH of hydrogel formulations was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurement of pH of each formulation was done in triplicate and average values were calculated[13].

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability study

The hydrogel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked[14].

Spreadability

Two glass slides of standard dimensions (6×2) were selected. The hydrogel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the hydrogel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the hydrogel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each hydrogel formulation [15,16].

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec), m = weight tied to the upper slide (20 grams),

l= length of glass slide (6cms), t = time taken is seconds.

Viscosity

The measurement of viscosity of the prepared hydrogel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^{0}C. The sufficient quantity of gel was filled in appropriate wide mouth container. The hydrogel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the viscometer. Samples of the hydrogel were allowed to settle over 30 min at the constant temperature (25 ±/1^{0}C) before the measurements[17].

Drug content

Accurately weighed equivalent to100 mg of topical hydrogel was taken in beaker and added 20 ml of phosphate buffer pH 7.4. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 ml of filtered solution was taken in 10 ml capacity of volumetric flask and volume was made upto 10 ml with phosphate buffer pH 7.4. This solution was analyzed using UV spectrophotometer at λ_{max} 275 nm.

***In-vitro* drug release studies using the prehydrated cellophane membrane**

The prepared hydrogel was evaluated for *in vitro* drug release. *In vitro* diffusion study was carried out in a Franz diffusion cell using cellophane membrane. The cellophane membrane was mounted on the Franz diffusion cell. Formulation was applied through donor compartment on the dialysis membrane. Reservoir compartment was filled with 25 ml phosphate buffer of pH 7.4 The study was carried out at 37 ± 1°C and at a speed of 100 rpm for 8 h. Samples were withdrawn from reservoir compartment at 1 h interval and absorbance was measured spectrophotometrically at 275.0 nm. Each time the reservoir compartment was replenished with the same quantity of 7.4 pH phosphate buffer [18,19].

Accelerated stability studies

Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines. The formulation packed in aluminium tube was subjected to accelerated stability testing for 3 months as per ICH norms at a temperature (40 ± 2oC) and relative humidity 75 ± 5%. Samples were taken at regular time intervals of 1month for over a period of 3months and analyzed for the change in pH, spreadability, drug content and *in-vitro* drug release by procedure stated earlier. Any changes in evaluation parameters, if observed were noted. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation.

RESULTS AND DISCUSSIONS

The absorption maxima of ACF were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer using concentration range of 5-25µg/ml ACF in 7.4phosphate buffers. ACF showed a linear relationship with correlation coefficient of 0.999 in the concentration range of 5-25µg/ml in phosphate buffer pH 7.4 Figure1. Melting point of drug was found 148-149^{0}C while it was 149-150°C reported in standard monograph. All the data of preformulation study were found similar as given in standard monograph which confirmed that the drug was authenticated and pure in form and it could be used for formulation development of ACF -loaded hydrogel.

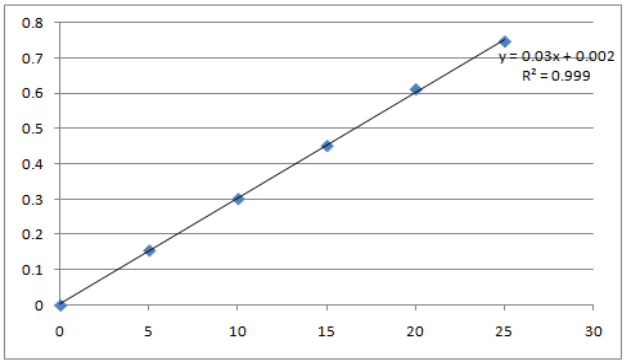

Fig.1 Calibration curve of ACF in phosphate buffer pH 7.4 at 275nm

Hydrogel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy

appearance. Results have been discussed in Table 2. The results of washability, extrudability and spreadability of all formulation were given in Table 3. From the result it was found that formulation F1-F5 has good washability ability, formulation F2, F3 has good Extrudability and Spreadability of all formulation was found to in range of 12.25to14.56. The viscosity of the hydrogel was obtained by using brookfield digital viscometer. The viscosity of the formulations increases as concentration of polymer increases and pH of prepared hydrogel were measured by using pH meter (Orion Research, Inc., USA). The pH of the hydrogel formulation was in the range of 6.95 to7.05 which considered acceptable to avoid the risk of skin irritation upon application to skin and drug content of F2 was found to be higher 99.7 table 4.

Table 2 Physical parameter of formulation batches

Formulation	Colour	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	White	Excellent	Excellent	None
F4	White	Excellent	Excellent	None
F5	White	Excellent	Excellent	None

Table 3 Result of washability extrudability and spreadability study

Formulation	Washability	Extrudability	Spreadability (gcm/sec)
F1	+++	++	12.25
F2	+++	+++	13.36
F3	+++	+++	14.56
F4	+++	++	13.23
F5	+++	++	14.56

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4 viscosity, pH and drug content

Formulation	Viscosity (cps)	pH	Drug Content
F1	9344± 2	7.05	98.5 ± 0.2
F2	9589± 2	7.02	99.7 ± 0.1
F3	9436± 1.5	6.95	99.5 ± 0.2
F4	9242± 2.5	6.98	99.4 ± 0.1
F5	9180± 1.5	7.05	99.2 ± 0.3

Release of drug from ACF hydrogel was significantly slower, which confirmed that slight prolonged drug release rate. Incorporation of carbomer affected the release rate of the drug. By increasing the amount of carbomer, the release rate of the drug decreased, which could be related to the increased rigidity of the formulation, followed by its decreased permeability for the drug. Optimized formulation F2 shows significantly improved in drug release rate as compare to marketed preparation. It was concluded that developed formulations deliver the drug for the treatment of OA Table 5.

Table 5 % Cum. drug release of formulation F1-F5

Time (min)	Cumulative % of drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**Marketed**
5	73.2 ± 0.3	29.3 ± 0.4	75.6 ± 0.5	52±1	45.9 ± 0.7	42.23
10	74.3 ± 0.2	38.0 ± 0.3	79.7 ± 0.2	58.4 ± 0.4	57.2 ± 0.05	65.56
15	76.4 ± 0.1	39.6 ± 0.3	81.4 ± 0.4	71.3 ± 0.2	64.3 ± 0.2	76.89
20	77.9 ± 0.1	47.9 ± 0.7	81.6 ± 0.2	73.4± 0.4	68.6 ± 0.5	-
30	80.8 ± 0.3	88.2 ± 0.5	82.6 ± 0.6	80.5 ± 0.3	75.1 ± 0.3	-

changes were not noticed. The formulation F2 was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters and given in the table 6.

Table 6 Physical parameters after accelerated stability study of formulation F2

Physical Parameter	Temperature: 40 ±2°C ;Relative humidity (RH): 75 ±5%RH			
	Initial	**After 1 month**	**After 2 month**	**After 3 month**
pH	7 ±0.06	6.9 ± 0.06	6.9 ± 0.06	6.9 ± 0.06
Assay	99.6 ± 0.1	99.5 ± 0.1	99.4 ± 0.1	99.3 ± 0.1
Viscosity	9589 ± 2	9591± 1.7	9595 ± 2	9597 ± 2.3

CONCLUSION

The Aceclofenac hydrogel for topical application was formulated using guar gum and Carbopol 940 and evaluation tests were performed. Proper selection of polymers and their proportions is a prerequisite for designing and developing a transdermal drug delivery system. The formulated gels showed good homogeneity, good stability and better drug release rates when compared to marketed formulation.

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