

Formulation and Evaluation of Mucoadhesive Oral Gel for Treatment of Oral Candidiasis

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ABSTRACT

Oral candidiasis, primarily caused by *Candida albicans*, is a prevalent opportunistic infection of the oral mucosa, especially among immunocompromised individuals and the elderly. Traditional antifungal treatments, particularly Fluconazole, are increasingly ineffective due to the emergence of resistant *Candida* strains. Fluconazole's effectiveness can be compromised by efflux pump activity in these resistant strains. Recent studies suggest that a non-steroidal anti-inflammatory drug, like Ibuprofen, can inhibit these efflux pumps, thereby enhancing Fluconazole's antifungal activity.

Mucoadhesive gels were prepared by the continuous stirring method with varying ratios of Fluconazole to Ibuprofen (1:1, 1:2, and 1:3) to improve Fluconazole's antifungal activity. Carbopol-934 and Hydroxy Ethyl Cellulose were used as mucoadhesive agents. pH of the prepared gels was adjusted using 10% Sodium hydroxide solution to make them compatible with the pH of the oral mucosa.

The prepared gel formulations were characterised for physical appearance, pH, viscosity, extrudability, mucoadhesive property and drug content. The surface pH of all the formulations was in the range of 6.71 to 6.76, which is acceptable for buccal pH. All three formulations have a viscosity of 12300-13200 cps at 10rpm and extrudability was at 87-94%, which shows ease of extrudability with ideal thickness. All three Formulations

Had shown moderate mucoadhesion. The in vitro drug release demonstrated that the prepared formulations provided a sustained release of Fluconazole and Ibuprofen. With 83.15% formulation, F3 showed higher drug release of Ibuprofen, and with 85.38%, F1 showed higher drug release of Fluconazole at the end of 6 hours. The formulation with a Fluconazole to Ibuprofen ratio of 1:2 showed optimal drug release and mucoadhesion, indicating potential for enhanced local treatment of oral candidiasis.

KEY WORDS: Fluconazole, Ibuprofen, Oral candidiasis, Drug resistance, Mucoadhesion.

I. INTRODUCTION

Oral candidiasis is an opportunistic infection of the oral cavity caused by overgrowth of *Candida* species, the commonest being *Candida albicans*. It is common and underdiagnosed among the elderly, particularly in those who wear dentures and in many cases is avoidable with a good mouth care regimen.¹ One of the most prescribed antifungal drugs for *Candida* infections is Fluconazole, a triazole antifungal. The azoles function by inhibiting the Cytochrome P450 enzyme Lanosterol demethylase (14 α -demethylase), encoded by ERG11, in the ergosterol biosynthesis pathway. Current treatment guidelines include Fluconazole as a primary therapeutic option for the treatment of these infections, but it is only fungistatic against *Candida* species, and both inherent and acquired resistance to Fluconazole have been reported.² This situation has prompted the search for alternative anti-*Candida* therapeutic agents. Furthermore, many currently used drug regimens are highly costly and lead to serious side effects.³

Ibuprofen is one of the favourite over-the-counter drugs, a non-steroidal anti-inflammatory drug with analgesic, antipyretic and anti-inflammatory properties. It is a non-selective inhibitor of the cyclooxygenase enzymes, which constitute COX-1 and inducible COX-2. It is true that most of the antimicrobial effects of Ibuprofen, as well as the effects of other non-antibiotics, happen at concentrations that are far above those that are normally achieved in the patient's blood upon administration of therapeutic doses. But the potential lies in the topical application of Ibuprofen and in the treatment of other localised infections. Additionally, it has been proven that low Ibuprofen plasma concentrations that may not be high enough for a direct antifungal activity are sufficient to induce efflux pump inhibition and the reversion of

the azole-resistant phenotype in *Candida* species.⁴ Oral delivery has so far been the most common and preferred route of administration for most of the therapeutic agents. The popularity of the oral route has been attributed to the patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing method, few sterility constraints, flexible design of dosage forms and generally improved shelf-life of the product. Mucoadhesive drug delivery has been a topic of interest in the design of drug delivery systems to lengthen the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the formulation with the underlying absorption surface, to improve and enhance the bioavailability of the drug. Mucoadhesive controlled drug delivery systems are beneficial, since they give a controlled drug release over a period and can also be utilised for localising the drug to a specific site in the body.⁵

Although a limitation of gel formulations lies in their inability to deliver a measured dose of drug to the site, gels have some advantages over other formulation types, such as relatively faster release of the incorporated drug, easy preparation, easier administration and higher biocompatibility. Mucoadhesion allows adhesion to the mucosa in the dental pocket, which decreases the chance of rapid elimination through normal catabolic pathways and decreases the risk of irritative or allergic host reactions at the application site. Mucoadhesive gels are easily dispersed

throughout the oral mucosa, even if drug dosing from these pharmaceutical forms may not be as accurate as from tablets, patches, or films.⁶

Thus, the aim of the work is to develop a mucoadhesive oral gel of Fluconazole and ibuprofen combination to combat Fluconazole resistance in the treatment of oral candidiasis.

II. MATERIALS AND METHODS

The Fluconazole and Ibuprofen act as active pharmaceutical ingredients, and other excipients such as Carbopol 934, Hydroxy Ethyl Cellulose (HEC), propylene glycol, sodium hydroxide, and menthol were used. All the materials procured and used were of analytical grade.

2.1 Drug Excipient Compatibility Studies:

FTIR absorption spectra of pure drug and physical mixture of drug with polymer were recorded in the range of 4000-400cm⁻¹ by using an FTIR spectrophotometer.

2.2 Formulation of Mucoadhesive Oral Gel containing a combination of Fluconazole and Ibuprofen:

Mucoadhesive gel containing a combination of Fluconazole and Ibuprofen was prepared by varying the concentration of Fluconazole: Ibuprofen to 1:1, 1:2 and 1:3. Composition of all three formulations i.e., F1, F2 and F3 are shown in Table 1.

Table 1. Components of Mucoadhesive oral gel

Components	Uses	F1	F2	F3
Fluconazole	Antifungal agent	5g	5g	5g
Ibuprofen	Analgesic	5g	10g	15g
Propylene glycol	Cosolvent	50ml	50ml	50ml
Carbopol 934	Mucoadhesive agent	1g	1g	1g
HEC	Gelling agent	1g	1g	1g
Menthol	Flavouring agent	0.2g	0.2g	0.2g
Sodium hydroxide	pH adjuster	Q.S.	Q.S.	Q.S.
Purified water	Solvent	Q.S. (Up To 100g)	Q.S. (Up to 100g)	Q.S. (Up to 100g)

Fig No. 1: Formulation of mucoadhesive oral gel



Accurately weighed amounts of Fluconazole, Ibuprofen and menthol were dissolved in a hot mixture containing propylene glycol. The required amounts of Carbopol-934 and Hydroxy Ethyl Cellulose was weighed and dispersed slowly into a beaker containing distilled water, with continuous stirring at 400-600 rpm for 1 hour, until a clear solution formed. Care was taken to avoid indispensable lumps of the polymers. Then the previous mixture containing the drug was added to the Carbopol-934 solution by stirring for 3 to 4 hrs to obtain a homogeneous dispersion. The final quantity was made up with distilled water. Care was taken to avoid the formation of air bubbles. The mixture was allowed to stand for the air bubbles to separate. The pH was further adjusted with 10% Sodium hydroxide solution for simulation with oral pH. The prepared gel was kept for 24 hrs for complete polymer desolvation.^{7,8}

III. EVALUATION OF MUCOADHESIVE ORAL GEL OF A COMBINATION OF FLUCONAZOLE AND IBUPROFEN

Mucoadhesive oral gel of a combination of Fluconazole and Ibuprofen was evaluated for the following properties:

3.1 Physical appearance

The prepared mucoadhesive formulations were checked by visual inspection, and surface texture was evaluated by touch or feel of the gel.

3.2 Determination of pH:⁹

+	:	Low pressure is required to pull
++	:	Moderate pressure is required to pull
+++	:	High pressure is required to pull

3.6 Determination of Drug content:¹³

A 1gm of developed gel was taken in a volumetric flask and dissolved in a solution containing 50 ml methanol and 50 ml of Phosphate

The pH of the formulations should be 6-7 to mimic the oral cavity condition. pH of the prepared gel was measured using a digital pH meter.

3.3 Viscosity:¹⁰

Viscosity of the formulation was determined using a Brookfield viscometer, Spindle (No: 64) type, model LVDV-E at 10 rpm. The gel was taken in the cup, and the spindle was dipped in it for about 5 minutes, and then the reading was taken.

3.4 Extrudability Study:¹¹

It is an empirical test to measure the force required for the formulation to extrude from the tube. The prepared gel was filled into a collapsible tube, and it was sealed, and the weight of the tube was recorded. A 1000 gm weight was placed on the tube, and the amount of gel that extruded out was collected and weighed. Then the percentage of gel extruded was calculated.

$$\% \text{ Extrudability} = \frac{\text{Initial wt of the tube (g)} - \text{Extruded wt(g)} \times 100}{\text{Initial wt of the tube (g)}}$$

3.5 Thumb test:¹²

Here, the adhesiveness was qualitatively measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. It provides useful information on mucoadhesive potential. The Mucoadhesiveness is graded as below-

buffer, pH 6.8, to make up the volume to 100mL. This mixture was mixed for 2 hours on a magnetic stirrer to get complete solubility of the drugs. This solution was filtered using the Millipore filter. After

suitable dilution, drug absorbance was recorded by using a UV-visible spectrophotometer at λ_{max} 205 nm and 261 nm using phosphate buffer (pH 6.8) as a blank.

3.7 In vitro drug release studies:¹⁴

The drug release of the mucoadhesive gel of a combination of Fluconazole and Ibuprofen was measured using a Franz Diffusion cell. Phosphate buffer of pH 6.8 was used as diffusion medium, and each Franz diffusion cell was filled with 100ml of the medium. Assembly was set, and the temperature was maintained at $37 \pm 0.5^\circ\text{C}$. 1gm gel was kept over the donor compartment, which was separated by the receptor compartment with the cellophane membrane. 5 ml aliquots of the sample were withdrawn at the initial and then at regular time intervals and replaced with an equal volume of Phosphate buffer pH 6.8 as fresh receptor medium. The samples were appropriately diluted with Phosphate buffer pH 6.8 and analysed spectrophotometrically (Double beam UV- visible spectrophotometer) at 205 nm and 261 nm.

IV. RESULT AND DISCUSSION

The study had been a satisfactory attempt to formulate a mucoadhesive oral gel of a combination of Fluconazole and Ibuprofen. Preformulation studies comply with the reported literature review. The Compatibility studies were performed using FTIR spectroscopy. The peaks obtained in the spectra of the physical mixture were correlated with peaks of the drug spectrum and interpreted. It was found that the peaks of drugs do not interact with the peaks of the mixture of excipients. Thus, it can be concluded that the drugs are compatible with the excipient mixture.

The formulated gels were evaluated to determine their properties, and the data are presented in Table 2. All the formulations were colourless and acceptable in terms of odour, Appearance and consistency. The prepared gels were clear without any gritty particles and were found to be non-irritating.

The formulations were subjected to pH analysis using a digital pH meter, and it was found that all the formulations had the desirable pH, which is compatible with use in buccal mucosa.

The Viscosity of the formulations was determined using the Brookfield Viscometer, and from the data, it is found that the viscosity of the formulations is in the range of 11300-13200cps at 10 rpm, which is ideal for the formulation prepared.

The extrudability of all the prepared formulations was determined, and found that all the formulations had good extrudability, which indicates the ease of extrusion of gel from the tube. With the extrudability of $93.38 \pm 0.46\%$, the formulation F1 was found to have higher extrudability compared to F2 and F3.

The thumb test was performed on all the prepared formulations to determine their mucoadhesion capabilities onto the oral mucosa. It was found that all the preparations were showing moderate adhesion to the thumb, which indicates the ease of application of formulations and their desirable adhesiveness towards the buccal mucosa.

The drug content of all the prepared formulations was measured using a UV-visible Spectrophotometer. The drug content of Ibuprofen was found 98.86% to 99.60%, and Fluconazole was found 98.69% to 99.53% in the prepared formulation.

In vitro diffusion studies of all the formulations were performed using Franz diffusion cells, and the data are shown in Figure No 2 and 3. From the obtained data, it is observed that formulation F3 was having maximum drug release of Ibuprofen with $83.15 \pm 0.031\%$ and the maximum drug release of Fluconazole was observed in formulation F1 with $85.38 \pm 0.001\%$ by 6 hours. Due to the lipophilic nature, both the drugs can easily penetrate through the lipoidal barrier of the oral mucosa, allowing the formulation to release the drugs for quicker action. By observing all the evaluation parameters, we can conclude that Formulation F2 is found to have better physical properties and drug release profile compared to F1 and F3.

Table 2. Evaluation of Mucoadhesive oral gel

Parameters	Formulations		
	F1	F2	F3
Colour	Colourless	Colourless	Colourless

Odour	Minty	Minty	Minty
Appearance	Clear	Clear	Clear
Consistency	Thick	Thick	Thick
pH*	6.72± 0.03	6.71±0.09	6.76±0.04
Viscosity (cps)	12340±120	12760±60	13200±124
% Extrudability	93.38±0.46	90.71±0.42	87.39±0.78
Adhesiveness	++	++	++
Drug Content			
Ibuprofen	99.60%	98.86%	99.20%
Fluconazole	98.92%	99.53%	98.69%

*Data expressed as a mean ±SD, n= 3

In vitro diffusion profile of Ibuprofen

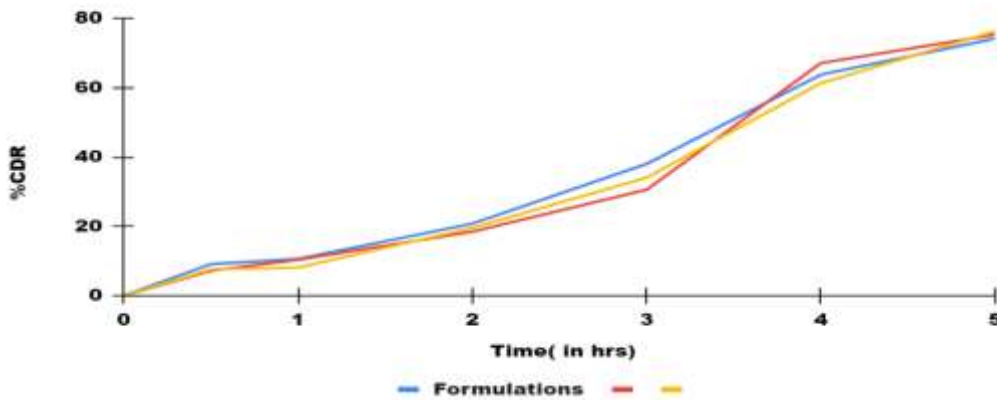


Fig.No:2. In vitro diffusion profile of Ibuprofen

In-vitro Diffusion Profile for Fluconazole

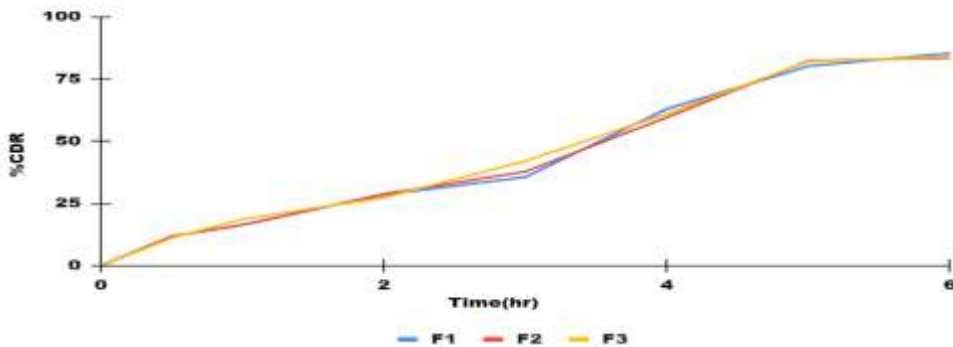


Fig.No:3. In vitro diffusion profile of Fluconazole

V. CONCLUSION

It was concluded from the study that F2 had better physical properties, drug content uniformity, mucoadhesion and in-vitro drug release when compared to F1 and F3 formulation due to the optimum composition of the formulation with the ratio of 1:2 of the two drugs. Further study of antifungal activity can be performed on *Candida* species and compared with the marketed product of Fluconazole to check the efficacy of the formulation.

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