# DESIGN OF PASTE BASED MICONAZOLE FORMULATION FOR THE TREATMENT OF PERIODONTITIS AND ORAL THRUSH IN CHILDREN

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## ABSTRACT

Periodontal disease develops usually because of two events in the oral cavity an increase in bacteria quantity and a change is balance of bacterial types from harmless to disease-causing bacteria. The present work is being focused on designing of Miconazole tooth paste to protect the gums, teeth and oral cavity from periodontal infections and oral thrsh results from improper fixation of artificial dentures. These paste formulation contain suitable combination of ingredients along with preservatives, was prepared and subjected to various physiochemical parameters like drug content, pH, Spreadability, tube extrudability, viscosity, microbiological and IR studies. *In-vitro* drug release was carried out in phosphate buffer (pH 6.4) and compared with marketed formulation. Stability studies of selected formulation were also done at ambient temperature (30°C&40°C) for the period of six months as per ICH guidelines. The selected formulations were subjected for primary oral mucosal irritation test healthy human volunteers for 72 hours and observed for any oral rashes, inflammation, itching, or redness on applied portions. Drug content, pH, Spreadability, Tube extrudability of the formulation was found to be 98.83%, 6.6, 7.5gm.cm/sec, 97.15% respectively. From rheogram it is concluded that formulation shows pseudoplastic flow property. From our study it is revealed that Miconazole dental paste formulation will be useful for treatment of periodontitis and oral thrush.

**KEY WORDS:** Periodontitis, oral thrush, Miconazole dental paste, dental disorders.

## 1.INTRODUCTION

Dental diseases are recognized as the major public problems through out the world. The region of the mouth that consists of the gum and supporting structures is called the periodontium (Pandit, 1997). Periodontal disease is one of the world's most prevalent chronic diseases with 36.8% of adult Americans estimated to have the disease. Periodontal disease has been considered as a possible risk factor in other systemic diseases such as cardiovascular disease, including coronary heart disease and stroke and pre-term low birth weight infants (Novak, 2003). Periodontal disease is a localized inflammatory response due to infection of a periodontal pocket arising from the accumulation of subgingival plaque (Southward and Godowaski, 1998). Untreated periodontitis results in the loss of the supporting structures of the tooth through resorption of alveolar bone and loss of periodontal ligament attachment (Novak, 2003). Periodontal disease develops usually because of two events in the oral cavity an increase in bacteria quantity and a change is balance of bacterial types from harmless to disease-causing bacteria. These harmful bacteria increase in mass and thickness until they form a film known as plaque (Liljenberg and Lindhe, 1980). The periodontal diseases are highly prevalent and can affect up to 90% of the worldwide population. The term periodontal disease usually refers to the common inflammatory disorders of gingivitis and periodontitis that are caused by pathogenic microflora in the biofilm or dental plaque that forms adjacent to the teeth on a daily basis. Gingivitis, the mildest form of periodontal disease, is highly prevalent and readily reversible by simple, effective oral hygiene (Haffajee, 1984). The immediate goal is to prevent arrest, control or eliminate periodontitis and to restore the lost, form, function, esthetics and comfort. Periodontal disease therapy has been directed at altering the periodontal environment to one, which is less conducive to the retention of bacterial plaque in the vicinity of gingival tissue (Ariaudo, 1969).

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## 2.MATERIALS AND METHODS

Miconazole (Alkem pharmaceuticals, Mumbai), Methyl parahydroxy benzoate (Loba Chemie Pvt. Ltd., Mumbai), Precipitated chalk, Glycerin, Alcohol (Qualigens Fine Chemicals, Mumbai), Tragacanth (S.D. Fine chemicals, Mumbai), White soap (Pooja enterprises, Mumbai), Saccharine (Central drug house Pvt. Ltd., Mumbai)

**Preparation of Dental Paste formulation**

Glycerin and gum were mixed together for 5 minutes with the help of mortar and pestle and added hot water, alcohol, soap, saccharine, preservative and flavor one after another on mixing for half an hour. The precipitated chalk sieved through 75µ mesh is slowly added to the above mixture and triturated for another half an hour until a smooth white paste is obtained. The drug Miconazole was incorporated by levigation method (table-1).

**Evaluation of Paste**

The paste was evaluated for pH, Drug content, Viscosity, Spreadability, Tube Extrudability, Drug diffusion, Microbiological study, Stability and primary oral mucosal irritation test on Healthy Human Volunteers.

**Determination of pH[7]**

Dispersed 5± 0.01gm of the Tooth Paste in 45 ml of water and determined the pH of suspension at 27°C using the pH meter (Shrikhande and Goupale, 2001). The results were mentioned in table-3.

**Drug content**

1 gm of tooth paste equivalent to 20 mg of drug was taken and dissolved in small quantity of methanol. Then the formulation is warmed on the water bath so that the drug present in the formulation was completely dissolved and the volume was made up to the mark which gives concentration of 1000mcg/ml. From this different concentrations of solution was taken in 10ml volumetric flask and volume was made upto 10ml with methanol and absorbance was measured by UV spectrophotometer at 272 nm against blank. The results were mentioned in table-3.

**Viscosity**

The viscosity of formulated Dental Paste was measured by Brook field Viscometer (LVDV-III ultra programmable Rheometer) using spindle CP-52 at varying speed and shear rates. The measurements were made over the range of speed setting from 0.10, 0.20, 0.30, 0.40 and 0.50 rpm with 60sec between two successive speeds as equilibration with shear rate ranging from 0.20 $sec^{-1}$ to 1.0 $sec^{-1}$. Viscosity determinations were performed at room temperature (B.I.S.,1993; Lieberman,1998; Alfred,1997; Subrahmanyam,2000; Lee,2009).

The viscosity data was plotted for Rheogram- Viscosity in cps v/s shear rate in $sec^{-1}$.

**Spreadability**

Spreadability is a term expressed to denote the extent of area to which the topical application spreads on application to oral on the affected parts. The therapeutic efficiency of the formulation also depends upon its spreading value. Hence, determination of Spreadability is very important in evaluating topical application characteristics. For the determination of Spreadability, 3gm sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5 minute. Thereafter weight (50gm) was added to the pan and the top plate was subjected to pull with the help of string attached to the hook. The time in which the upper glass slide moves the lower plate to cover a distance of 10cm is noted. A shorter interval indicates better Spreadability (Sethi,2001; Patel and Kamani,2009). The results were mentioned in Table-3.

The Spreadability (S) can be calculated using the formula

$$S = m.l/t$$

Where,

S – Spreadability, m- Weight tied to upper glass slide, l - Length moved on glass slide, t - Time taken.

**Tube extrudability**

In the present study, the method adopted for evaluating Paste formulation for extrudability was based upon the quantity in percentage Paste extruded from tube on application of finger pressure. More quantity extruded better was extrudability. The formulation under study was filled in a clean, aluminum collapsible tube with a nasal tip of 5mm opening and applies the pressure on the tube by the help of finger. Tube extrudability was then determined by measuring the amount of Paste extruded through the tip when a pressure was applied on tube. The results were mentioned in table-3.

**Drug diffusion**

A glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter and 3.1 cm inner diameter was used as permeation cell. A cellophane membrane

prehydrated in distilled water (24 hrs. before use) was fixed to the one end of the cylinder with the aid of an adhesive to result in permeation cell. One gram of semisolid formulation was taken in the cell (donor compartment) and the cell was immersed in beaker containing 100ml of drug free pH 7.4 phosphate buffer as receptor compartment. The cell was immersed to a depth of 1 cm below the surface of receptor fluid. The medium in the receptor compartment was agitated using a magnetic stirrer and temperature of 37± 1°C was maintained. Samples (5ml) of the receptor compartment were taken at various intervals over a period of half an hour with replacement of equal amount of free receptor fluid. The samples were estimated by measuring the absorbance at 272 nm in a 1700 UV Shimadzu spectrophotometer (Karale,2004; Morteza,2000). The results were mentioned in table-2.

**Stability studies**

The prepared 2% Miconazole Dental Paste formulations were filled in the collapsible tubes and stored at ambient temperature (30°C & 40°C) for the span of six months. 1gm of Paste formulation was taken out at different time intervals (one month interval) and analyzed for drug content, physical appearance, pH and rheological properties (Chaudhary and Kumar,1996).

**Microbiological studies**

Miconazole is known to possess superior antibacterial activity against a wide range of microorganisms, a local drug delivery such medicated paste, utilizing the drug at dental pocket be a much effective treatment in periodontitis. In present work, antibacterial activity of Miconazole was tested by used against causative microorganism of periodontitis on agar plates. By taking pus of oral cavity of diseased patient suffering from periodontitis, containing microorganism such as *Actinomycetemcomitans* and *Porphyromonas gingivalis*. Using the standard agar cup- plate method. Pus sample was collected from local dental college under the supervision of dental professors (Nessem,2001; Cruickshank,1968; Ananthanarayan,1997; I.P.,2007, 1985).

**Infrared spectral analysis**

IR spectral analysis is one of the most powerful analytical technique which offers the possible chemical identification. In the present work, IR spectrum of Miconazole pure drug and Miconazole with other excipients in formulation was studied for their interactions.

**Primary oral mucosal irritation test in Healthy Human Volunteers**

The prepared formulations were used to carry out oral mucosal irritation studies on healthy human volunteers. The study was conducted under the supervision of staff, Dept.Periodontology, Al-Badar Dental College and Hospital, Gulbarga.

**Test procedure**

Volunteers were provided with a 10 gm tooth paste base prepared and a tooth brush and asked to brush the teeth everyday for three consecutive days. The oral mucosal irritation test was performed on three healthy human volunteers for each formulation base without drug presence in it (2 male and 1 female) by applying paste formulations. The volunteers were of age group between 22-28 years and weighing 50-70 Kgs. The test was performed primarily by examining each volunteer to notice any change in tissues before and after oral application of formulations. Then photographic imaging of oral cavity of human volunteers was taken out after subsequent application for 72 hrs i. e. at completion of study period and these images were compared determining the difference with the images taken at $0^{th}$ hr of study i.e. prior to first application of formulations. Oral mucosal irritation was evaluated by questioning the human volunteers at regular interval of time about the feeling of irritancy, rashes, inflammation or pain at applied sites.

## 3.RESULTS AND DISCUSSION

Miconazole is a drug of choice for the treatment of periodontitis and oral thrush. In the present study an attempt has been made to prepare dental paste of Miconazole. The percentage drug content of prepared paste formulation was found to be 98.83%. pH of the formulation was shown nearly neutral pH range (6.6). The Spreadability and tube extrudability of formulation is 7.5 gm.cm/sec & 97.15% respectively. Results showed that the prepared formulation showed good Spreadability and tube extrudability property. The viscosities of the formulation were measured at varying speed and shear rates. Apparent viscosity and rheological behavior of the formulation lead to consistency. The data of Paste formulations has shown shear thinning/ pseudoplastic behavior at ambient temperature where there is decrease in viscosity by increasing shear rate (graph of viscosity Vs shear rate ) this shear thinning behavior is a desirable property for

oral preparations, as they should be thin during application and thick otherwise (Figure-1). At the end of 180 min the percentage amount of drug released from F was found to be 82.84% with respective to the Marketed Formulation (MF) having 61.04%. The release of drug from these formulations were found to be governed by diffusion process since the plot of percentage cumulative drug release Vs square root of time were found to be linear. The prepared dental paste formulation passed stability studies with no much significant changes in physical appearance, pH, drug content, Spreadability and tube extrudability. In antimicrobial activity the results obtained were shown photographically as equal zone of inhibition (Figure-2). IR study concluded that all the peaks of the pure drugs are also observed in different formulation with slight modification. The result concludes that there is no drug-excipients interaction. The results shown that the formulation was devoid of any primary oral mucosal irritation or sensation or erythema, or edema even after 72 hrs of application (Figure-3).

## 4.CONCLUSION

From our study it is revealed that Miconazole dental paste formulation will be useful for treatment of Periodontitis and oral thrush. The present work is being focused on designing of medicated tooth pastes to protect the gums, teeth and oral cavity from periodontal infections and oral thrush results due to improper fixation of artificial dentures and also various dental diseases.


## 5.ACKNOWLEDGEMENT

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**Table-1: Formulation code (F)**

| Sr. No. | Ingredients | Quantity in gms. |
|---|---|---|
| 1. | Miconazole | 2.00 |
| 2. | Precipitated Chalk | 44.00 |
| 3. | Powdered Gum Tragacanth | 1.00 |
| 4. | Pulverized Neutral White Soap | 4.1 |
| 5. | Glycerin | 24.5 |
| 6. | Saccharine | 0.1 |
| 7. | Methyl Parahydroxy Benzoate | 0.1 |
| 8. | Alcohol | 5.0 |
| 9. | Water | 18.7 |
| 10. | Flavor | 0.5 |
| | **Total** | **100.00** |

**Table-2: Comparative *in-vitro* drug release profile of Miconazole (2%) dental paste (F) with Marketed Formulation (MF)**

| Sr. No | Time (min) | Square root of time | Cumulative percent drug released | | Cumulative percent drug remaining | | Log Cumulative percent drug remaining | |
|---|---|---|---|---|---|---|---|---|
| | | | F | MF | F | MF | F | MF |
| 1 | 0 | 0.0000 | 0.000±0.000 | 0.000±0.000 | 100 | 100 | 2 | 2 |
| 2 | 5 | 2.236 | 19.53±0.0000 | 23.54±0.7000 | 80.46 | 76.46 | 1.9055 | 1.8834 |
| 3 | 10 | 3.162 | 26.33±0.3500 | 32.96±0.1429 | 73.66 | 67.04 | 1.8672 | 1.8263 |
| 4 | 15 | 3.872 | 37.14±0.3450 | 34.88±0.3350 | 62.85 | 65.12 | 1.7983 | 1.8137 |
| 5 | 20 | 4.472 | 50.23±0.1750 | 37.84±0.0000 | 49.59 | 62.16 | 1.6953 | 1.7935 |
| 6 | 25 | 5.000 | 71.68±0.7280 | 47.09±0.5750 | 28.31 | 52.74 | 1.4519 | 1.7221 |
| 7 | 30 | 5.477 | 82.84±0.5200 | 61.04±0.1550 | 17.15 | 39.14 | 1.2342 | 1.5926 |

* Each reading is a mean of three replicates.* Each sample of 1 gm. Paste contains 20mg, of drug.

**Table-3: Stability studies data of Miconazole Dental Paste (F)**

| Sr. No | Storage temp. | Time interval (days) | Appearance | pH | Drug content | Spreadability (gm.cm/sec) | Extrudability |
|---|---|---|---|---|---|---|---|
| 1. | 30°C | 30 | White | 6.6 | 98.83% | 7.5 | 97.15% |
| 2. | | 60 | White | 6.7 | 98.55% | 7.2 | 97.56% |
| 3. | | 90 | White | 6.6 | 98.65% | 7.3 | 97.98% |
| 4. | | 120 | White | 6.8 | 98.12% | 7.6 | 97.23% |
| 5. | | 150 | White | 6.7 | 98.15% | 7.5 | 97.12% |
| 6. | | 180 | White | 6.6 | 98.70% | 7.7 | 97.15% |

**Fig-1: Viscosity vs. Shear rate graph for (F)**

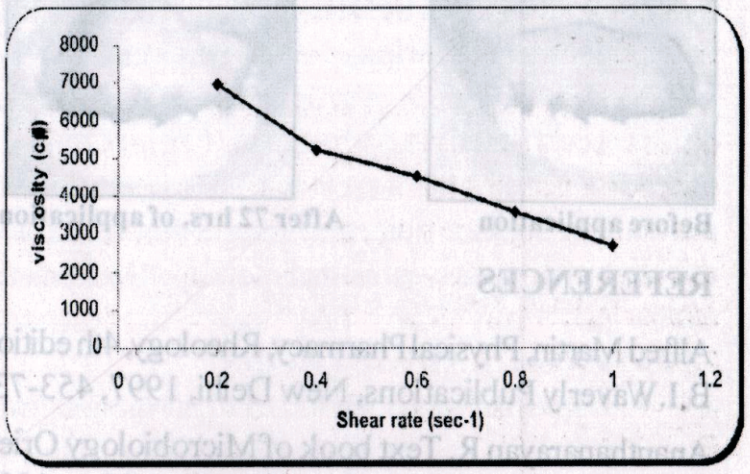
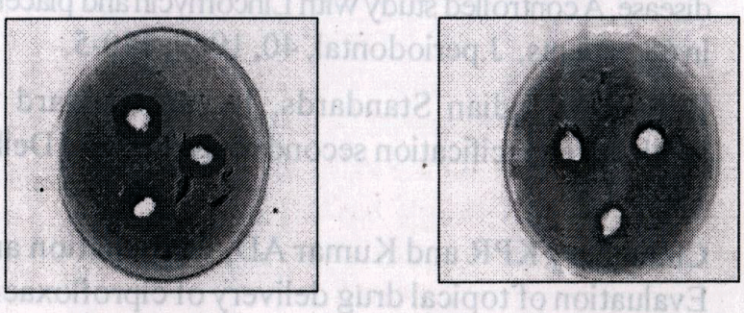
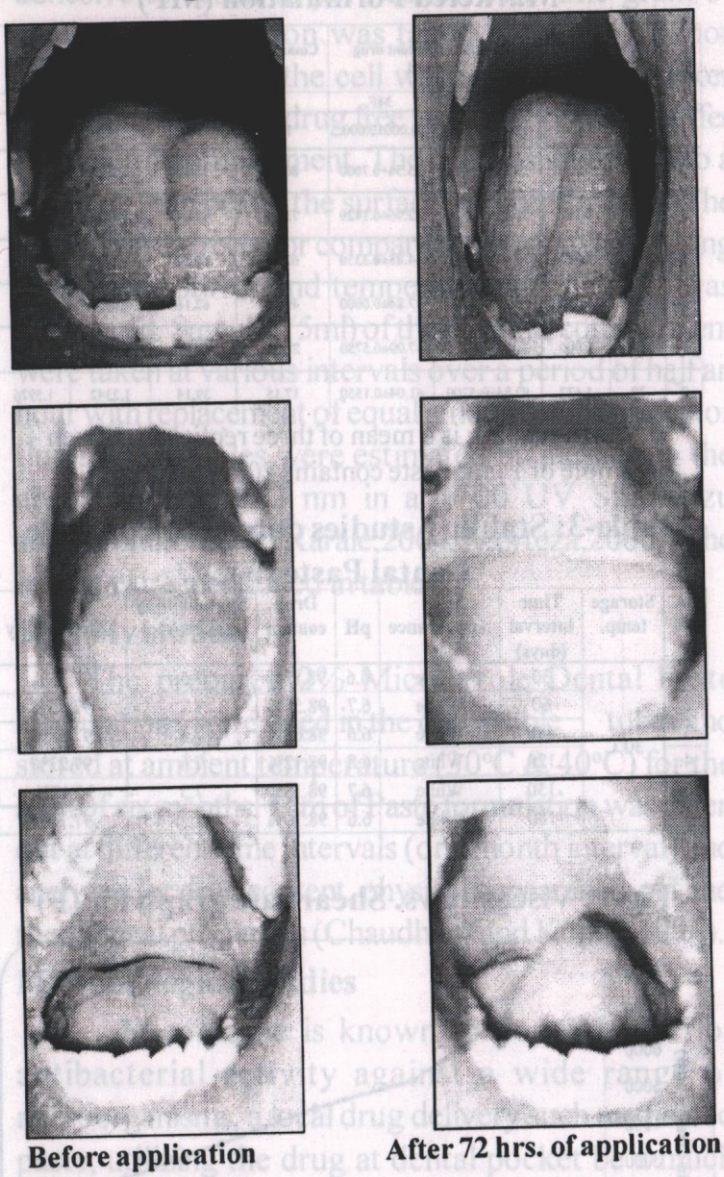



**Fig-2: Comparative Zone Inhibition Study of Drug in the Formulation With pure drug**



**Pure Drug** **Formulation (F)**

**Fig-3: Primary Oral mucosal irritation test of one group of Human Volunteers**



Before application | After 72 hrs. of application

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