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Research Paper

Formulation Development & Evaluation of Topical Gel Formulations Using Different Gelling Agents and Its Comparison with Marketed Gel Formulation

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Diclofenac Sodium, a non-steroidal anti-inflammatory drug, has been used in the treatment of rheumatoid arthritis and osteoarthritis. This study was conducted to develop and evaluation of gel formulations by using Guar gum alone and in combination with different gelling agents: Carbopol 934 P, hydroxypropylmethylcellulose (HPMC), gelatin, sodium alginate, sodium carboxymethylcellulose (CMC) and its comparison with marketed gel formulation. The gel formulations were evaluated for physical appearance, drug release and stability. The drug release from all gelling agents through a standard cellophane membrane was evaluated using Franz-Diffusion Cell. All gel formulations showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. These gel formulations were further compared with marketed diclofenac sodium gel. Among all the gel formulations, Carbopol with HPMC in ratio of 1:3 showed superior drug release than followed by Carbopol: sodium CMC, Carbopol 934, marketed gel and Carbopol: guar gum. Drug release decreased with increase in polymer (Carbopol 934) concentration. Stability studies showed that the physical appearance, rheological properties and drug release remained unchanged upon storage for three months at ambient conditions.

Keywords: Osteoarthritis, Franz- Diffusion Cell, Rheumatoid arthritis, Hydroxy Methyl Cellulose and Sodium Carboxy Methyl Cellulose.

INTRODUCTION:

Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration [1]. Due to the first past effect only 25- 45% of the orally administered dose reaches the blood circulation. In order to bypass these disadvantages the gel formulations have been proposed as topical application [2]. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through skin to reach the target tissue. The release of the drug from topical preparations depends on the

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physicochemical properties of the vehicle and the drug employed. In order to enhance drug release and skin permeation, methods such as the selection of a suitable vehicle5, co-administration of a chemical enhancer [3] have been studied. Gel base formulation makes the drug molecules more easily removable from the system then cream and ointment [4, 5]. Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily Spreadable, easily removable, emollient, nonstaing, compatible with several excipients and water-soluble or miscible[6]. Diclofenac Sodium is chemically [o-(2, 6-Dichloroanilino) phenyl] acetic acid. Diclofenac Sodium is a non steroidal anti-inflammatory drug with analgesic properties. Diclofenac Sodium is a potent inhibitor of both COX enzymes. Oral dose of diclofenac potassium causes an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or the intestines which could be fatal. Due to the presence of these oral adverse effects necessitate the need for investigating other route of drug delivery of diclofenac potassium. Transdermal delivery of the drug can improve its bioactivity with reduction of the side effects and enhance the therapeutic efficacy (7-8). This study was conducted to develop and evaluation of gel formulations by using Guar gum alone and in combination with different gelling agents: Carbopol 934 P, hydroxypropylmethylcellulose (HPMC), gelatin, sodium alginate, sodium carboxymethylcellulose (CMC) and its comparison with marketed gel formulation. The gel formulations were evaluated for physical appearance, drug release and stability. The drug release from all gelling agents through a standard cellophane membrane was evaluated using Franz-Diffusion Cell

MATERIALS

Diclofenac Sodium (Gift sample, Anantha Drugs Ltd., Ganganagar (Raj.)) carbopol-934, Na CMC salt medium viscosity 200-400 cPs, HPMC (K4M), sodium alginate, propylene glycol, triethanolamine, , sodium hydroxide, potassium dihydrogen orthophosphate, ethanol used were analytical grade. (Research- Lab Fine Chem Industries, Mumbai, India)

Equipments

Digital balance (Shimadzu Corporation, Japan), UV-Visible spectrophotometer (UV-1800 Shimadzu corporation, Japan), pH meter, Magnetic stirrer, Water bath shaker (Servewell Instruments and Equipments Pvt. Ltd.Banglore, India), Brookfield LVDV-II +Pro Viscometer (Brookfield Engineering Laboratories, Inc. USA), Franz-Diffusion Cell (Orchid,

Table 1: Plan of Formulation

Formu-lation	Polymer	Conc.	Drug (gm)	Isopropyl alcohol (g)	Propylene glycol (g)	Distilled Water (g)
F1	Carbopol 934 P	4% w/w	3% w/w	5	5	Up to 100
F2	HPMC	3% w/w	3% w/w	5	5	Up to 100
F3	Sodium CMC	5% w/w	3% w/w	5	5	Up to 100
F4	Sodiumalginate	5% w/w	3% w/w	5	5	Up to 100
F5	Gelatin	5% w/w	3% w/w	5	5	Up to 100
F6	Guar gum	5% w/w	3% w/w	5	5	Up to 100
F7	Carbopol 934P: HPMC	1:3	3% w/w	5	5	Up to 100
F8	Carbopol 934P: HPMC	2:2	3% w/w	5	5	Up to 100
F9	Carbopol 934P: HPMC	3:1	3% w/w	5	5	Up to 100

DEMDC 06 PLUS), Stability Chamber (Thermo lab, TDT-06, Mumbai, India).

METHODS

Preparation of gels formulations:

About 3g of diclofenac sodium was weighed and dissolved in 5g of isopropyl alcohol. To this solution, specified quantity of propylene glycol wad added and dissolved (solution A). Weighed quantity of

Table 2: Drug Content of Gel Formulations

Formulation Code	% Drug Content
F_1	98.98±0.023
F_2	98.14±0.040
F_3	98.51±0.109
F_4	98.07±0.150
F_5	97.55±0.080
F_6	91.67±0.127
F_7	97.99±0.115
F_8	98.20±0.121
F_9	101.2±0.173
F_{10} *	98.70±0.144

gelling agents and their combinations (Guar gum, Carbopol 934 P, hydroxypropylmethylcellulose (HPMC), gelatin, sodium alginate, sodium carboxy-methylcellulose (CMC)) were added to the 75g of distilled water containing 0.1g of sodium metabisulphide as antioxidant and stirred to dissolve the same (solution B). Solution A and B were mixed thoroughly and the final weight was made up to 100g. All the samples were allowed to equilibrate for at least 24 h at room temperature prior to performing rheological measurements [9-13].

Physical examination

The prepared aceclofenac gels were inspected visually for their color, homogeneity, consistency, spreadability and phase separation.[14]

pH

The pH was measured in each gel, using a pH meter, which was calibrated before each use with standard buffer solutions at pH 4, 7, 9. The electrode was inserted in to the sample 10 min priors to taking the reading

at room temperature.[16]

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. [15]

Grittiness

All the formulations were evaluated microscopically for the presence of particles if any no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation. [15]

Viscosity

The measurement of viscosity of the prepared gel was done with a Brookfield viscometer. The gels were rotated at 50 rpm using spindle no. 95. At each speed, the corresponding dial reading was noted. [15]

Spreadability

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load, lesser the time taken for separation of two slides, better the spreadability [15]. It is calculated by using the formula:

$S = M. L / T$

Where M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Drug content studies

To ensure uniform formulation of the gel, it was sampled from the different locations in the mixer and assayed for the drug content. Drug content of the gels was determined by dissolving an accurately weighed quantity of gel (about 1 gm) in about 100 ml of pH 6.8-phosphate buffer. [17-18].

Table 3: Evaluation parameters of developed gels and marketed gel

Formu-lation	Physical Appearance	pH	Spreadability (g.cm./sec.)	Consistency (60 sec.)	Homogenecity
F1	White transparent	6.94	5.7	5.0mm	Homogenous
F2	White viscous	6.85	5.5	5.5mm	Homogenous
F3	White viscous	6.76	5.0	5.6mm	Homogenous
F4	Brownish gummy	6.65	5.8	5.5mm	Homogenous
F5	Transparent	6.82	5.5	6.0mm	Homogenous
F6	Brownish viscous	5.94	4.0	4.5mm	Slightly Homogenous
F7	White transparent	6.88	5.5	5.5mm	Homogenous
F8	White transparent	6.78	5.0	5.0mm	Homogenous
F9	Brownish white transparent	6.81	6.5	3.0mm	Homogenous
F10*	White transparent	6.57	5.6	5.7mm	Homogenous

** Marketed formulation*

Table: 4 Rheological study of developed gels and marketed gel

Formulation	Spindle No.	RPM	Viscosity (cP)	% Torque
F1	95	50	8520	90.9
F2	95	50	7378	98.4
F3	95	50	6742	92.4
F4	95	50	3456	95.2
F5	95	50	2225	72.1
F6	95	50	4645	65.7
F7	95	50	4450	91.8
F8	95	50	4514	60.2
F9	95	50	4790	51.1
F10*	95	50	3453	82.7

** Marketed formulation*

These solutions were quantitatively transferred to volumetric flasks and appropriate dilutions were made with the same buffer solution. The resulting solutions were then filtered 0.45 mm membrane filters before subjecting the solution to spectrophotometric analysis for aceclofenac at 276 nm. Drug content was determined from the standard curve of diclofenac sodium [Table 6].

In Vitro Release

The *in vitro* release experiments were carried out by using Franz-diffusion cells apparatus from different formulations. An exact amount of formulations (1.0 g) was spread out on membrane positioned between the donor and receptor chambers with an available diffusion area. The receptor compartment was filled with phosphate buffer pH 6.8 and continuously stirred with a small magnetic bar at a speed of 50 rpm during the experiments to ensure homogeneity and maintained at 37.2±0.5 ^{0}C. The samples were withdrawn at various time intervals and replaced with the same volume of PBS. Sink conditions were met in all cases. The samples were analyzed spectrophotometrically at 276 nm [Table 5].

Stability study

For the evaluation of stability study, maintaining the formulations at an ambient condition over a period of three months. The drug content was determined periodically after the 1st ,2nd and 3rd month after topical gel preparations [Table 6].

RESULTS AND DISCUSSION

Characterization of Formulations

The pH values of all developed formulations (F1 to F9) and marketed gel formulation ranged from 5.94±0.18 to 6.94±0.27, which are considered acceptable

to avoid the risk of irritation after skin application.[19] The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of marketed gel was found to be 5.6g.cm/sec while formulation number F9 in which Carbopol and Guar gum were used as gelling agent in ratio of 3:1 was found to be 6.5g.cm/sec, indicating spreadability of F9 containing diclofenac sodium gel formulation was good as compared to the marketed gel formulation.The consistency reflects the capacity of the gel, to get ejected in uniform and desired quantity when the tube is squeezed. Consistency is inversely proportional to the distance traveled by falling cone. Consistency of marketed gel was found to be 5.7mm while formulation number F9 in which Carbopol and Guar gum were used as gelling agent in ratio of 3:1 was found to be 3.0mm. Hence, the consistencies of developed gel formulations containing diclofenac sodium were better as compared with marketed gel. The marketed gel and prepared gel formulations were shared a smooth and homogeneous appearance.

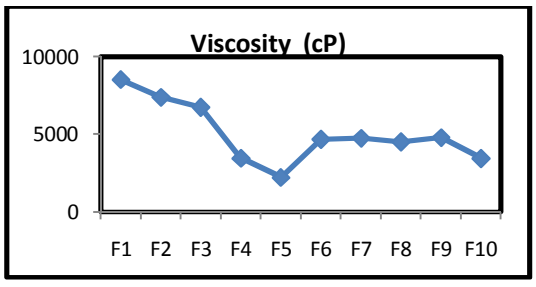

Fig. 1 Developed gel v/s Viscosity

The gelatin, Carbopol 934 and their combinations of diclofenac sodium gels were transparent while HPMC and Na CMC gels were white viscous and sodium alginate and guar gum gels were brownish gummy with smooth and homogeneous appearance. Viscosity is an important physical property of topical formulations, which affects the rate of drug release; in general, an increase of the viscosity

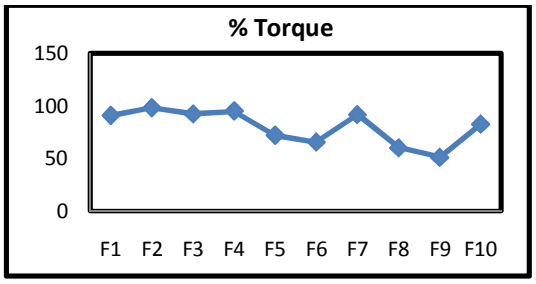

Fig. 2. Developed gel v/s %Torque

vehicles would cause a more rigid structure with a consequent decrease of the rate of drug release. During the stability studies the appearance was clear and no significant variation in pH was observed.

Formulation number F9 in which Carbopol and Guar gum were used as gelling agent in ratio of 3:1 was found more stable in comparison of marketed formulation F10, Percentage assay was found to be 100.2 %w/w and 98.41 %w/w respectively. In vitro Drug release study showed that % Release was found 84.67 in Formulation number F9 in which Carbopol and Guar gum were used as gelling agent in ratio of 3:1 whereas marketed formulation F10 showed release of 90.06 %.

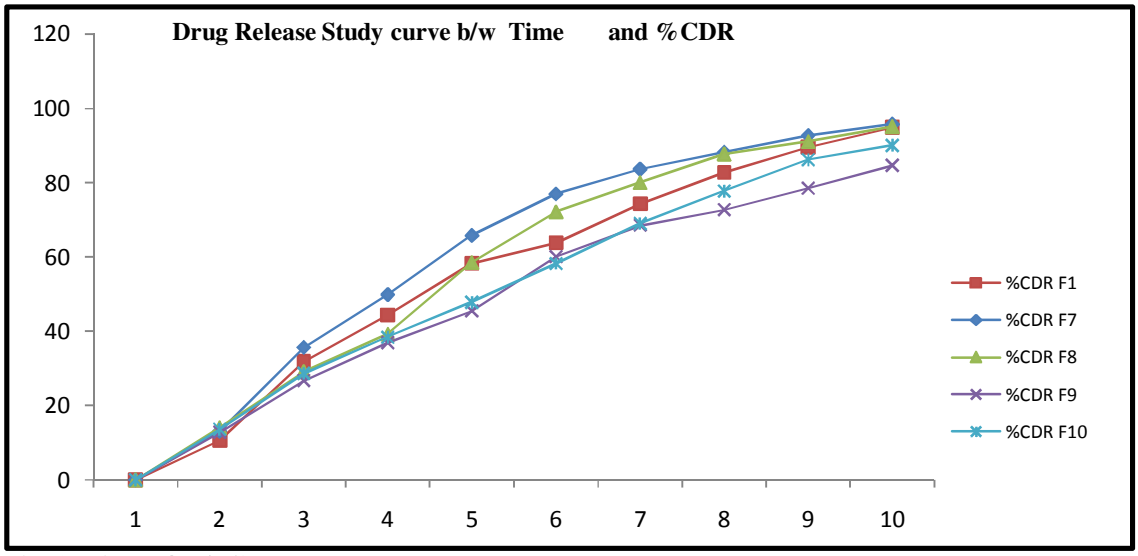

Fig. 3. Time v/s % CDR

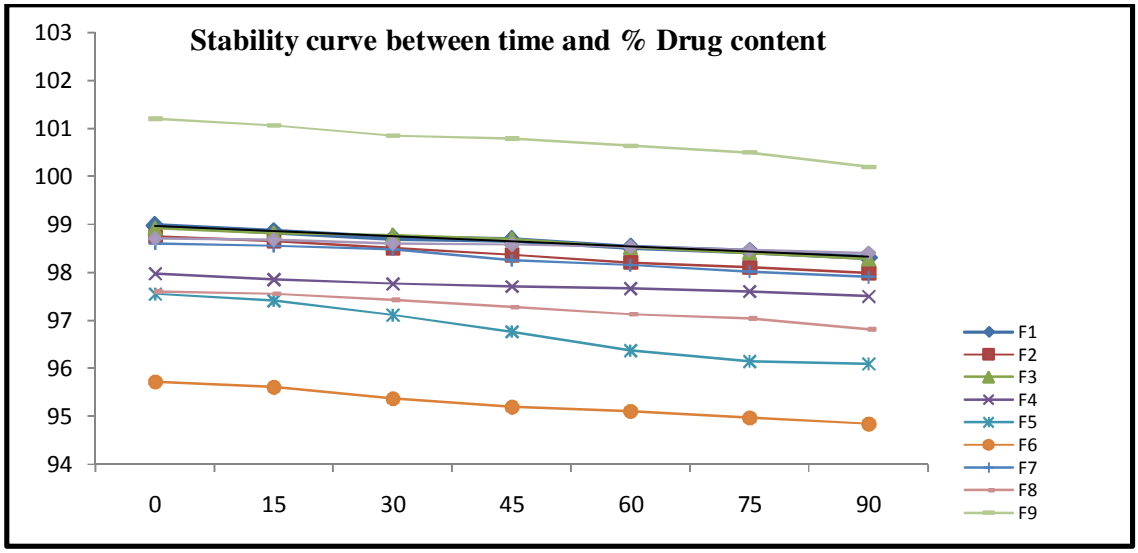

Fig. 4. Time v/s % Drug Content

Table: 6 Drug Content Determination of Developed Gels and Marketed Gel for Accelerated Stability Testing

Days	Percent Drug Content									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	99.88	98.75	98.92	97.98	97.55	95.72	98.6	97.61	101.2	98.7
15	98.85	98.66	98.82	97.85	97.41	95.61	98.56	97.55	101.06	98.68
30	98.71	98.5	98.78	97.77	97.11	95.37	98.48	97.43	100.85	98.61
45	98.67	98.37	98.69	97.71	96.77	95.2	98.25	97.28	100.78	98.58
60	98.53	98.21	98.52	97.67	96.37	95.11	98.15	97.13	100.64	98.53
75	98.44	98.11	98.41	97.61	96.15	94.97	98.02	97.04	100.5	98.47
90	98.31	97.99	98.28	97.5	96.1	94.85	97.9	96.82	100.2	98.41

Formulation containing carbopol with HPMC has showed better release of 95.77 %. Viscosity is an important physical property of topical formulations, which affects the rate of drug release; in general, an increase of the viscosity vehicles would cause a more rigid structure with a consequent decrease of the rate of drug release.[20-13]

CONCLUSION

From above results, we can conclude that Diclofenac Sodium gel formulations prepared with different gelling agents: Carbopol 934, HPMC, Sodium CMC, Guar gum, Gelatin, sodium alginate and their combinations showed acceptable physical properties and drug release study. All prepared gel showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. It can be concluded that formulation number F9 in which Carbopol and Guar gum were used as gelling agent in ratio of 3:1 produced better spreadability and consistency as compared to marketed diclofenac sodium gel. The developed F9 gel formulation showed good homogeneity, good stability and drug release study. It can be concluded that formulation F7 containing Carbopol 934 with HPMC(in ratio of 1:3) has showed better release of 95.77 % as compared with marketed gel formulation. It can be concluded that a combination of gelling agent (Carbopol 934 + Guar gum in ratio of 3:1) can be used for various topical gel formulations for external application.

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