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RESEARCH ARTICLE
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COMPARATIVE STUDY OF HYDROCORTISONE IN-SITU GEL AND BUCCAL MUCOADHESIVE FILM FOR EFFECTIVE MANAGEMENT OF APHTHOUS ULCERS

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Abstract:
The in-situ gels and film were developed by using methylcellulose, based on the concept of temperature dependant gelling system. The sol-to-gel transformation occurred during the reduction of temperature. The in-situ gels were evaluated for gelling capacity, drug content, viscosity & in-vitro release were as in the film it evaluated for tensile strength, folding endurance, thickness etc. The experimental part shows that viscosity of the sol was increased by increasing the concentration of polymer. All the results were found to be satisfactory, when compared between the in-situ gels and films. The has shown the best formulation because of their therapeutic efficacy and provided sustained release of the drug over a period of time. These results demonstrate that the developed system is an alternative to conventional drug delivery system, patient compliance, industrially oriented and economical.

Key words: *In situ*, Film, Methylcellulose, Gellation temperature & gellation time.

Introduction:

In situ gel:*In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. The development of *in situ* gel systems has received considerable attention over the past few years[7]. Capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort[8]. *In situ* gel can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption, they swell to form a strong gel that is capable of prolonging the residence time of the active substance, *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes.

IMPORTANCE OF IN SITU GELLING SYSTEM:

The major importance is the possibilities of administrating accurate and reproducible quantities compared to already formed gel.*In-situ* forming polymeric delivery system having advantages like ease of administration and reduced frequency of administration improved patient compliance and comfort.Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye and undergoes a sol-gel transition from instilled dose.Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects**.**

Oral Films:

A Film can be defined as a dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be bio adhesive polymer), which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in that oral cavity (i.e., buccal, palatal, gingival, lingual or sublingual, etc.) to provide rapid local or systemic drug delivery[16].Peroral dosage forms can be distinguished as solid or liquid oral dosage form in which the prior fall in category of pills, capsules, granules and powders. While the later includes solution/ suspensions or emulsions offering more advantages over monolithic solid dosage forms. However, they also possess certain disadvantages such as finding non-toxic excipients and need preservatives, which might cause adverse effects in children, microbiological stability, and also shows problems with the taste masking and dose accuracy. To overcome these problems associated with the liquid's dosage forms, oral dissolving tablets were designed in early centaury which slowly led to their further development and thus came the existence of oral disintegrating films.

APHTHOUS ULCER:

Aphthous comes from the greek word "aptha" which means ulcer, the medical literature continues to refer these as oral lesions as aphthous ulcer. Aphthous ulcer are round or oval with grayish yellow, has surrounded by crateriform base surrounded by an erythematous halo of inflamed mucosa. The ulcer usually occurs on the nonkeratinized oral mucosa, including the lips, the buccal mucosa, the floor of the mouth, the soft palate, and the ventral surface of the tongue. Regions of keratinized oral mucosa, such as the hard palate, the gums, and the dorsal surface of the tongue, are uncommon locations.

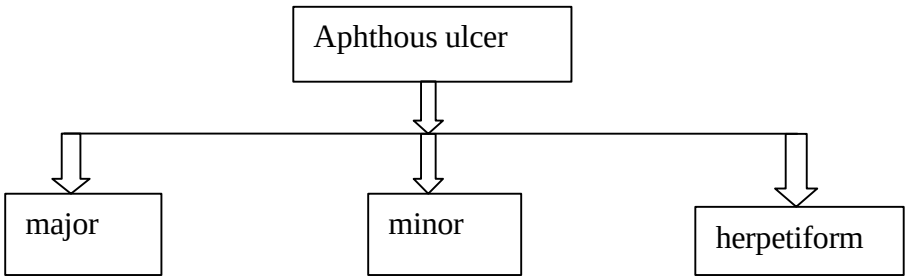


Figure: Classification of aphthous ulcer

The aphthous ulcer has been classified into 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. These ulcers are self-limiting and resolve in 7–10 days without scarring. Major aphthous involves 1–10 ulcers at a time, the ulcers exceed 1 cm in diameter, and they persist for up to six weeks. Major aphthae are a cause of significant dysphagia and often result in extensive scarring. In herpetiform aphthae there are 10–100 ulcers at a time, ulcer size is usually 1–3 cm, and the ulcers form clusters that coalesce into widespread areas of ulceration lasting 7–10 days.Corticosteroids are

a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories. The adrenal cortex secretes glucocorticoids (GC), mineralocorticoids (MC) and androgens. Corticosteroids are involved in a wide range of physiologic processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.Glucocorticoids have potent anti-inflammatory actions, including the reduction in the number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils, at sites of inflammation. Glucocorticoids decrease the production of cytokines, chemokines, and eicosanoids and enhances the production of macrophage migration inhibitory factor.

Preformulation Studies:

Calibration curve of Hydrocortisone:

The absorbance was measured in a UV spectrophotometer (Shimadzu UV"1800) at 242 nm in methanol. Calibration curve was plotted as shown in the figure.

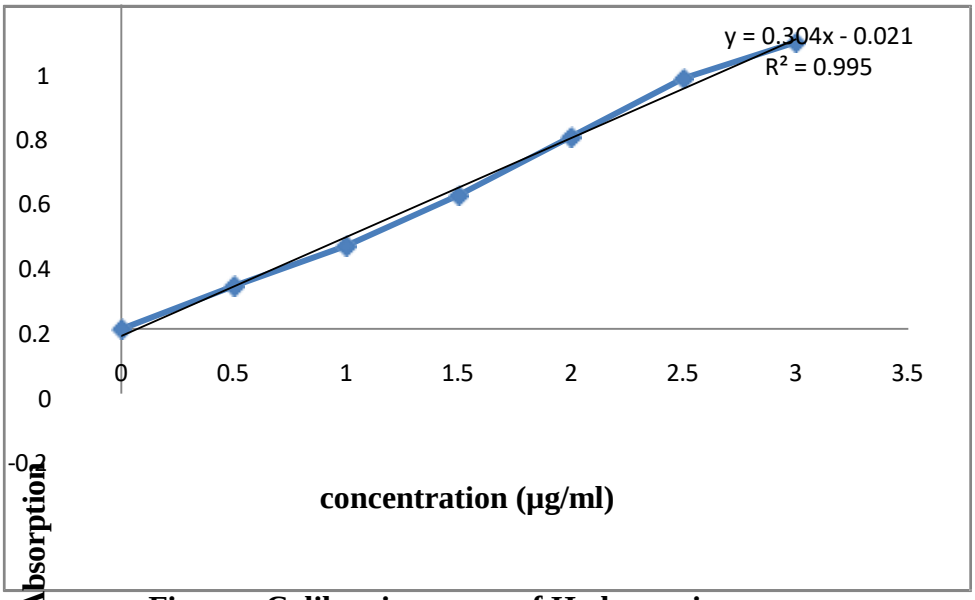


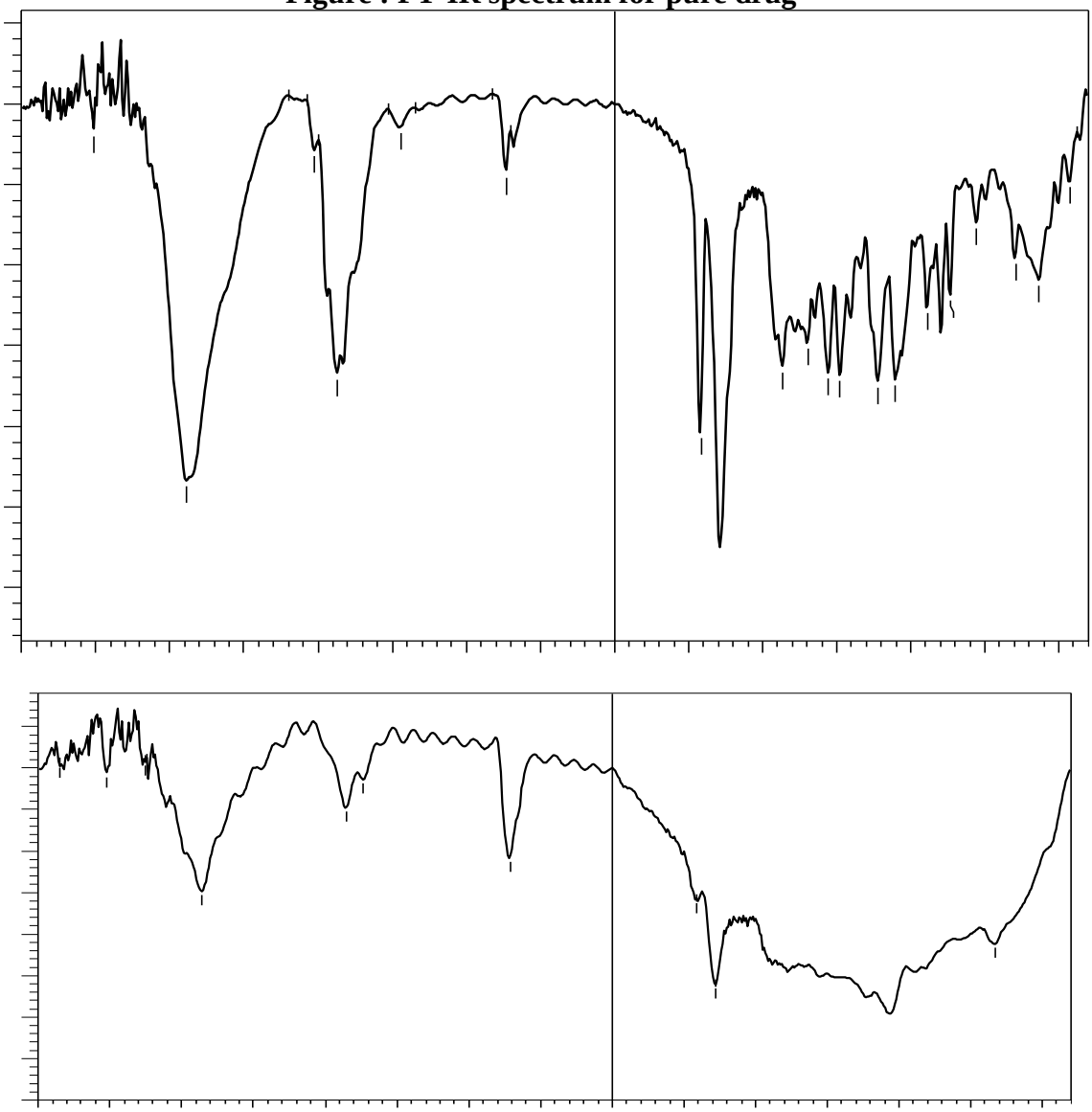
Figure : Calibration curve of Hydrocortisone

FT-IR spectrum

Infra-red spectra of pure drug Hydrocortisone 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.

Figure : FT-IR spectrum for pure drug



ATERIALS AND METHODS:

Table: Formulation design of *in situ* gel

Batch Code	Hydrocartisone (%w/v)	Methyl cellulose (%w/v)	Sodium citrate (%w/v)	Triethanolamine	Distilled Water
F1	1	0.25	0.25	Q.S	Q.S
F2	1	0.50	0.25	Q.S	Q.S
F3	1	0.75	0.25	Q.S	Q.S
F4	1	1.00	0.25	Q.S	Q.S
F5	1	1.25	0.25	Q.S	Q.S
F6	1	1.50	0.25	Q.S	Q.S
F7	1	1.75	0.25	Q.S	Q.S
F8	1	2.00	0.25	Q.S	Q.S

Preparation of *in situ* gelling system:

For the preparation of methyl cellulose containing *in situ* gel formulations, sodium citrate was added to distilled water with continuous stirring until clear solution was obtained. Methyl cellulose was

added to above solution with continuous stirring and allowed to hydrate overnight. Calculated amount of Hydrocartisone (1% w/v) drops triethanolamine was added separately and then added to polymer solution under constant stirring. The formulation design Of Hydrocartisone in situ gel was tabulated. The optimization concentration of methyl cellulose was selected on the basis of gelation temperature and gelation time. Further, the prepared formulations were evaluated for various characterization studies.

Formulation design of oral films:

Batch Code	Hydrocar tisone (%w/v)	Methyl cellulose (%w/v)	Sodium citrate (%w/v)	Propylin glycol	Distilled Water
F1	1	0.25	0.25	0.25	Q.S
F2	1	0.50	0.25	0.50	Q.S
F3	1	0.75	0.25	0.75	Q.S
F4	1	1.00	0.25	1.00	Q.S
F5	1	1.25	0.25	1.25	Q.S
F6	1	1.50	0.25	1.50	Q.S
F7	1	1.75	0.25	1.75	Q.S
F8	1	2.00	0.25	2.00	Q.S

Evaluation of hydrocortisone *in situ* gels:

Determination of pH

The pH of *in situ* gels was determined using a calibrated pH meter. The readings were taken for average of 3 samples. Methylcellulose exhibited pH values in the range of 5.8 to 6.9 at 25°C which is tabulated in Table.

Formulation code	pH
F1	5.8±0.008
F2	5.9±0.057
F3	6.2±0.044
F4	6.4±0.072
F5	6.9±0.090
F6	6.5±0.051
F7	6.8±0.018
F8	6.8±0.005

***In vitro* gelling capacity:**

It was found that the gel intensity was increased when the concentration of polymers was increased. Experimental parts (Table) have showed that the formulation F7 and F8 were satisfactory to cause gelation.

Formulation code	Gelling capacity
F1	+
F2	+
F3	+
F4	+
F5	++
F6	++
F7	+++
F8	+++

+ - Gels after few mints disappear rapidly
++ - Immediately gelling re-disappeared after hour
+++ - Immediately gelling staying for hours

Spreadability Test:

With increase in the concentration of the polymeric component, viscosity of the solution was increased. At the same time Spreadability of the formulation was reduced. This can be observed from the evaluation tests data compiled in Table. F1 formulation showed a higher Spreadability compared to F8 formulation because gel strength and viscosity of F8 formulation were higher. Consequently, its Spreadability was less.

Formulation code	**Spreadability**
F1	12 ± 0.03
F2	13.6 ±0.15
F3	14.2 ±0.11
F4	16 ±0.09
F5	18.3±0.05
F6	22.5 ±0.18
F7	26.8 ±0.06
F8	30± 0.011

Drug content:

The drug content estimation was done and the absorbance were measured by UV spectrophotometer (Shimadzu UV"1800), drug content was calculated (Table 14). Drug content of all formulations was found between 76.4±0.051 to 97.6±0.093 w/v.

Table: Drug content of *in situ* gel

Formulation Code	**Absorbance (nm)**	**Conc. of drug µg/ml**	**% of Drug**
F1	0.206	0.700	80.3±0.012
F2	0.196	0.66	76.4±0.051
F3	0.208	0.707	81.1±0.076
F4	0.217	0.738	84.7±0.082
F5	0.250	0.850	97.6±0.093
F6	0.218	0.741	85.1±0.091
F7	0.247	0.840	96.4±0.097
F8	0.243	0.826	94.8±0.066

Evaluation of oral films:

Surface PH of the films:

The surfaces PH of all films were 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.

Table: Surface PH of the films:

Formulation Code	Surface PH
F1	6.48±0.013
F2	6.37±0.027
F3	6.50±0.018
F4	6.52±0.016
F5	6.79±0.024
F6	6.55±0.022
F7	6.62±0.015
F8	6.49±0.019

Thickness:

The thickness was measured with a screw gauge at different places of the MDFs in order to evaluate the reproducibility of the preparation method. Around 90% of wet film thickness was lost during drying. The results are given in Table 20. For the prepared film a good uniformity of thickness was observed.

Table: Thickness:

Formulation Code	Thickness (μm)
F1	450±0.06
F2	467±2.04
F3	458±1.08
F4	470±0.09
F5	490±0.03
F6	475±0.07
F7	476±1.66
F8	480±2.04

Drug Content:

Films of 0.5 cm^2 were cut from different places of the whole films and Hydrocortisone content was estimated. The results are given in Table 21. These results indicated a good uniformity of Hydrocortisone within films, and overall good solubilisation of Hydrocortisone in the formulations was observed.

Table : Drug Content

Formulation Code	Conc. Of polymer % w/v	Absorbance (nm)	Conc. of drug µg/ml	% of Drug
F1	0.25	0.240	0.816	93.7
F2	0.50	0.239	0.812	93.2
F3	0.75	0.242	0.823	94.5
F4	1.00	0.245	0.833	95.6
F5	1.25	0.252	0.857	98.4

F6	1.50	0.246	0.836	96.0
F7	1.75	0.250	0.850	97.6
F8	2.00	0.248	0.843	96.8

Tensile Strength:

MDFs should possess moderate tensile strength, high % elongation (% E), low EM, and high percent of drug release. The results revealed that all the films showed moderate tensile strength values. Among all formulations, F5 formulation showed highest % E and tensile strength when compared with other formulations. The nature and concentration of polymer affects tensile strength and % elongation. Formulation F5 having optimum concentration of methylcellulose (1.25%) showed highest % of tensile strength and % elongation. The results were given in Table.

Table : Results of Tensile strength

Formulation code	**Tensile strength** (kg/ mm^2)	**% Elongation**
F1	0.454±0.015	5.67±0.013
F2	0.476±0.093	5.92±0.043
F3	0.479±0.081	5.99±0.042
F4	0.614±0.034	6.67±0.071
F5	0.672±0.044	7.67±0.005
F6	0.534±0.072	6.1±0.008
F7	0.510±0.008	6.01±0.072
F8	0.489±0.023	5.52±0.003

Folding Endurance*:*

All the prepared MDFs have an acceptable folding endurance. In folding endurance test no films developed any visible cracks or breaks, thus showing good folding endurance. F8 has higher folding endurance when compared with other MDFs. The results were shown in Table.

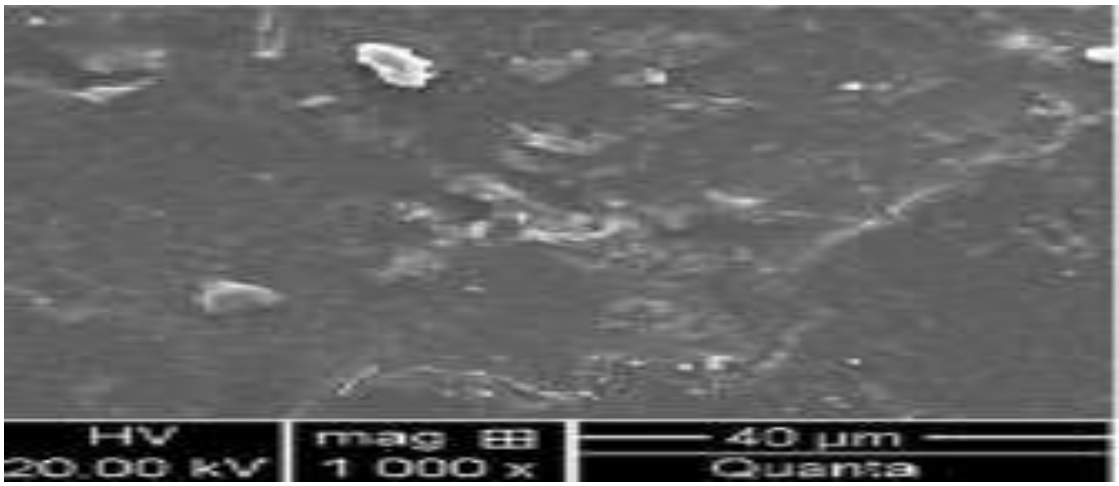
Table : Folding Endurance

Formulation Code	**Folding endurance**
F1	80
F2	95
F3	113
F4	122
F5	130
F6	134
F7	140
F8	146

Scanning electron microscopy of oral film:

One of the oral film formulations was subjected to SEM studies to assess changes in its

surface morphology (Fig.). Initially prepared film revealed smooth and compact surfaces but, after dissolution studies, the film appeared porous and showed significant changes in texture and clearly visible pores. This might be due to the uptake of water resulting from the presence of methylcellulose in the formulations. Based on these results, it can be concluded that the methylcellulose in patches absorbs water and significantly affects their surface morphology and leads to the formation of pores in accordance with the in vitro dissolution data.



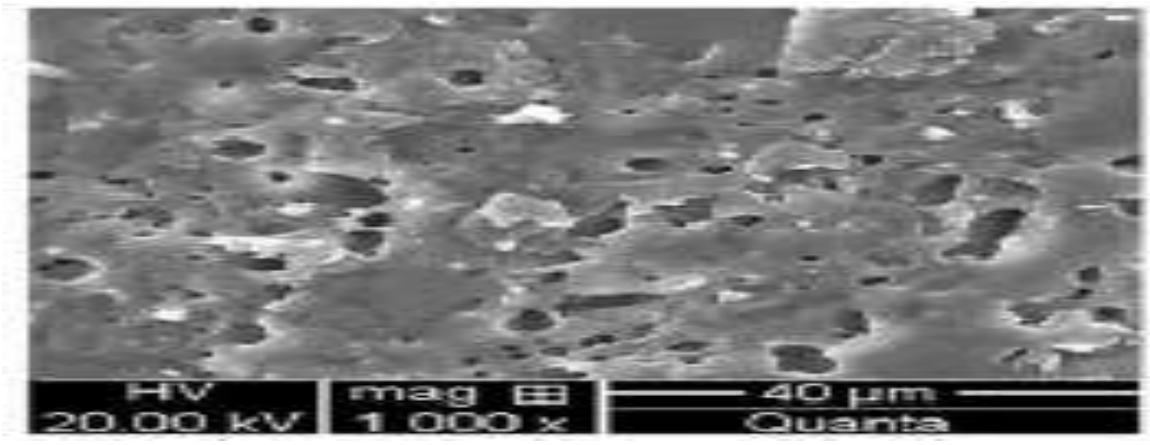


Figure: SEM image of oral film
Figure: SEM image of oral film after dissolution

CONCLUSION:

The present work is an attempt to develop a *in situ* gels and films of Hydrocortisone from temperature induced gelling system. The study has demonstrated various aspects and from the results obtained, it was concluded that

✓ *In situ* gel formulation of Hydrocortisone with mucoadhesive properties is useful to prolonging residence time in mouth.

✓ The developed formulation can release the drug at controlled rate for prolonged duration.

✓ Local drug delivery may be an advantageous in treatment, since it would probably eliminate side effects, which occur with systemic dosing.

✓ Effective and prolonged release of drug could be achieved without much systemic load with comparatively less frequency of administration.

✓ This type of drug delivery system can serve as a novel approach for treating mouth infections with better patient compliance.

✓ The optimized formulations F5 (Methylcellulose 1.25%), F6 (Methylcellulose 1.50%), F7

(Methylcellulose 1.75%) were liquid before instillation into mouth and underwent rapid gelation upon instillation into mouth.

✓ The formulations were found to be clear, having good *in situ* gelling capacity and a drug content 84-96%.

✓ Optimised formulations were sterile and showed sustained drug release over 8 hrs.

Hence from the above results we can conclude that it is possible to formulate *in situ* gels and films of Hydrocortisone using Methylcellulose for treating aphthous ulcer. In that the (F5) film formulation has shown the best release studies when compared to other formulation, and when compared between the *in-situ* gels and films formulation the films is having sustained and prolonged release of the drug compared to the *in-situ* gel.

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