Formulation Design of Hydrocortisone Films for The Treatment of Aphthous Ulcer

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Abstract:

INTRODUCTION: Research and developments in oral drug delivery has evolved to changeover of solid dosage forms from tablets to oral films. These films offer an elegant route for systemic drug delivery, with the advantage for the patients who are suffering from the difficulty of swallowing larger oral dosage forms. Aphthous ulcers are the most common oral lesions which occurs as a round or oval, with a greyish yellow, crateriform base. For the treatment of aphthous ulcer various marketed product are available such as vitamin B12 tablet, benzydomine hydrochloride mouth wash or spray, steroid lozenges and local anaesthathatics. Hence hydrocortisone is selected as choice of drug for the treatment of aphthous ulcer which exhibits anti-inflammatory and immunosuppressant properties inhibiting the clinical manifestations.

METHODS: The main aim of the present study is to develop a hydrocortisone film in order to improve the therapeutic efficacy and bioavailability of hydrocortisone for the treatment of aphthous ulcer. The hydrocortisone film was developed containing various concentrations of methylcellulose and propylene glycol (0.25 - 2.0 %w/v) by solvent casting method. Prepared films were evaluated for various characterization studies like, film forming capacity, visual appearance, thickness, weight variation, folding endurance, surface pH, drug content, disintegration time, tensile strength, in vitro release study, ex-vivo study and stability studies.

RESULTS: Total eight formulations were developed out of that, formulation F2 (1.25%w/v) is considered as the optimized formulation as it showed the best results with respect to all characterization studies. The disintegration time (44sec) and maximum in vitro drug release i.e., 97.55% was observed. Further, no significant changes were observed during stability studies for the optimized formulation.

CONCLUSION: From the study, it was concluded that hydrocortisone oral films can be formulated as a potentially useful tool for an effective treatment of aphthous ulcer with improved bioavailability, rapid onset of action and with increased patient compliance

Keywords: Aphthous ulcers, Hydrocortisone, Oral Films, Solvent casting method, Tensile strength, Ex-vivo study,
1. **INTRODUCTION:**

From past few decades there is a tremendous change in designing various drug delivery systems to achieve rapid onset of action. Travelling through various milestones from discovering a conventional tablet, capsules, modified release tablets and capsules, oral disintegrating tablets wafers to achieve oral drug administration were quite popular. Now aspiring another milestone in novel era of formulating films. Mouth dissolving films are novel dosage forms that disintegrates or dissolves in the oral cavity. These are ultra-thin postage stamp size formulations with an active agent or pharmaceutical excipients. These dosage forms are placed on the tongue or any mucosal tissue. When wet with saliva, the films rapidly hydrate and adhere on to the site of application. It rapidly dissolves or disintegrates to release the drug for mucosal absorption or with modification, allows for oral GIT absorption with quick dissolving properties. An important benefit of these dosage forms is accurate dosing as compared to liquid dosage form. Films are the most advanced form of oral solid dosage forms since they improve the efficacy of APIs by dissolving within a minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin.

Aphthous ulcers belongs to the group of chronic inflammatory diseases of the oral mucosa. The most characteristic symptom of the disease is the recurrent onset of single or multiple painful erosions and ulcers that appear mainly on unattached oral mucosa of the lips, cheeks and tongue. Occasionally the lesions may also be observed on strongly keratinized palatal and gingival mucosa. The eruptions are surrounded by a characteristic erythematous halo and covered with fibrous coating. Aphthous ulcer is classified as minor, major and herpetiform. Minor Aphthous ulcer involves the presence of one to five ulcers at a time, with each ulcer less than 1 cm in diameter. In major there are 1–10 ulcers at a time, the ulcers exceed 1 cm in diameter, and they persist for up to six weeks. In herpetiform recurrent aphthous ulcer there are 10–100 ulcers at a time, its size is usually 1–3 cm, and forms clusters that coalesce into widespread areas of ulceration lasting 7–10 days. These ulcers are only herpes-like in appearance.
Corticosteroids are a class of drugs that includes steroid hormones. Topical corticosteroid was used in the aphthous ulcer is intended to limit the inflammatory process associated with the formation of aphthae. Corticosteroids may act directly on T lymphocytes or alter the response of effector cells to precipitants of immunopathogenesis. Hydrocortisone is a corticosteroid with both glucocorticoid and to a lesser extent of mineralocorticoid activity. It exhibits anti-inflammatory and immunosuppressant properties inhibiting the clinical manifestations. Hydrocortisone is chemically designated as pregn-4-ene-3,20-dione,21 (acetyloxy)-11,17-dihydroxy-, (11β)-. It is a white to partially white, odourless, crystalline powder. Which is well absorbed after oral administration achieving peak blood concentrations after one hour. Plasma protein binding is greater than 90%, primarily bound to plasma globulin as globulins have a high affinity for hydrocortisone but low binding capacity. These pharmacokinetic parameters make hydrocortisone a suitable candidate for film formulation.

Thus, the main objective of the present investigation is to formulate oral films containing, hydrocortisone by solvent casting method which is simple and cost-effective to minimize the first pass effect, increase the oral bioavailability, to provide rapid onset of action thereby increasing patient compliance.

Although the research concerning local drug delivery for the treatment of aphthous ulcer has attracted much attention. There is greater potential in the treatment offered by local drug delivery and research as proved this to be an alternative method of current conventional treatment.

2. Material and Methods

2.1 Materials:
Hydrocortisone was procured from Yarrow Chem. Products, Mumbai. Methyl cellulose and sodium citrate were procured from S.D. fine chemical, Mumbai. All other ingredients used were of analytical grade.

2.2 Formulation method of mouth dissolving films:
Different composition formulas were optimized as a primary film former for the formulation (Table 1). Aqueous solution of methylcellulose was prepared by dissolving it in 50 ml of hot water with continuous stirring to form a homogeneous solution and then kept the solution for swelling of the polymer. Propylene glycol and sodium citrate were dissolved in 10 ml of distilled water and the drug was also separately dissolved in distilled water to form solution. Both of these solutions were
mixed in polymer solution with continuous stirring and kept for 2 hours for the removal of the air bubbles. Then the prepared solutions were cast onto moulds and kept in air for drying, then in hot air oven for 24 hours at 40°C. Finally, films were removed from the mould, cut 0.5 cm × 0.5 cm size.

2.3 Evaluation Parameters for Films:
2.3.1 FTIR studies:
The compatibility of drug in the formulation was confirmed by IR spectra of pure drug alone and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by KBr Disc method.

2.3.2 Scanning electron microscopy (SEM):
The morphology and surface topography of the film were examined by scanning electron microscopy. The samples to be examined were mounted on the SEM sample stab using a double-sided adhesive tape. The samples mounted were coated with gold (200˚A) under reduced pressure (0.001 torr) for 5min to improve the conductivity using an Ion sputtering device.

2.3.3 Differential Scanning Colorimetry (DSC):
Thermal properties of pure drug and the formulation were evaluated by Differential Scanning Colorimetry. It is used to determine drug excipient compatibility studies, and also used to observe more phase changes, such as glass transitions, crystallization, amorphous forms of drugs and polymers. The analysis was performed at a rate 5°C to 200°C temperature range under nitrogen flow.

2.3.4 Thickness:
The thickness of film was evaluated using a screw gauge with a range of 0–10mm and revolution 0.001 mm. Anvil of the thickness gauge was turned and the film was inserted after making sure that the pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down. The estimations were carried out in triplicate.

2.3.5 Variation of Mass:
Mass of 0.5cm² film from different batches of the formulations was noted on electronic balance. The estimations were carried out in triplicate.


2.3.6 Folding Endurance.
Folding endurance was determined by repeated folding of the film at the same place till the film breaks. This gives an indication of the brittleness of the film. The number of times the film was folded without breaking was computed as the folding endurance value. The estimations were carried out in triplicate.

2.3.7 Surface pH
The surface pH of film is determined in order to investigate the possibility of any irritation in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to keep the surface pH as close to neutral as possible. A combined pH electrode is used for this purpose. Film is slightly wet with the help of water and the pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed in triplicate and mean ± S.D calculated.

2.3.8 Drug Content:
The film of 0.5 cm² film was taken in a 10ml volumetric flask and dissolved in 5ml of methanol and then final volume was made up with methanol. Samples were suitably diluted with artificial saliva and the absorbance was measured at 242 nm. The estimations were carried out in triplicate.

2.3.9 In Vitro Disintegration Studies:
Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. In case of films the disintegration and dissolution procedures are hardly distinguishable. If the films disintegrates it concurrently dissolves in a small amount of saliva which makes it difficult to mimic these natural conditions and measures with an adequate method. However, in the present investigation two methods of disintegration were adopted.

A. Drop Method.
In the first method one drop of distilled water was dropped by a pipette onto the oral films. The films were placed on a glass slide and then the glass slide was placed planar on a Petridis. The time until the film dissolved and caused a hole within the film was measured. The estimations were carried out in triplicate.

B. Petridish Method.
In this method 2mL of distilled water was placed in a Petridish and one film was added on the surface of the water and the time required until the oral film dissolved completely was measured. Drug-loaded films were investigated under both methods. The estimations were carried out in triplicate.
2.3.10 Tensile Strength.
Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

\[
\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}
\]

It was measured using Shimadzu AG-100kNG (Winsoft tensile and compression testing). The film of size 5 × 5 cm² and free of physical imperfections was placed between two clamps held 10mm apart. The film was pulled by a clamp at a rate of 5 mm/min. The whole experiment was carried out in triplicate.

2.3.11 In Vitro Dissolution Studies.
The in vitro dissolution studies were conducted using 500 ml of artificial saliva as dissolution medium with modified type I dissolution apparatus. A temperature of 37°C and 50 rpm was used. Each film with a dimension of appropriate size equivalent to 5 mg of hydrocortisone was placed on a watch glass covered with nylon wire mesh. The watch glass was then dropped into a dissolution flask Figure 1. 5 ml samples were withdrawn at 1, 2, 3, 4, 5, 6, 7 and 8 hrs time intervals and every time replaced with 5 mL of fresh dissolution medium. The samples were analyzed by measuring absorbance at 242 nm. The dissolution experiments were conducted in triplicate.

2.3.12 Ex-Vivo Diffusion Studies:
Ex-vivo release study was conducted using fresh chicken skin, the skin was soaked in the sodium bromide solution for 5-6 hrs and washed with water so as to remove the adhering fat tissue. Than the skin was mounted in the diffusion cell containing phosphate buffer of pH 6.8. The temperature of the medium thermostatically controlled at 37±1.0°C and 5ml of the sample were withdrawn at predetermined intervals and were spectrophotometrically estimated at 242 nm against their respective blank formulation.

2.3.13 Drug release kinetics:
Investigation for the drug release from the films was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism was understood by fitting the data to Kosemeyer Peppas.

2.3.14 Stability study
Stability study for oral films is carried out for all the batches for a short-term period of three months. After predetermined time intervals, the films are evaluated for the drug content, pH, thickness, disintegration study and physical appearance.

3 Results and Discussion:

3.1 FTIR Studies:
Infra-red spectra of pure drug Hydrocortisone and combination of drug with polymers (Methyl cellulose) were obtained and shown in figures. All the characteristic peaks of Hydrocortisone were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of the drug and the formulation and its shown in the Figure 2.

3.2 SEM Analysis.
Macroscopically the prepared Hydrocortisone film were clear. The scanning electron photomicrograph of the selected films at 400x magnification are shown in Figure 3. The SEM photographs of films showed smooth surfaces without any scratches or transverse striations indicating that Hydrocortisone is uniformly distributed and no crystals of Hydrocortisone were observed in the films.

3.3 DSC study:
The DSC study of pure drug showed sharp endothermic peak at 220.26°C. Similar endothermic peaks were obtained in the formulations at 202.62°C clearly indicated that there was no drug polymer interaction. Results of DSC thermogram were shown in the Figure 4.

3.4 Thickness of the films:
The thickness was measured with a screw gauge at different places of the film in order to evaluate the reproducibility of the preparation method. The thickness was found to be in the range of 470 ± 0.09 to 490 ± 0.03 µm. Around 90% of wet film thickness was lost during drying. The results are given in Table 2. For the prepared film a good uniformity of thickness was observed.

3.5 Weight variation of the films:
Films of 0.5 cm² were cut from different batches and weighed. The weights of different formulation were found to be in the range of 0.0098 to 0.0100(g) and the results are given in Table 2. Same mass of film was obtained with three batches of films indicating reproducibility of preparation method and formulation.
3.6 Folding endurance
All the prepared films have an acceptable folding endurance. The folding endurance test was found to be in the range of 122 to 146 folds and no films developed any visible cracks or breaks, thus showing good folding endurance. Among the five different formulation the formulation F5 has higher folding endurance due to the presence of higher concentration of methylcellulose (2.00% w/v) when compared with other films. The results were shown in Table 2.

3.7 Surface pH of the films
The surfaces pH of all films was found to be in the range of 6.37±0.08 to 6.79 ± 0.01. It assured that there will not be any kind of irritation to the mucosal lining of the oral cavity and the results were tabulated in the Table 2.

3.8 Disintegration Time
The disintegration time was found to be in the range of 40 to 55 sec in drop method were as in Petri dish method it was found to be in the range of 43 to 56 sec are given in Table 2. These results indicated that the formulation F1 disintegrated faster than the other formulations in drop method. With the Petri dish method F1, F2 and F3 formulations disintegrated/dissolved faster than the other formulations.

3.9 Drug Content
Films of 0.5 cm² were cut from different places of the whole films for the estimation of drug content. The results were found to be in the range of 95.6 to 98.4% are given in Table 3. These results indicated a good uniformity of Hydrocortisone within films, and overall good solubilisation of Hydrocortisone in the formulations was observed.

3.10 Tensile Strength
Films should possess moderate tensile strength, high % elongation (% E) and high percent of drug release. The results revealed that all the films showed moderate tensile strength values ranges from 0.614 to 0.872 (kg/mm²), among all formulations, F2 formulation showed highest % E and tensile strength when compared with other formulations. The nature and concentration of polymer affects tensile strength and % elongation. Formulation F2 having optimum concentration of methylcellulose (1.25%) showed highest % of tensile strength and % elongation. The results were given in Table 3.

3.11 In Vitro Dissolution Studies
The hydrocortisone films were prepared by using Methyl cellulose as film forming polymers with sodium citrate. The *in vitro* dissolution profiles of Hydrocortisone film were performed for all the different formulation are shown in Figure 5. The cumulative percent released Hydrocortisone was up to the end of 8 h. The release rate from different films shows that, release of drug was increased with increase in the concentration of release retardant polymer at certain level i.e. 1.25%, further increase in concentration of the polymer concentration decreases the release behavior of formulation significantly.

### 3.12 Release kinetics:
In order to determine release kinetics, data of release profile were subjected to various kinetics models. The release exponent ‘n’ values of korsmeyer- peppas model was found in between 1.564 to 1.853, indicating the drug release pattern was super case II mechanism. The data of kinetics studies were dissipated in Table 4.

### 3.13 Ex-vivo studies:
Among the five-different formulation the best formulation was selected from the film were subjected to *ex-vivo* release study through chicken skin using diffusion cell. The *ex-vivo* release would give a better estimate of drug permeation characteristics through animal skin. The amount of drug permeated through skin after 8 hrs from the formulation was shown in the Figure 6.

### 3.14 Stability study
The selected optimized formulation F2 was subjected to short term accelerated stability studies for three months at 25º/60% and 40º/75% RH, the samples were evaluated for any physical changes, disintegration rate, pH and drug content. No discernible change in the physical appearance was seen in the samples and the disintegration rate, pH and drug content values was found to be same. The film was white smooth, non-sticky and flexible after the stability studies.

### 4 Conclusion:
The main objective of the study was to formulate and evaluate oral film containing Hydrocortisone. The films can be easily formulated by solvent casting method by using polymers such as methylcellulose of different ratios with suitable plasticizer like propylene glycol. Compatibility of Hydrocortisone with polymers was confirmed by FTIR, SEM and DSC studies. It was observed that the physicochemical characteristics such as uniformity of weight, thickness, folding endurance, surface
pH, and uniformity of drug content of all the film samples showed satisfactory results with respect to variation of these parameters between films of same formulation. Tensile strength and percentage elongation of the films were increased with increase in the concentration of methylcellulose polymer. Disintegration time of the films was found to be 40 to 55 sec. Based on the physicochemical parameters and *in vitro* drug release studies, formulation F2 and F4 were considered as the best formulations which exhibited the drug release of 97.54% and 94.29% respectively at the end of eight hours. *Ex vivo* drug release studies through chicken skin also showed similar results. Present study reveals that all the five formulated films showed satisfactory film parameters. Out of these five formulations the formulation F2 (1.25% w/v) has shown better results when compared to other formulation. From the present investigation it can be conclude that film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

**ACKNOWLEDGEMENT**

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References:

Table 1: Formulation design of oral film

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Hydrocortisone (%w/v)</th>
<th>Methyl cellulose (%w/v)</th>
<th>Sodium citrate (%w/v)</th>
<th>Propylene glycol</th>
<th>Distilled Water</th>
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<tr>
<td>F1</td>
<td>1</td>
<td>1.00</td>
<td>0.25</td>
<td>1.00</td>
<td>Q. S</td>
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<tr>
<td>F2</td>
<td>1</td>
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<td>Q. S</td>
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<td>F3</td>
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<tr>
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<td>1.75</td>
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Table 2: Characterization studies:

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<th>Formulation Code</th>
<th>Variation of Mass (g)</th>
<th>Thickness (μm)</th>
<th>Surface pH</th>
<th>Disintegration time (sec)</th>
<th>Folding endurance</th>
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<td></td>
<td></td>
<td></td>
<td>Drop method</td>
<td>Petridish method</td>
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<tr>
<td>F1</td>
<td>0.0098±0.0004</td>
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<td>6.52±0.016</td>
<td>40±0.045</td>
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<td>490±0.03</td>
<td>6.79±0.024</td>
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<td>6.55±0.022</td>
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<td>6.49±0.019</td>
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Table 3: Tensile Strength and Elongation Strength:

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<tr>
<th>Batch Code</th>
<th>Tensile strength (kg/ mm²)</th>
<th>Elongation (%)</th>
<th>Drug Content (%)</th>
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<tr>
<td>F1</td>
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Table 4: Release exponent values and rate constant values for different formulation

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<th>KINETIC MODELS</th>
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<tr>
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<tr>
<td>F5</td>
<td>0.979</td>
<td>0.319</td>
<td>0.856</td>
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Table 5: Stability study

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<th>Formulation (F2)</th>
<th>Surface pH</th>
<th>Disintegration time (sec)</th>
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<td></td>
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<td>Drop method</td>
<td>Petridish method</td>
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<tr>
<td>Before</td>
<td>6.79±0.024</td>
<td>44±1.27</td>
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<td>After</td>
<td>6.74±0.015</td>
<td>46±1.03</td>
<td>460±1.22</td>
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Figure 1: A. FTIR of pure drug, B. FTIR of drug with polymer
Figure 2: A. SEM of formulation (F1) B. SEM of formulation (F2) C. SEM of formulation (F3) D. SEM of formulation (F4) E. SEM of formulation (F5)
Figure 3: A. DSC of pure drug  B. DSC of polymer  C. DSC of formulation (F1)  D. DSC of formulation(F2)  E. DSC of formulation (F3)  F. DSC of formulation (F4)  G. DSC of formulation (F5)
Figure 4: Comparative drug release profile of the formulations

Figure 5: Ex-vivo release studies