



New Drug Delivery system

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Abstract

Background: Local drug delivery has always been chosen as a better treatment protocol over systemic therapy to avoid any systemic effects, maximize efficacy and minimize systemic side effects. Mouthwashes, suspensions, paints, lozenges, ointments, gels and toothpastes etc have been various modes of delivery researched upon. With the reign of materials used in dentistry, denture resin having been the most commonly and frequently used material was chosen to study the application of drug delivery.

Aim and Objective: The aim of the study is to ensure the drug leaching activity, the effect of modulation of concentration of the drug on the microbial inhibitory activity, as well as the efficacy as compared to the pure form of the drug.

Material and Method: Three experimental groups were chosen which were as follows: the first group the denture resin was impregnated with 150gm of Fluconazole powder; the second group the denture resin was impregnated using 300gm of Fluconazole powder, whereas the third group was used as control which contained 10mcg Fluconazole paper disc. The three discs, one from each group was placed over Sabouraud Dextrose Agar medium containing *C. Albican* species and cultured for 24 hours at 30 °C. The readings were noted after 24 hours to measure the zone of inhibition. The readings were again taken after 48 hours to re-establish the efficacy.

Results: The results of our study reported gradually increasing leaching activity over 48 hrs. 60mcg concentration of the drug concentration in the disc showed similar effects as compared to 10mcg of the pure drug.

Conclusion: Within the limitations of the present investigation resin system can be used for intraoral delivery of antifungal drugs. The concentration of the drug mixed with the denture material can be modulated to achieve the desired concentration of the drug acting at the local site.

Keywords: Drug Delivery, antifungal, denture stomatitis, Fluconazole, Local drug

INTRODUCTION

Local drug delivery has always been chosen as a better treatment protocol over systemic therapy to avoid any systemic effects, maximize efficacy and minimize systemic side effects. The opportunistic oral candidal infection is a major concern in dentistry, which occurs as an inflammatory condition of denture stomatitis compromising the mucosal surface beneath dentures. Particularly, denture stomatitis affects 65% of healthy adult mouths.[I] In spite of its multifactorial etiology, *Candida albicans* has been established as a primary etiologic agent[II, III]

The various treatment options available for the treatment of denture stomatitis mainly include systemic antifungal drugs and recently popularized topical gels.

Conventionally various antifungal drugs have been administered topically or systemically for the management of oral candidiasis. Amphotericin B and Nystatin are commonly used and prescribed topical antifungals agents, however recently fluconazole and ketoconazole have been used as systematic antifungal treatment. Chlorhexidine gluconate has been also reported as a treatment alternative owing to its antimicrobial properties against a broad spectrum of organisms.[IV, V, VI, VII, VIII, IX]

The delivery of drugs for the topical treatment or prevention of diseases of the teeth, periodontium and oral mucosa has been attempted by a wide variety of methods. These include mouthwashes, suspensions, paints, lozenges, ointments, gels and toothpastes.[XI]

Several researchers investigated the feasibility of using drug delivery system by incorporation of antifungal or antimicrobial agents, with denture acrylic resin[XII] or with soft liners.[XIII] The idea suggested the use of polymerized

acrylic as carriers for drugs orally.[XIV] Various studies have been conducted on the same trying various modalities such as soft liners placed in dentures have been used as carriers for antifungal drugs in treating denture stomatitis.[XV, XVI] It has been found that the release of the drug out of the polymeric carriers continued for more than 100 days.[XVII] However, the physical properties of the resin were affected due to the presence of the drug particles, which may dissolve and result in porosity in the acrylic base.[XVIII]

This study aims at not only ensuring the drug leaching activity but also the effect of modulation of concentration of the drug on the microbial inhibitory activity, as well as the efficacy as compared to the pure form of the drug.

MATERIALS AND METHODS

A room temperature-polymerized poly methyl methacrylate acrylic resin (RR Cold cure, DPI, India) was employed. The mixing ratio and the conditions for processing and polymerization recommended by the manufacturer were strictly followed. These were 5 g / 3 ml polymer powder monomer liquid ratio for mixing. Three groups of medicated samples were prepared (Figure I). The first group was impregnated with 150gm of Fluconazole powder; the second group was impregnated using 300gm of Fluconazole powder, whereas the third group was used as control which contained 10mcg Fluconazole paper disc. The drugs were added in the specified ratio to the acrylic resin powder then the mixture of the powders with the liquid monomer were stirred for 15 seconds and left standing for 4 minutes until plastic dough was formed. It was then packed in a specially constructed disc-shaped steel mould to produce a disc specimen (3.8 mm diameter

and 1.0 mm thickness) such that they would contain 30mcg and 60mcg of the drug respectively. After packing the mould, it was allowed to stand and cure for 15mins.

5 petri dishes in which Sabouraud Dextrose Agar medium was prepared and *Candida Albicans* species was cultivated over it. The three discs, one from each group was placed over the agar medium and cultured for 24 hours at 30 °C. The readings were noted after 24 hours to measure the zone of inhibition. The readings were again taken after 48 hours to re-establish the efficacy.

RESULTS AND DISCUSSION:

The discs were cultured over 24 and 48 hours. The zone of inhibition was noted by measuring the diameter of the zones. [Figure I] The values were noted for all the 5 samples of each group in Table I. Paired t test was used to compare the mean values of the zone of inhibition between 24 and 48 hours of each disc and noted in Table II. The statistical analysis was performed using SPSS software version 24.

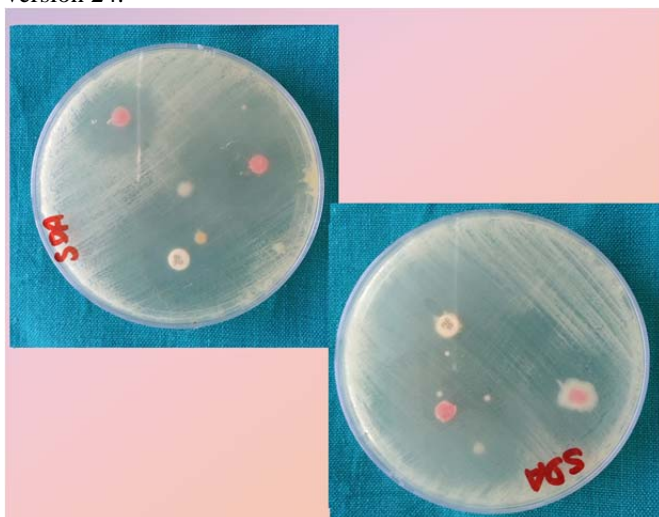


Figure 1 showing the zone of Inhibition around the 3 discs

Studies have reported that elution of Fluconazole antifungal drug from auto-polymerized acrylic resin specimens doped by Fluconazole demonstrated a relatively high initial release of the drug into distilled water during the first 24hrs.[IV] However the results of our study reported gradually increasing leaching activity over 48 hrs. Studies

have further demonstrated a slower and steadier diffusion for up to twenty-eight days.

Recent advances reported by Wen et al, where in they grafted poly(2-hydroxyethyl methacrylate) (PHEMA) onto poly(methyl methacrylate) (PMMA)-based denture resins through plasma-initiated grafting polymerization. The effects of reaction conditions on grafting and the physical properties of the resulting resins were evaluated. The grafted resins showed significantly increased drug binding capability toward clotrimazole, one of the most widely used antifungal drugs. The new clotrimazole-containing resins provided sustained drug release for longer than 28 days, and the released drugs demonstrated potent, long-term biofilm-controlling effects against *Candida*, pointing to an attractive strategy in controlling CADs and related fungal infections. [XIX]

The release of Fluconazole from the poly methyl methacrylate, drug release devices, to distilled water indicated that polymerization of the PMMA acrylic resin did not adversely affect the two antifungal drugs nor did doping the PMMA acrylic resin with Fluconazole alter the diffusion characteristics of the resin. [IV,XX]

The results of the present investigation highlighted the remarkable release behavior of the antifungal drugs contained within the denture resin. The diffusion profile revealed by the drug impregnated acrylic discs demonstrated significantly higher concentrations of the released drugs than the released concentration from the control disc of lower concentration. The concentration of the drug can be altered by the operator however the effectiveness of the release was a concern. But the study results have demonstrated that the release of the drug can be modulated with the drug dosage and can be achieved to similar levels as the pure drug form. The enhanced drug release behavior demonstrated by the acrylic discs was consistently high at the outset and continued to be significantly improve with time test period.

Studies have reported methacrylate based polymers absorb up to 30% water depending on the osmolarity of the external solution which in turn forms crazes and surface porosity in the brittle poly (methyl methacrylate). This enhances the Fluconazole delivery from the polymeric system.[Error! Bookmark not defined.,XX]

Table I. shows the mean and standard deviation of the zone of inhibition noted in the 3 groups after 24 and 48 hours.

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	GR1HRS24	18.0000	5	.61237	.27386
	GR1HRS48	20.3000	5	.44721	.20000
Pair 2	GR2HRS24	35.4000	5	.54772	.24495
	GR2HRS48	44.7000	5	.44721	.20000
Pair 3	GR3HRS24	30.1000	5	1.14018	.50990
	GR3HRS48	39.7000	5	.44721	.20000

Table II. shows the comparison of the Mean and Standard deviation of the zone of inhibitions of the groups at 24 and 48 hours.

		Paired Differences			95% Confidence Interval of the Difference	95% Confidence Interval of the Difference		df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean					
Pair 1	GR1HRS24 - GR1HRS48	-2.30000	.75829	.33912	-3.24154	-1.35846	-6.782	4	.002
Pair 2	GR2HRS24 - GR2HRS48	-9.30000	.44721	.20000	-9.85529	-8.74471	-46.500	4	.000
Pair 3	GR3HRS24 - GR3HRS48	-9.60000	.96177	.43012	-10.79419	-8.40581	-22.320	4	.000

Similar findings have been previously reported in a study that used the same polymeric system for delivery of hydrocortisone.[XXI]

As Fluconazole-supplemented dentures resins were tested for the release the antifungal drugs in controlled concentrations, it became essential to investigate whether the concentrations of the released drugs were high enough to affect an antifungal activity upon the growth of *Candida albicans* which is the common pathogen that causes denture-induced stomatitis lesions. This entailed the microbiological investigation conducted in this study which ascertained that the released concentrations of the antifungal drugs did induce antifungal effect against *Candida albicans* by inhibiting its growth in Sabourauds culture.

These findings confirmed those of an earlier study which also showed that Fluconazole diffuses out of an auto-polymerized acrylic resin in fungicidal concentrations.[XII]

The results of the present investigation indicates that Fluconazole has a powerful antifungal effect, proved by its capacity of inhibiting the growth of *Candida albicans*.

CONCLUSION:

Within the limitations of the present investigation resin system can be used for intraoral delivery of antifungal drugs. The concentration of the drug mixed with the denture material can be modulated to achieve the desired concentration of the drug acting at the local site. A gradual increasing concentration of the drugs at the site of the pathology where candida infection is usually found can show beneficiary effects in cases of denture stomatitis, wherein the causative agent can aid in the treatment.

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