

## Development and Evaluation of Medicated Chewing Gums of Fluconazole For The Treatment of Oral Candidiasis

K. SashiKiran Chowdary<sup>1</sup>, Mohammed Gulzar Ahmed<sup>1\*</sup> and R. Narayana Charyulu<sup>2</sup>

<sup>1</sup>Department Of Pharmaceutics, Sri Adichunchanagiri College Of Pharmacy, Karnataka - 571448

<sup>2</sup>Department Of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Mangalore, Karnataka



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### Abstract:

. Chewing gum is one of the most popular dosage form, used for delivering the many active components. Most of the chewing gums were used for smoking cessation (containing the nicotine) and also used for oral and dental hygiene. Fluconazole is an anti-fungal drug. It is one of the active ingredients used to treat oral candidiasis. In the present work medicated chewing gum of fluconazole was developed to treat oral candidiasis. The study includes formulation and evaluation of medicated chewing gum of fluconazole. The chewing gum formulations were made using a gum base. The concentration of gum base was varied in the formulation to study its effect on in-vitro drug release. Formulations were developed by conventional/traditional method. The prepared formulations were evaluated for various parameters like physical appearance, weight variation, drug content in-vitro and in-vivo drug release behavior. Stability studies were conducted. From this study it could be concluded that it is possible to design medicated chewing gum containing fluconazole, mainly for the treatment of oral candidiasis and related conditions where efficacy and enhanced patient compliance are of paramount importance.

**Keywords:** Medicated chewing gum, Fluconazole, Oral candidiasis, Conventional/traditional method.

### Introduction

In the recent years scientific and technological advancements have been made in the research and development of oral drug delivery systems. The reasons that the oral route achieved such popularity may be primarily due to its ease of administration.<sup>1</sup> Chewing gums may offer a number of advantages over conventional tablet administration; convenient and individually controlled release of the active substance, effective buccal drug administration for treatment of local oral diseases or avoidance of first pass metabolism, just to mention a few.<sup>2</sup> Most of the chewing gum were used for smoking cessation (containing the nicotine) and also used for oral and dental hygiene (consisting of fluoride and carbamide etc).<sup>3</sup>

Oral candidiasis represents a serious problem for children with cancer. The mortality rate of this infection has increased due to fungal septicemia, associated with a primary buccal infection.<sup>4</sup> Oral candidiasis, a frequent and important nosologic entity of the buccal cavity is caused by the pathogenic action of *Candida* species.

The colonization for species of *Candida* genus in patients with cancer and their later dissemination, associated with long term episodes of neutropenia, use wide spectrum antibiotics, treatment with corticosteroids and cytostatic substances, invasive surgical procedures (central and bladder catheters), xerostomia and prolonged hospitalization time.<sup>5</sup>

The conventional formulations for the local delivery of drugs to the oral cavity are the mouth paints, rinses, troches, creams and suspensions.<sup>6</sup>

Fluconazole, a synthetic antifungal agent of the imidazole class, is used to treat candidiasis.<sup>7</sup>

Thus it was attempted to design medicated chewing gum containing fluconazole, mainly for the treatment of oral candidiasis and related conditions where efficacy and enhanced patient compliance are of paramount importance.

## MATERIALS AND METHODS

### Materials

Fluconazole was received as gift sample from Micro labs. Pvt. Ltd. India. Gum base was received as gift sample from wrigleys confectionaries. Mumbai. Fructose, glycerin, poly Ethylene Glycol 200, Mint flavor and propyl paraben were purchased from SD Fine Ltd., India.

Formulation of medicated chewing gum

Gum base is softened by melting method and placed in a kettle mixer to which accurately weighed active ingredient(fluconazole), bulk sweeteners(fructose), and other excipients like softeners(glycerin), humectants(poly ethylene glycol), flavours(mint) and preservatives(methyl paraben) are added at a definite time. The gum is then sent through a series of rollers that form into a thin, wide ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavour. In a carefully controlled room, the gum is cooled for upto 48 hours. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

### Evaluation of fluconazole medicated chewing gum

#### Buccal absorption studies:<sup>8</sup>

100 mg of the fluconazole was dissolved in 100ml of Simulated salivary fluid (SSF) to prepare 1mg/ml concentration solution. This is the primary stock solution. 5ml of 1mg/ml solution of fluconazole is swirled in the buccal cavity for one minute and then expelled into the beaker and check the volume of it. From this take 1ml solution and dilute to 50ml using SSF to get a concentration of 20µg/ml. The absorbance of the sample solution was read at 263nm.

#### Procedure for estimation of drug content

Beaker was filled with 100 ml SSF. The chewing gum was placed in the equipment and the instrument was operated for a period of 60 min at a chewing frequency of 56 strokes/min to ensure total release of the drug from

the formulation in SSF. From the dissolution medium 5ml was withdrawn and volume made upto 10ml with SSF and the absorbance of the resulting solution was readed at 263nm.

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#### In-vitro drug release studies

Test was filled with 50 ml SSF. The chewing gum was placed in the equipment and the instrument was operated at a chewing frequency of 56 strokes/min. From the dissolution medium 5ml was withdrawn at regular intervals of 5, 10, 15, 20, 25, 30 and volume made upto 10ml with SSF and the absorbance of the resulting solution was readed at 263nm.

#### In-vivo drug release studies:

The formulated chewing gum of each formulation has been chewed for 30 min. The aliquots of 5ml saliva was withdrawn for each time interval of 5, 10, 15, 20, 25 and 30 min and the absorbance of the resulting solution was readed at 263nm.

## RESULTS AND DISCUSSION

### Buccal absorption studies

As the formulation is intended to be used in the buccal cavity, buccal absorption study of the drug was conducted. The results are given in the table 2. The study showed that fluconazole has a buccal absorption of about 68-70%.

### In-vitro drug release profile

The prepared formulations were analysed for their *in-vitro* drug release profiles. The study was conducted for a period of 30 min using SSF as the dissolution medium. The chewing gum frequency of 56 strokes/min was applied. The results of cumulative drug release are given in table 15. Formulation S3 showed highest drug release of 83.9% at the end of 30 min and the formulation S1 showed lowest drug release of 78.4% at the end of 30 min. The order of drug release of different formulations is as under S3>S2>S1

### In-vivo drug release profile

The prepared formulations were analysed for their *in-vivo* drug release profiles. The study was conducted for a period of 30 min.

**Table 1: Formulations containing various concentrations of excipients**

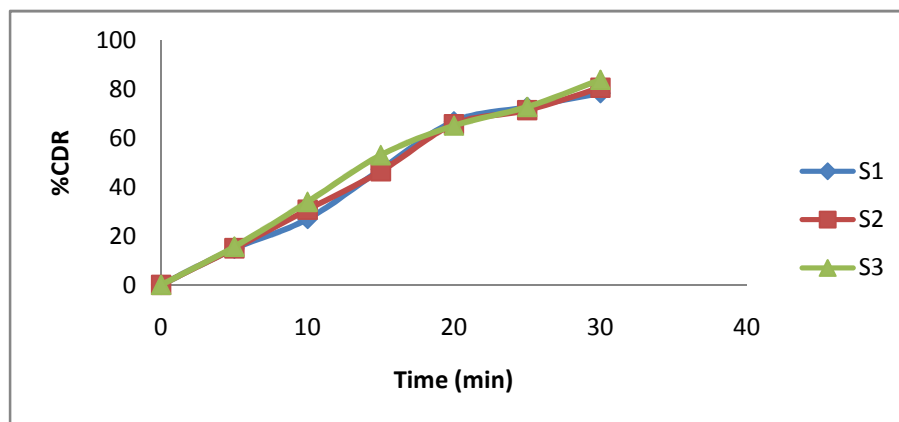
Ingredients(mg)	Formulations		
	S1	S2	S3
Drug	100	100	100
Gum base	350	400	300
Bulk sweeteners	400	350	450
Softeners	50	50	50
humectants	50	50	50
Flavours&Preservatives	q.sq.s		q.s

**Table 2: Buccal absorption studies**

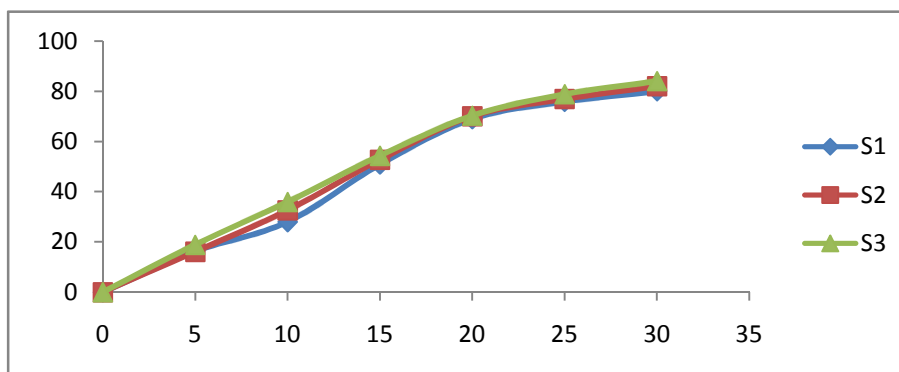
Trail no	Absorbance (nm)	Conc (mcg/ml)	% of drug absorbed	% of drug unabsorbed
1	0.010	6.25	68.75	31.25
2	0.0096	6	70	30

**Table 3: Post formulation evaluation parameters**

Formulation	Drug content (%)
S1	93.05±0.13
S2	94.38±0.35
S3	96.50±0.23



**Fig. 1: Cumulative percentage release Vs time profile of formulations**



**Fig. 2: In-vivo drug release studies**

The results of cumulative drug release are given in table 16. Formulation S3 showed highest drug release of 83.98% at the end of 30 min and the formulation S1 showed lowest drug release of 79.94% at the end of 30 min. The order of drug release of different formulations is as under S3>S2>S1

## CONCLUSION

- Fluconazole shows a buccal absorption of about 68-70 % which makes it a drug choice in preparing medicated chewing gum containing anti-fungal agents.
- The formulation containing 30% gum base i.e. S3 showed good drug release rate but these formulation did not show sufficient chewing gum like consistency. Thus the formulations containing 35% gum base i.e. S2 are more promising in delivering the drug at required rate and at the same time maintain the chewing gum like consistency.
- Formulation S3 showed highest drug release of 83.9% at the end of 30 minutes and Formulation S1 showed lowest drug release of 78.46% at the end of 30 minutes. The drug release profiles were found to be satisfactory and hence the therapeutic dose of fluconazole (100mg) can be effectively administered through chewing gums. Fluconazole being bitter in taste can be reduced using fructose.
- It is seen that as the concentration of the gum base is increased in the formulation, the drug release was decreased.
- Thus it can be said that with varying the concentration of gum base in the formulation, the drug release can be controlled.

Thus we have successfully formulated medicated chewing gums containing anti-fungal agent (fluconazole). The study showed that modifying parameters like gum base concentration, the drug release from the chewing gum can be adjusted to the desired rate and the same time reduces the taste of bitter drugs.

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