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Research Article

FORMULATION AND EVALUATION OF CLOBETASOL PROPIONATE GEL

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ABSTRACT

The aim of the study was to formulate Clobetasol propionate into a gel formulation using carbopol-934, Hydroxypropyl methylcellulose K4M, sodium alginate, Carboxymethylcellulose Sodium as gelling agents. In all the gels formulated, the concentration of propylene glycol and ethanol was kept constant at 15% and 40 % respectively. Clobetasol propionate was used in the concentration of 0.05% in all the gel formulations. Propylene glycol served as a co-solvent for drug. Triethanolamine was used to neutralize carbopol gel systems. Methyl paraben and propyl paraben were used as preservatives. A total of twenty two formulations were prepared with 6 formulation containing combination of various gelling agents. The total concentration of gelling agent in these six formulations was kept constant at 2%. The Remaining sixteen formulations were prepared with the use of four different gelling agents viz., Carbopol-934, Hydroxypropyl methylcellulose K4m, Carboxymethylcellulose Sodium and Sodium Alginate. Four formulations were prepared with each gelling agent in concentration ranging from 0.5-2.0%. Formulations were evaluated for pH, homogeneity, grittiness, viscosity, spreadability, drug content and In-Vitro drug release studies. Drug content was high (>98 %) in gels. Carbopol-934 and Hydroxypropyl methylcellulose K4M gels showed higher release of .the drug compared to Carboxymethylcellulose Sodium and Sodium Alginate The viscosity of carbopol-934 gels was very high as compared to Hydroxypropyl methylcellulose K4M gels but both gels showed decrease in drug release with increase in polymer concentration. Similarly, gels prepared with combination of carbopol-934 and Hydroxypropyl methylcellulose K4M showed better drug release than gels prepared with Carboxymethylcellulose sodium and sodium alginate.

Keywords: Clobetasol Propionate, Topical, gel, Carbopol-934, HPMC, Sodium Alginate, Carboxymethylcellulose Sodium.

INTRODUCTION

Topical drug delivery systems

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical activities may or may not require intra-cutaneous penetration or deposition [1]. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments [2]. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. 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 are other advantage of topical preparations[3]. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in pain management, contraception, and urinary incontinence.

A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin [4].The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel [5]. Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are nonsticky, requires low energy during formulation, are stable and have aesthetic value. Clobetasol propionate belongs to the class of corticosteroids and is believed to have anti-inflammatory, antipruritic, and vasoconstrictive properties [6]. The anti-inflammatory action of CP may be due to its binding to specific glucocorticoid receptors (GR), which through a cascade of events decreases the production of pro-inflammatory prostaglandins, leukotrienes and thromboxanes and leucocyte migration. It is the most potent of currently available topical steroids as predicted by the vasoconstrictor assay. In psoriasis, it has proved significantly more effective than class II steroids and as or more effective than the only marketed class I steroid. In the more steroid-responsive eczemas, the superior efficacy of clobetasol is also apparent, but less striking. Clobetasol prolongs remission rates, making intermittent treatment schedules feasible and minimizing inherent potential steroid side effects. Clobetasol may also be useful in the treatment of a myriad of other skin conditions [7].0.05% clobetasol propionate has been shown to be effective and convenient in treatment of moderate to svere scalp psoriasis[8,9]. The aim of the study is to develop and evaluate a topical gel of clobetasol propionate using various polymers like Carbopol-934, Hydroxypropyl methylcellulose K4M (HPMC K4m), carboxymethylcellulose sodium (SCMC) and sodium alginate (SA) in different concentrations.

MATERIALS AND METHODS

Material

Different grades of Hydroxypropyl methylcellulose viz., HPMC K4m, K15m and K100m were gift samples from Colorcon Asia Pvt. Limited, Goa. Carbopol-934 was purchased from loba chemicals, Mumbai Sodium alginate (SA) was purchased from Oswal scientific store. Carboxymethylcellulose sodium was purchased from loba chemicals, Mumbai, ethanol was purchased from chamgshu yanguan chemical, China, hydrochloric acid was purchased from Fisher scientific, Mumbai, Propylene Glycol was purchased from Oswal scientific store, and Triethanolamine (TEA) was purchased from Magus Chemical and scientific equipments. All other chemicals used were of analytical grade. Double distillation water (DDW) was prepared using in – house distillation unit (fabricated at Jencons).

Preparation of Gels

Various gel formulations were prepared using carbopol -934, Hydroxypropyl methylcellulose K4m (HPMC K4M), Carboxymethylcellulose Sodium (SCMC) and Sodium Alginate (SA)

as gelling agents. Required quantity of gelling agent was weighted and dispersed in a small quantity of distilled water to form a homogeneous dispersion. The drug was dissolved in Propylene glycol and added to the above solution. Other excipients (methyl paraben and propyl paraben) were also added with continuous stirring. In. carbopol gels, pH of the gel was brought to skin pH by Triethanolamine (TEA). The final weight of the gel was adjusted to 50 grams with distilled water. The gels were stored in wide mouthed bottles. Entrapped air bubbles were removed by keeping the gels in vacuum oven for 2 hours. The composition of various gel formulations is shown in Table No.1

Table1: Formulation code of clobetasol propionate gel

Formulation code	Drug	Carbopol - 934	HPMC K4M	Carboxymethyl cellulose Sodium	Sodium alginate	Propylene glycol	Ethanol	Methyl Paraben	Propyl Paraben	Triethanolamine	Distilled water
F1	0.05	0.5	-	-	-	15	40	0.3	0.6	Q.S	Q.S
F2	0.05	1.0	-	-	-	15	40	0.3	0.6	Q.S	Q.S
F3	0.05	1.5	-	-	-	15	40	0.3	0.6	Q.S	Q.S
F4	0.05	2	-	-	-	15	40	0.3	0.6	Q.S	Q.S
F5	0.05	-	0.5	-	-	15	40	0.3	0.6	Q.S	Q.S
F6	0.05	-	1.0	-	-	15	40	0.3	0.6	Q.S	Q.S
F7	0.05	-	1.5	-	-	15	40	0.3	0.6	Q.S	Q.S
F8	0.05	-	2.0	-	-	15	40	0.3	0.6	Q.S	Q.S
F9	0.05	-	-	0.5	-	15	40	0.3	0.6	Q.S	Q.S
F10	0.05	-	-	1.0	-	15	40	0.3	0.6	Q.S	Q.S
F11	0.05	-	-	1.5	-	15	40	0.3	0.6	Q.S	Q.S
F12	0.05	-	-	2.0	-	15	40	0.3	0.6	Q.S	Q.S
F13	0.05	-	-	-	0.5	15	40	0.3	0.6	Q.S	Q.S
F14	0.05	-	-	-	1.0	15	40	0.3	0.6	Q.S	Q.S
F15	0.05	-	-	-	1.5	15	40	0.3	0.6	Q.S	Q.S
F16	0.05	-	-	-	2.0	15	40	0.3	0.6	Q.S	Q.S
F17	0.05	1.0	1.0	-	-	15	40	0.3	0.6	Q.S	Q.S
F18	0.05	1.0	-	1.0	-	15	40	0.3	0.6	Q.S	Q.S
F19	0.05	1.0	-	-	1.0	15	40	0.3	0.6	Q.S	Q.S
F20	0.05	-	1.0`	1.0	-	15	40	0.3	0.6	Q.S	Q.S
F21	0.05	-	1.0	-	1.0	15	40	0.3	0.6	Q.S	Q.S
F22	0.05	-	-	1.0	1.0	15	40	0.3	0.6	Q.S	Q.S

Evaluation of Gels

A. pH Measurement [10]

The pH of various gel formulations was determined by using digital pH meter.1 g of gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

B. Homogeneity [11]

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container.

C. Grittiness [12]

Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

D. Viscosity Measurement [10, 13]

Brookfield digital viscometer was used to measure the viscosity of prepared gel formulations. The spindle no. 6 was rotated at 10 rpm. The reading, near to 100 % torque was noted. Samples were measured at 30 ± 1 °C.

E. Spreadability [14]

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value It was determined by wooden block and glass slide apparatus. Weights of about 2 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides. Spreadability was then calculated by using the formula:

S = M.L / T

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

F. Drug content [15]

A specific quantity (1 g) of developed gel was taken and dissolved in 100mL of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 h on mechanical shaker in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 293 nm using phosphate buffer (pH 7.4) as blank.

G. In-vitro Drug Diffusion Study [16]

In-vitro drug release studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated gels were weight up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 RPM; the temperature was maintained at 37 ± 0.50 °C. The samples of 1 mL were withdrawn at time interval of 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450 and 480 minutes and analysed for drug content spectrophotometrically at 240 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal.

H. Stability Study [17]

The selected formulations which showed better results (F17-F22) was packaged in air tight plastic container or aluminium container. They were then stored at 40 °C / 75 % RH, for three months and were evaluated for their pH, homogeneity, grittiness, percent drug release at 8 hours and viscosity.

RESULTS AND DISCUSSION

For the gels prepared using different polymers, the pH varied between 6.8 to 7.1.In all the gels prepared, no signs of grittiness were found. Spreadability varied between 4.98±1.43 – 62.69±1.28.The percent(%) drug content was found to be varying between 98.5±0.4 - 99.6±0.3.The percent drug release after 8 hours(Q8) was found to be between 22.98±1.2 – 71.66±1.4.The viscosity of the gels was found to be between 427±15 – 65059±26.The results of characterization of the formulations F1-F16 are shown below in table 2 and 3.

Table 2: Characterization of clobetasol propionate gels (F1 – F16)

Parameters → Formulations ↓	Homogeneity	Grittiness	pH
F1	+++	-	6.9
F2	+++	-	7.0
F3	++	-	7.1
F4	+++	-	6.9
F5	+++	-	7.0
F6	++	-	6.8
F7	+++	-	7.1
F8	+++	-	7.1
F9	+++	-	7.0
F10	++	-	6.9
F11	+++	-	6.8
F12	+++	-	6.9
F13	++	-	7.0
F14	+++	-	6.9
F15	++	-	7.0
F16	++	-	6.9

+ Satisfactory, ++ good, +++ very good, - no grittiness

Table 3: Characterization of clobetasol propionate gels (F1 – F16)

Parameters → Formulations ↓	Spreadability (g.cm/s) (Mean ±SD)*	Percentage Drug Content (Mean ±SD)**	Percentage Drug Release after 8 hours (Q_8) (Mean ±SD)***	Viscosity (centipoise) (Mean ±SD)****
F1	24.87±1.50	99.6±0.3	68.50±3.2	36601±14
F2	19.34±1.56	99.2±0.2	61.28±1.5	41625±11
F3	11.34±1.21	99.1±0.1	59.99±0.9	50025±16
F4	10.58±1.38	99.5±0.3	54.28±1.5	56228±32
F5	62.69±1.28	99.1±0.2	71.66±1.4	427±15
F6	56.17±1.37	98.9±0.3	67.26±1.9	904±21
F7	47.26±1.21	98.7±0.2	52.82±2.3	1425±19
F8	43.36±1.14	99.0±0.3	47.49±2.2	2204±08
F9	25.26±1.56	98.5±0.4	38.51±1.3	26500±29
F10	18.69±1.67	99.2±0.2	22.23±1.2	41115±85
F11	6.26±1.39	98.7±0.3	29.36±2.1	59645±27
F12	4.98±1.43	99.3±0.2	28.29±1.0	76159±56
F13	30.58±1.71	99.4±0.1	51.36±2.3	15226±08
F14	27.36±1.35	99.2±0.3	35.67±1.6	23289±17
F15	13.32±1.03	98.8±0.3	25.47±2.3	48659±13
F16	5.31±1.56	99.4±0.1	22.98±1.2	65059±26

, **, ***, * Each value is average of three independent determinations; S.D – Standard deviation**

Table 4: Characterization of gels with Carbopol-934 and Hydroxypropyl methyl cellulose (F17 – F22)

Parameters → Formulations ↓	Homogeneity	Grittiness	pH
F17	+++	-	6.9
F18	+++	-	7.2
F19	+++	-	7.1
F20	++	-	7.2
F21	+	-	6.8
F22	++	-	7.1

+ Satisfactory, ++ good, +++ very good, - no grittiness

Table 5: Characterization of gels with Carbopol-934 and Hydroxypropyl methyl cellulose (F17 – F22)

Parameters → Formulations ↓	Spreadability (g.cm/s) (Mean ±SD)*	Percentage Drug Content (Mean ±SD)**	Percentage Drug Release after 8 hours (Q_8) (Mean ±SD)***	Viscosity (cps) (Mean ±SD)****
F17	31.86±1.84	99.7±0.2	78.73±5.0	27325±26
F18	16.54±1.26	99.2±0.2	42.13±2.0	47560±17
F19	21.59±1.08	99.2±0.5	48.20±2.7	36500±19
F20	26.17±1.28	98.5±0.2	52.13±2.0	32574±15
F21	30.48±1.39	98.5±0.1	42.20±2.3	15248±26
F22	20.36±1.65	98.2±0.2	44.26±1.2	36427±11

, **, ***, * Each value is average of three independent determinations; S.D – Standard deviation; g.cm/s is grams.centimeter per second; cps is centipoise.**

Results from our preliminary batches (F1-F16) showed that carbopol-934and HPMC K4M gels have better percent drug release as compared to sodium alginate and carboxymethylcellulose sodium gels. Hence on the basis of analysing all these parameters, it was decided to use combination of different polymers to formulate clobetasol propionate gel. Batch no. F17 – F22 were prepared using different combinations of carbopol-934, HPMC K4M, SCMC and SA. The data for physiochemical characterization of these batches are shown in Table 4 and 5.The pH varied between 6.8 – 7.2.The % drug content was found to be in the range of 98.5 – 99.7%. The percent drug release after 8 hours (Q_8) was found to be between 42.13±2.0 – 78.73±5.0.The viscosity measurements varied between 15248±26 – 47560±17 Centipoise (cps).

Stability Studies

Formulation which showed promising results, were subjected to stability studies at ambient room conditions for 3 months. After 3 months (90days), no grittiness was found. Also, the homogeneity of the gels did not change. There was virtually no change in pH, drug release and viscosity. It indicates that the drug was stable in gels even after three months of short term storage. The results are presented in table no.6.

Table 6: Stability data for clobetasol propionate gels (F17-F22)

Formulation	pH Initial	pH 90 days	% Drug Release at 8 hours Initial (Mean ±SD)*	% Drug release at 8 hours 90 days (Mean ±SD)**	Viscosity (cps) Initial (Mean ±SD)***	Viscosity (cps) 90 days (Mean ±SD)****
F17	6.9	6.8	78.73±5.0	78.49±4.8	27325±26	27321±22
F18	7.2	7.2	42.13±2.0	41.97±1.9	47560±17	47522±25
F19	7.1	7.0	48.20±2.7	48.18±2.6	36500±19	36502±14
F20	7.2	7.1	52.13±2.0	52.01±2.0	32574±15	32571±14
F21	6.8	6.8	42.20±2.3	42.12±2.1	15248±26	15243±24
F22	7.1	7.0	44.26±1.2	44.21±1.3	36427±11	36426±09

*, **, ***, **** Each value is average of three independent determinations; S.D = Standard deviation; cps = centipoise.

CONCLUSIONS

Results indicated that the carbopol-934 and HPMC K4M gels show higher release of the drug compared to other gelling agents. The viscosity of carbopol-934 gels was very high as compared to HPMC K4M gels but both gels showed decrease in drug release with increase in polymer concentration. Similarly, gels prepared with combination of carbopol-934 & HPMC K4M better drug release than gels prepared with carboxymethylcellulose sodium and sodium alginate. Thus, clobetasol propionate gels can be successfully prepared using carbopol-934 and HPMC K4M as gelling agents and further optimization of their concentration of gelling agents can enhance the formulation properties.

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