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Design, Development and Evaluation of Oral Gel for Mouth Ulcer

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A B S T R A C T

The goal of this work is to create hydrocortisone in situ gels and films using a temperature-induced gelling technique. Several aspects of the study were presented, and based on the results, it was determined that the in situ gel formulation of hydrocortisone with mucoadhesive properties is helpful in extending the drug's residence time in the mouth. The developed formulation can release the drug for an extended period of time at a controlled rate. Since local medication administration is likely to prevent adverse effects that arise with systemic doses, it may be beneficial in therapy. With a somewhat lower frequency of delivery, an effective and extended release of the medication might be obtained with little systemic burden. With improved patient compliance, this kind of medication delivery device may be a cutting-edge method of treating oral infections.

Therefore, based on the data above, we can say that methylcellulose can be used to create hydrocortisone gels and films in situ for the treatment of aphthous ulcers.

Keywords: Oral Gel, Mouth Ulcer, Sustained release formulation. Aphthous ulcer.

1. Introduction

One kind of mucoadhesive drug delivery technology is in situ gel forming drug delivery. Over the past several years, there has been a lot of interest in the development of in situ gel systems7. ability to maintain comparatively stable plasma profiles while delivering the medication continuously. When these hydrogels come into touch with bodily fluids or experience a pH shift, they gel from being liquid at room temperature. These are distinguished by their cation-induced, pH-dependent, and temperature-dependent gelation. In situ forming drug delivery systems provide potential benefits over traditional controlled release formulations, including a straightforward manufacturing procedure, convenience of administration, decreased frequency of administration, enhanced patient compliance, and comfort[8].

Applying liquid in situ gel to the medication absorption site is simple. Oral, ophthalmic, rectal, vaginal, injectable, and intra-peritoneal methods are used to give in situ gels, which expand to produce a powerful gel at the site of drug absorption that can extend the active substance's residence time[9].

In situ gelling system approaches:

The many methods for an in situ gelling system include:

1. In situ gel system that responds to stimuli 10.

2. Systems of in situ gels that are triggered by temperature or pH

3 In situ gel systems that are osmotically induced (ion activated systems) 11, 12.

4. Systems of chemically generated in situ gels 13, 14.

1.1 In Situ Gelling System Importance:

• The ability to provide precise and repeatable amounts in comparison to gel that has already formed is of utmost relevance.

• Benefits of the in-situ forming polymeric delivery system include increased patient comfort and compliance, as well as convenience of administration and decreased frequency of administration.

• The use of gel systems, which are administered as drops into the eye and go through a sol-gel transition from the instilled dosage, can help overcome the poor bioavailability and therapeutic response displayed by traditional ophthalmic solutions due to the quick precorneal clearance of the drug.

• The best dose form is a liquid that can maintain medication release and stay in touch with the eye's cornea for a long time.

• Some unfavourable side effects might arise from decreased systemic absorption of the medication discharged through the nasolacrimal duct.

1.2 Aphthous Ulcer:

Aphthous is derived from the Greek word "aptha," which meaning ulcer. These oral lesions are still referred to as aphthous ulcers in medical literature. Round or oval in shape, aphathous ulcers are greyish yellow in colour and have a crateriform base encircled by an erythematous ring of inflammatory mucosa. The nonkeratinized oral mucosa, which includes the lips, the buccal mucosa, the floor of the mouth, the soft palate, and the ventral aspect of the tongue, is where ulcers typically develop. It is rare to see areas of keratinised oral mucosa such the gums, the hard palate, and the dorsal surface of the tongue.

2. Material and Methods

Apparatus and chemicals: Hydrocortisone by Cipla Pithampur Indore, Methyl cellulose by IPCA Ratlam, Sodium citrate, Propylene glycol, Tri-ethanol amine by S.D. Fine Chem. Ltd, Mumbai.

2.1 Methods: Preparation of in situ gel

To create in situ gel formulations with methyl cellulose, sodium citrate was added to distilled water and stirred constantly until a clear solution was achieved. With constant stirring, methyl cellulose was added to the aforesaid solution and left to hydrate for the entire night. Triethanolamine and a calculated quantity of hydrocartisone (1% w/v) were added separately, and the polymer solution was continuously stirred. Hydrocartisone in situ gel's formulation design was tabulated. The gelation temperature and gelation duration were used to determine the optimal methyl cellulose content. The produced formulations were also assessed for a number of characterisation investigations.

Table 1: Preparation of in situ gel

Batch Code	Hydrocartisone (%w/v)	Methyl cellulose (%w/v)	Sodium citrate (%w/v)	Triethan olamine	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

3. Experimental work

3.1 Preformulation Studies

The study of a medical ingredient's physical and chemical properties, both alone and in conjunction with excipients, is known as preformulation. Preformulation studies aim to identify the physicochemical properties and excipients that may affect the manufacturing process, formulation design, and pharmacokinetic-biopharmaceutical aspects of the final product.

3.2 Determination of Solubility

Since solution clarity is a crucial need, solubility is a significant factor in formulations. Hydrocartisone's solubility was examined in a range of solvents, including distilled water, methanol, propanol, and acetone.

3.3 UV and FTIR Spectroscopy

Methanol was used to create a solution of hydrocartisone at a concentration of 10µg/ml, and a Shimadzu (UV-1700) double beam spectrophotometer was used to capture the UV spectrum. The 200–400 nm range was used to scan the solution.

To determine if the medication and polymer were compatible, FT-IR spectroscopy was used. The conventional FT-IR spectrum of the pure drug was compared with the FT-IR spectra of the drug containing polymers.

4. Result and discussion

4.1 Determination of λ max

The λ max of Hydrocortisone was found to be 242 nm in methanol.

4.2 Result of Solubility

Studies on drug solubility have been conducted using a variety of solvents. It was discovered that hydrocortisone was soluble in methanol. According to the results, hydrocortisone dissolves quite well in methanol. It is less soluble in water than acetone and more soluble in methanol than in other solvents.

4.3 UV Spectroscopy

A Shimadzu UV1800 UV spectrophotometer was used to test the absorbance in methanol at 242 nm. The resulting absorbance was tabulated as shown in Figure 1 displays the plotted calibration curve.

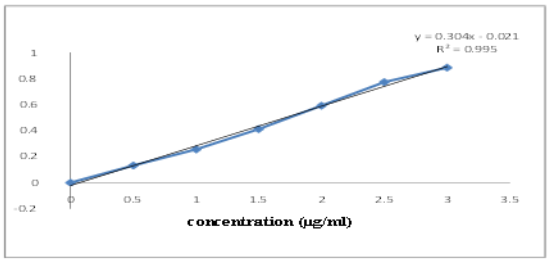

Fig 1. Lambda max determination of Hydrocortisone

4.4 FT-IR Spectroscopy

Figure 2 displays the infrared spectra of the medicine hydrocortisone in its pure form as well as the drug's combination with polymers (methyl cellulose).The spectrum of the medication and polymer combination showed all of the distinctive peaks of hydrocortisone, demonstrating the compatibility of the two substances. The spectrum verified that the drug's chemical integrity has not changed significantly. All of the IR spectra had the Hydrocortisone functional group peaks, which were listed in the table.

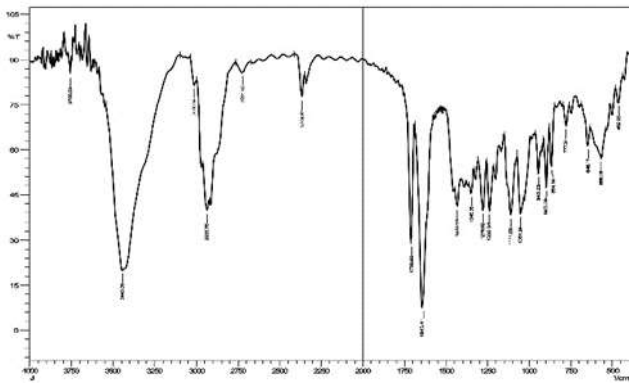

Fig 2. FT-IR of pure drug Hydrocortisone

4.4.1 Drug - Excipients Compatibility Study

FT-IR Spectroscopy

Figure 3 displays the infrared spectra of the medicine hydrocortisone drug's combination with polymers (methyl cellulose).

The spectrum of the medication and polymer combination showed all of the distinctive peaks of hydrocortisone, demonstrating the compatibility of the two substances.

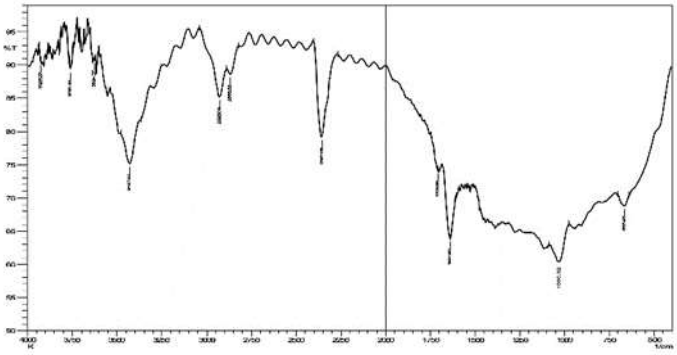

Figure 3 FT-IR Spectra of Formulation

4.5 Evaluation of Hydrocortisone in situ gels

4.5.1 Clarity Test:

The produced formulas' clarity was tested visually against a black and white backdrop. The entire composition passed the clarity test, and there was no indication of contamination.

4.5.2 Determination of pH

A pH meter that had been calibrated was used to measure the pH of in situ gels. Three samples were averaged when the measurements were obtained. At 25°C, methylcellulose showed pH values between 5.8 and 6.9, which are listed in Table 9.

4.5.3 In vitro gelling capacity

It was discovered that increasing the polymer concentration improved the gel's intensity. According to experimental results (Table.10), formulations F7 and F8 were adequate for causing gelation.

4.5.4 Viscocity and Rheology of in situ solutions

The Brookfield viscometer was used to measure the viscosity of in situ solutions (Table.11). F1 (0.25%) had the lowest viscosity of any formulation, while F8 (2%) had the highest viscosity. This indicates that a higher concentration of polymers results in a higher viscosity of the solution.

4.5.5 Syringeability of in situ gel

Formulations F1 through F3 pass the syringeability test and are readily ejected from the syringe with a 20 gauge needle. It's possible that formulations F4 and F8's greater methyl cellulose content is the reason they fail the syringeability test.

4.5.6 Spreadibility Test

The solution's viscosity increased as the polymeric component's concentration rose. The formulation's spreadability decreased concurrently. The data gathered from the evaluation tests in Table 13 shows this. Due to the increased gel strength and viscosity of the F8 formulation, the F1 formulation demonstrated a higher spreadability than the F8 formulation. Its spreadability decreased as a result.

4.5.7 Drug Content

Using a UV spectrophotometer (Shimadzu UV"1800), the drug content was estimated and the absorbance was measured. The results are shown in Table 14. All formulations had drug contents ranging from 76.4±0.051 to 97.6±0.093 w/v.

4.5.8 In-vitro release of study

Table 2 display the hydrocartisone's in vitro diffusion profile from gels with varying methylcellulose concentrations. The lowest drug release (84.86%) was seen in formulation F1 (0.25%), whereas the largest drug release (96.819±0.022%) was observed in formulation F5 (1.25%). Initial burst release was greater in in-situ gel formulations over the first six hours of the trial. We learnt from the in-vitro release trials that the formulation F5 had the highest release rate, but that the drug's release rate dropped as the gel concentration grew. We may infer from the experimental data that the release pattern was dependent on the polymer concentration.

Table 2: In vitro release studies of in situ formulations

Time Hours	**% CUMULATIVE DRUG RELEASE**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	4.078±0.012	8.588±0.013	12.238±0.023	10.520±0.014	16.962±0.021	13.956±0.016	0.191±0.046	15.67±0.023
2	8.156±0.025	23.059±0.017	24.598±0.012	21.575±0.027	27.006±0.008	23.541±0.033	19.706±0.023	25.49±0.015
3	21.794±0.014	35.225±0.022	38.675±0.032	32.848±0.034	39.128±0.014	35.014±0.021	39.075±0.035	39.97±0.033
4	33.135±0.022	44.362±0.018	44.610±0.016	43.050±0.006	55.565±0.019	44.145±0.025	43.788±0.017	45.91±0.009
5	51.094±0.021	56.690±0.007	58.624±0.019	55.389±0.015	64.959±0.004	62.270±0.037	64.489±0.004	64.00±0.017
6	65.170±0.014	64.970±0.021	64.989±0.025	67.748±0.023	76.645±0.024	68.246±0.005	73.650±0.033	69.12±0.036
7	77.268±0.016	77.504±0.016	79.651±0.005	79.464±0.027	85.992±0.037	79.039±0.003	88.103±0.052	80.550±0.034
8	84.861±0.015	85.357±0.005	86.66±0.010	88.596±0.012	96.819±0.022	94.525±0.021	91.233±0.018	90.472±0.022

4.9 Kinetic Study

For each formulation, the regression values for the zero order kinetics of in-situ gel vary from 0.916 to 0.993, whereas the first order kinetics range from 0.155 to 0.553. The R2 value varies from 0.730 to 0.898 when Higuchi's model is applied. The drug release was caused by the Super case II release mechanism, according to the Korsemeyer-Peppas model, which displayed R2 values of 0.501 to 0.611 for each of the "n" values ranging from 1.592 to 1.6011.

Table 3: Kinetic study of formulation

Formulation Code	**KINETIC MODELS**				
	Zero order	**First order**	**Higuchi**	**Korsmeyer**	
	R2	**R2**	**R2**	**N**	**R2**
F1	0.956	0.436	0.730	1.538	0.452
F2	0.995	0.377	0.879	1.611	0.492
F3	0.993	0.254	0.898	1.530	0.350
F4	0.995	0.236	0.867	1.583	0.387
F5	0.990	0.171	0.898	1.514	0.250
F6	0.993	0.155	0.898	1.522	0.275
F7	0.982	0.552	0.815	1.806	0.688
F8	0.986	0.186	0.902	1.498	0.264

4.10 Stability Studies of best formulation

Table 4: Stability study of selected formulation

No. of days	% Drug content							
	F1	**F 2**	**F 3**	**F 4**	**F 5**	**F6**	**F7**	**F8**
15	80.3	76.4	81.10	84.70	97.61	85.15	96.40	94.80
30	80.29	76.39	81.09	84.69	97.59	85.12	96.38	94.79
45	80.27	76.37	81.08	84.67	97.58	85.11	96.37	94.77
60	80.26	76.35	81.06	84.66	97.56	85.10	96.36	94.75
75	80.25	76.34	81.04	84.65	97.55	85.08	96.35	94.74
90	80.24	76.32	81.05	84.63	97.52	85.06	96.32	94.73

5. Conclusion

The hydrocortisone in situ gels using a temperature-induced gelling technique. Various aspects of the study were presented, and based on the results, it was determined that the in situ gel formulation of hydrocortisone with mucoadhesive properties is helpful in extending the drug's residence time in the mouth. The developed formulation can release the drug for an extended period of time at a controlled rate. Thus, methylcellulose can be utilised to produce hydrocortisone gels and films in situ for the treatment of aphthous ulcers, according to the findings above. The (F5) film formulation has shown the best release tests when compared to other formulations. Furthermore, the films show a longer and more prolonged release of the medication than the in-situ gel when comparing the compositions of the two materials.

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