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RESEARCH ARTICLE

Controlling Acute Inflammation with Dexamethasone in a Sustained Release Hydrogel Formulation

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Abstract: Abstact:

Dexamethasone is a potent candidate for hydrogel preparation for topical dosages form because it has metabolis by first pass metabolismand has 10% of dexamethasone is protein bound these factors promote researchers to choose this drug for the formulation of controlled release formulation which maintain adequate concentration inside body. The objective of this study was to formulate and evaluate hydrogels containing dexamethasone as a drug substance in combination with suitable co-solvents and preservatives. Preparad dexamethasone hydrogel by optimizing the ratio between carbopol and triethylamine and good quality maintained good quality of physiochemical parameter like pH, drug content, viscocity, , % entrapment, *in vitro* release behavior of hydrogel by franz diffusion cell. Release profile of dexamethasone was fit into release kinetic models to determine the mechanism of drug release and it was observed that the release was zero order system. The developed hydrogel was therapeutically efficient, stable and *in-vitro* release for 8 hour was observed.

Keywords: Dexamethasone, hydrogels, carbopol and triethylamine.

Introduction:

Polymeric hydrogels are rapidly developing new group of materials, gaining wide application in the fields of pharmacy, medicine and agriculture. hydrogels are cross-linked polymeric networks absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials[1]. Hydrogels are crosslinked polymeric networks, which have the ability to hold water within the spaces available among the polymeric chains. The hydrogels have been used extensively in various biomedical applications, viz. drug delivery, cell carriers and/or entrapment, wound management and tissue engineering.

Topical application of gels overcome the problems to be associates with other dosage forms are: Avoidance of first pass metabolism. Convenient and easy to apply. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc. Achievement of efficacy with lower total daily dosage of drug by continuous drug input. Avoids fluctuation in drug levels, inter- and intrapatient variations. Ability to easily terminate the medications, when needed. A relatively large area of application in comparison with buccal or nasal cavity Ability to deliver drug more selectively to a specific site. Avoidance of gastro-intestinal incompatibility. Providing utilization of drugs with short biological half-life, narrow therapeutic window. [2]

Inflammation and fibrosis at the implant site may be controlled with the use of steroidal and non-steroidal anti-inflammatory drugs. Since long-term systemic use of these drugs leads to unwanted side effects, localized and sustained delivery of anti-inflammatory drugs has been investigated.[3]

Dexamethasone is a glucocorticoid with a relevant clinical use mainly due to its anti-inflammatory and immunosuppressive effects. However, the great number of side effects, such as hypertension, hydroelectrolytic disorders, hyperglycemia, peptic ulcers, and glucosuria, restricts the use of dexamethasone in prolonged therapy[4]. Topical administration of dexamethasone is clinically used for the treatment of many ocular disorders, or diseases, like uveitis, allergic conjunctivitis, and corneal postoperative period, as well as for the treatment of skin disorders such as atopic dermatitis, allergic dermatitis, eczematous dermatitis, psoriasis, acne rosacea, and phimosis. Over the last years many efforts have been made not only to improve the efficacy and bioavailability of drugs but also to reduce their adverse effects by means of the development of novel drug carrier systems [5].

Material and methods:

Dexamethasone was provided Bal Pharma Pvt.Ltd, Bangalore. Carbopol 934 was purchased from Fisher scientific, Ethanol and Methyl paraben were purchased from NR Chemicals industries, Mumbai, India. Triethylamine and Polyethylene glycol were purchased from Loba Chamical, Mumbai, India.

Formulation of Hydrogel:

The various formulation of Dexamethasone hydrogels were developed with different compositions. Polyethylene glycol-400 was used for solubilization of Dexamethasone. aqueous phase (70%) was slowly added in oil phase (30%) with constant stirring using mechanical stirrer. The required amount of drug Dexamethasone was dissolved in varied amount of TEA as mentioned in the formulation table. Then methyl paraben is dissolved in EtOH and 10ml of water , after 0.2g carbopol 934 was add with continuous stirring and heating at 50^0c around 30min and allow to cool at room temperature until homogenous gel formed .the gel was sonicated for 10min to remove any trampled air bubbles then it was add to the drug as portion wise with stirring and finally adjusted to 20g with distilled water.

Table 1: Formulation of Dexamethasone Hydrogel:

Ingredients	**Formulation 1**	**Formulation 2**	**Formulation 3**
Dexamethasone	0.15g	0.15g	0.15g
Polyethylene glycol	1.0g	1.0g	1.5g
Methyl paraben	0.08g	0.06g	0.07g
Carbopol 934	0.2g	0.08g	0.09g
Ethanol	8.0g	8.0g	8.0g
Triethanolamine	0.40g	0.35g	0.45g
Distilled Water	q.s.	q.s.	q.s.

EVALUATION OF HYDROGEL

Morphology of hydrogels

Prepared hydrogels were examined for its morphological characteristics such as color and texture. Photographs of hydrogels prepared by chemical polymerization are given in figure 4.3a. Appearance of hydrogel after water absorption is shown in figure 4.3b.

Swelling behaviour of hydrogel:

The hydrogel (0.5 gm) was immersed directly in freshly prepared 0.1 M Phosphate buffer of pH 1.4, 5.4, 7.2 and distilled water for 48 hours at room temperature to study the swelling behaviour. The swollen product was then weighed again to get the final weight and percentage swelling was calculated as follows: % Swelling = (W e - W d) / W d × 100; Where We is the weight of the product after hydration for 48 hours, and Wd is the weight of the dried product.[6]

Percentage yield

The empty container was weighed in which the gel formulation was stored then again the container was weighed with gel formulation. Then subtracted the empty container weighed with the container with gel formulation then it gives the practical yield. Then the percentage yield was calculated by the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \text{ X } 100$$

Drug content

Weighed 10 gm of each gel formulation were transferred in 250 ml of volumetric flask containing 20 ml of 0.1N NaOH and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of above solution was further diluted to 10 ml with 0.1N NaOH and again 1ml of the above solution was further diluted to 10 ml with 0.1N NaOH. The absorbance of the solution was measured spectrophotometrically at 241 nm. Drug content was calculated by the following formula.

$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \text{ X Dilution factor X } \frac{1}{1000}$$

Determination of pH

Weighed 50 gm of each gel formulation were transferred in 10 ml of beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 3– 9 to treat the skin infections.[7]

Spreadability [8]

The spreadability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm^2) after 1minute. The standardized weight tied on the upper plate was 125gm.

Viscosity Estimation

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-Bar spindle in combination with a helipath stand.

a) **Selection of spindle:** Spindle T 95 was used for the measurement of viscosity of all the gels.
b) **Sample container size:** The viscosity was measured using 50 gm of gel filled in a 100ml beaker.
c) **Spindle immersion:** The T-bar spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch bottom of the jar.
d) **Measurement of viscosity:** The T-bar spindle (T95) was used for determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. Which affect the viscosity was maintained during the process. The helipath T- bar spindle was moved up and down giving viscosities at number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.

***In-Vitro* Diffusion Study**

The abdominal skin of Albino mice, weighing 20 – 25gm of 8 – 10week old was shaved using hand razor and clean the skin with hot water cotton swab. 5 gm of gel was applied uniformly to skin. The skin was mounted between the compartments of the Frantz diffusion cell with stratum corneum facing the donor compartment. Reservoir compartment was filled with 100 ml phosphate buffer of pH 7.2.

The study was carried out at 37 ± 1°C and speed was adjusted until the vortex touches the skin and it carried out for 4½ hr. 5 ml of sample was withdrawn from reservoir compartment at 30 min interval and absorbance was measured spectrophotometrically at 241nm. Each time the reservoir compartment was replenished with the 5 ml volume of phosphate buffer pH 7.2 solutions to maintain constant volume.[9]

Results and Discussion:

Formulation Design;

Three formulations of gel containing were prepared using various polymers viz PEG, methyl paraben, carbopol in different ratios (Table 1) until a suitable gel was formed. Methyl paraben were used as preservative and carbopol were used in gel forming agent.

Evaluation of formulated gel

Physical evaluation

Gel formulations were found to be translucent in nature with ethanolic odour, smooth feel on application and homogenous.

Spreadibility

Results of the spreadability testing are shown in table 5. All the prepared gels using different polymers in different concentrations were spreadable on the skin surface. The addition of propylene glycol to all the prepared formulae improved the physical characteristics concerning spreadability, consistency and skin feel. Also, its addition helped the dissolution of the drug and prevented its precipitation upon storage.

Viscosity

The data represent that with increase in the concentration of polymer viscosity was increased.

The viscocity of Dexamethasone hydrogel were 6540-9746cps.

Drug Content:

The content of Dexamethasone in all the gels was found to be within permissible limits (>96%). This indicates that the drug was uniformly distributed throughout the formulations as evident from the low standard deviation value. The results obtained as Drug content form 96.25-97.73.

pH

The pH of the developed formulations was in accordance with that of human skin pH enduring them more acceptable to avoid the risk of irritation upon application. The result of pH was 6.7-7.0.

Table 2: Several results of Hydrogel

Formulation Code	**Drug content (%)**	**pH**	**Spread ability** ($gm.cm^{-2}$)	**Viscosity Estimation** (cps)
F1	96.25 ± 0.018	6.7	11.08 ± 0.088	9467.03
F2	97.73 ± 0.042	6.9	11.75 ± 0.317	6540.06
F3	96.58 ± 0.073	7.0	10.75 ± 0.078	9746.37

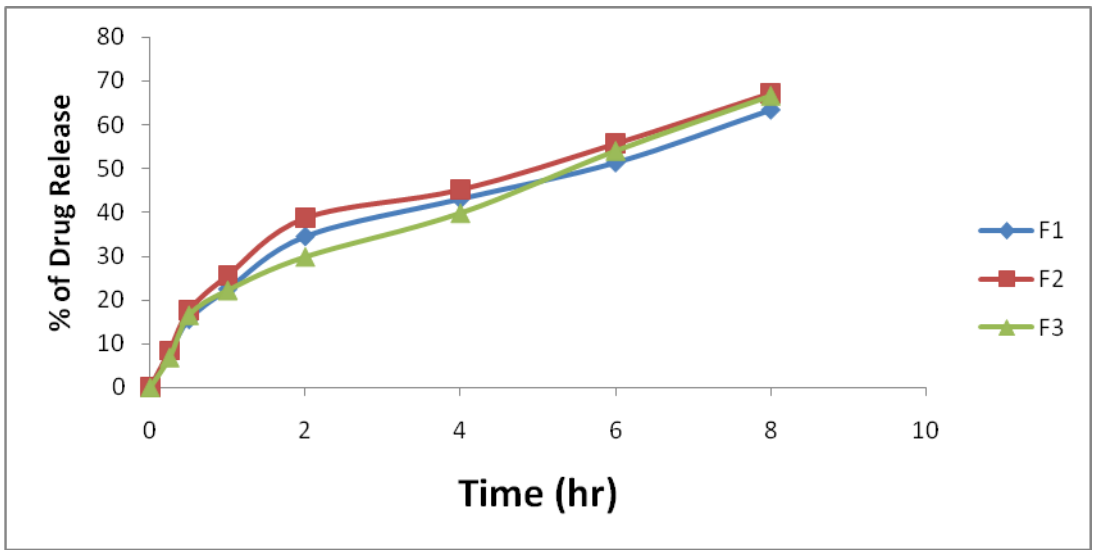
***IN-VITRO* DIFFUSION STUDY**

The in-vitro release studies were carried out by using Franz diffusion cell. In order to obtain the rate of release, the release study showed that the Dexamethasone was released in sustained manner due to the presence of the sustained release polymer Carbopol and PEG. The drug release of formulation F1 was found to be 63.360 % due to minimum concentration of Carbopol 934, on the other hand formulation F2 and F3 shown the release of 67.181% and 66.522% respectively. The % release rate of Dexamethasone from different formulation (F1, F2 & F3) in different time intervals were shown in fig 1.

Table 3: Invitro drug Release Study of Hydrogel

Time (min)	**F1**	**F2**	**F3**
0	0.000	0.000	0.000
0.25	7.894	8.438	6.834
0.5	15.545	17.606	16.476
1	22.462	25.572	22.148
2	34.458	38.674	29.770
4	43.036	45.142	39.765
6	51.315	55.659	53.971
8	63.360	67.181	66.522

Fig 1: In-vitro Drug Release Data of Dexamethasone Hydrogel



Conclusion:

Hydrogels are three dimensional crosslinked matrices which have recently become one of the most widely used material for biomedical applications. The ability of the gel to imbibe biological fluids accounts for its biocompatibility and its use in varied clinical applications, ranging from drug delivery carriers, encapsulation matrices, and food additives. Drug delivery is one of the most prominent fields of research today, and the development of biocompatible, flexible and strong materials is one of the main concerns. Dexamethasone release from the polymer was studies in Hydrogel was phosphate buffer of pH 7.2 upto 8 hrs. The release profiles of these Hydrogel are given in table no.3 and shown in graph no 1. From among all the developed formulation, F2 shows better drug diffusion for a period of 8 hours and good Rheological properties. Therefore, it was selected as the best formulation.

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