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Review Article

Drug Delivery through Denture-Base Resins – A Systematic Review

Maleeha Nayyer, Shahreen Zahid, Muhammad Kaleem, Bilal Ahmed, Hudia Rizwan
National University of Science and Technology, Islamabad.

Abstract

The purpose of this article was to review current literature on the usage of denture bases as potential drug-release devices (DRDs) for the treatment of oral conditions such as Candida associated denture stomatitis (CAD) and recurrent ulcers. Relevant publications from the year 1983 to 2014 were included by searching 'denture bases' and 'drug delivery' using [MeSH terminology].Specific inclusion and exclusion criteria were set. Most studies were done in vitro. It was concluded during the review that various therapeutic agents such as Fluconazole, Chlorhexidine gluconate and Hydrocortisone Sodium Succinate have been successfully incorporated in denture base resins. Drugs leach out steadily from poly methyl methacrylate (PMMA) specimens for a period of 28 days. In case of *rechargeable* denture bases, the elution continues for longer periods. A lot of ongoing research is being done on the incorporation of silver nanoparticles and monitoring its antimicrobial activity.

Key words: Denture bases, drug delivery, drug carrier systems, PMMA resin, MMA resin.

Introduction

According to epidemiological studies, about 70% of removable denture wearers suffer from Candida associated denture stomatitis (CAD).[1] The hydrophobic and rough surface of the denture contributes to pathogenic adhesion and biofilm formation, which ultimately leads to inflammation.[1] Other factors such as normal aging phenomenon, malnutrition, high intake of carbohydrates, diminished salivary flow, diabetes mellitus and immunosuppression also contributes to the increased susceptibility of fungal infections.[2]

Recent advances in the drug delivery advocates incorporation of silver nanoparticles in the denture base resin specimens because of their antimicrobial effects.[3] Conventional approaches include use of systemic antifungal drugs like Fluconazole and Miconazole and topical agents such as Nystatin and Amphotericin B.[4]

A better approach is to fabricate such acrylic dentures which may act as DRDs (Drug releasing devices) from which antifungal drugs elute and inhibit microbial growth.[4] Most commonly used agents for such purposes are chlorhexidine acetate and digluconate which are commonly used as antiseptic mouthwash due to its broad-spectrum antimicrobial activity.[5] However, when used as a mouth wash, most of the agents are removed from the mouth during the first hour, due to the diluting effect of the saliva. Their incorporation in denture base resins is a novel approach.[5] Other drugs like Fluconazole and Miconazole in specified concentrations[6] and hydrocortisone sodium succinate (HSS) are also mentioned in literature as Drug delivery devices for treatment of recurrent ulcers.[7] Fluoride ions have also been used because of their anti-cariogenic effects on the abutment teeth.[8]

Full electronic search strategy was applied. Two eminent database sources were used for this purpose; PubMed and Elsevier Sciencedirect. Articles were also searched on the popular search engine Google Scholar. When the MeSH terminology "drug delivery system" was searched, a total of 1695 results were displayed". The terms "drug carrier systems" and "PMMA resins" yielded no significant results. The Table below summarizes the results (Table-1).

Out of 40 specific results, 9 were discarded on the basis of their title like "drug delivery in orthopedic implants" and "pharmaceutical polymers". Thirty one articles were categorized on the basis of the eligibility criteria. Figure-1 illustrates this process. Inclusion criteria included the articles which discussed denture bases as potential drug-release devices and full text articles

Corresponding Author:
Maleeha Nayyer
National University of Science and Technology
Islamabad.
Email: mnayyer25@gmail.com

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Authors Contribution

SZ and MK have done the conceptualization of project. MN did data collection and literature search. Drafting, Revision and manuscript writing was done by MN and BA. HR did the formatting of manuscript.

Table 1: Sources used for literature search.

Source	*Phrases used/MeSH Terminology*	*Date (mm/dd/yy)From*	*Date (mm/dd/yy) To*	*Filter*	*Results*
PubMed	"Denture bases" and "Drug Delivery Systems"	04-03-15	04-08-15	Books	5
Sciencedirect	"Denture bases" and "Drug delivery systems"	04-03-15	04-08-15	Books	27
Google Scholar	"Denture bases" and "Drug delivery systems"	04-03-15	04-08-15	Books	8
			Total		40

as well as abstracts were available. Other materials such as tissue conditioners and acrylic liners used for drug delivery and surface coating of denture bases were not included in the domain of drug delivery.

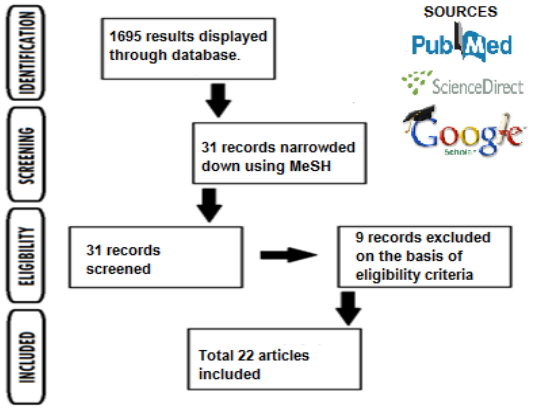

Figure 1: Flow diagram illustrating the methodology.

Discussion

Drug-delivery is a relatively new arena for denture bases therefore the number of articles available was limited. Using inclusion criteria, out of 30 articles searched, 9 were excluded and 22 were selected for the review. Excluded studies either used tissue conditioners and liner materials as Drug-delivery devices,[9-12] or were those that discussed surface modification by coating of Titanium dioxide.[13] or where liners and conditioners (plasticized gels) were used.[12]

Full text of 28 articles were available while for 3 articles, only abstract was accessible. Most of the studies comprised of in-vitro experiments while only one study was conducted on rats and two clinical trials were done in humans. Both of these were also included in this review[7,14,15]

The relevant findings from the articles that were included in the review is given in Table-2.

The review showed that majority of the studies had used chlorhexidine digluconate or acetate incorporated in the denture bases. Chlorhexidine in a concentration of 0.2% is commonly used as mouth wash because of its antiseptic and antimicrobial effects. Its maximum safe dose is 10%.[5] Recent studies advocate the use of silver ions and silver nanoparticles. This trend is shown in Figure-2.

Sources of silver nanoparticles include silver-ion loaded inorganic carrier [1] and reduction of silver nitrate with sodium citrate.[16] Anti-adhesion effects of silver nanoparticles were observed at a concentration of 5%.[17] Sources of silver ions included silver sulfadiazine [18] and silver nitrate solutions.[19] Silver ions are not generally well-tolerated as compared with silver nanoparticles. Researchers have implanted ions using plasma-based ion implantation and later analyzed them using X-ray photo-electron spectroscopic analysis.[3]

Specimens of specified diameter were created from heat-cure PMMA resins or self-cure PMMA resins in the studies. In some studies, certain modifications were made for example; incorporation of Meth acrylic acid (MAA) and polyethyl methacrylate (PEM).[10,11] The new resins had a much higher capability to bind and absorb antifungal drugs and demonstrated sustained drug delivery for a few weeks. Scanning electron microscopy (SEM) images of biofilm revealed that the control resin of PMMA alone, showed no visible inhibitory zone where as the drug containing 10% MAA resin showed a significant zone of inhibition and no adherent Candida species.[4] The monomer with drug-binding functional group, N-vinyl-2-pyrrolidinone (NVP), was grafted onto poly (methyl methacrylate) denture resins through plasma-initiated grafting polymerization. PNVP grafting significantly increased the drug absorption capability of the resulting denture materials. Further, the new materials showed sustained drug release and provided antifungal effects for weeks (in case of chlorhexidine digluconate) to month (in case of miconazole) and also made the specimens disc capable of being charged again.[2] In one study, surface pre-reacted glass monomer filler (SPRG) was incorporated for fluoride release.[20]

Most commonly used therapeutic agents include chlorhexidine digluconate, chlorhexidine acetate and fluconazole.[10,11] Incorporation of higher concentrations of Chlorhexidine resulted in reduced fracture toughness but fluconazole had no profound effect.[17] Other agents used were nystatin,[21] miconazole[22] and hydrocortisone sodium succinate (HSS).[7]

Elution profiles were analyzed in various extraction mediums using High Performance Liquid Chromatography (HPLC). Gas chromatography is a novel technique in which eluates are centrifuged. This technique is highly accurate. These methods demonstrated a high rate of elution for the first week with sustained release up to 4

Table 2: Relevant findings from literature.

No.	Author	Year	Type of Study	Sample Design	Therapeutic agent delivered and Method of incorporation (if mentioned)	Relevant Findings	Inclusion/ Exclusion Criteria.
(1)	Li et al	2014 Full Text	In vitro exp	Nano-silver particles were mixed and homogenized in a ball mill to fabricate such acrylic specimens which contained Nano-silver particles at concentrations of **1, 2,3** and **5% w/w**).	**Nano silver base inorganic antibacterial agent (NSBIAA).** It is a silver ion loaded inorganic carrier which was used for delivery.	The inhibitory effect on biofilm was observed using **XTT reduction** and **Crystal Violet assays**. Biofilm architecture was severely destroyed. **Confocal scanning laser microscopy (CLSM)** was also used.	Included.
(2)	Sun et al	2013 Full Text	In vitro exp	A monomer with a specific binding functional group **N-Vinyl-2-pyrrolidinone (NVP),** was grafted on the PMMA resins by **plasma-initiated grafting polymerization**. Sample discs were created. C.albicans strains were used.	**Chlorhexidine gluconate** And **Miconazole**. Both **5%** by wt.	NVP grafting significantly enhanced the drug absorption capability and made the discs **rechargeable. Drug quenching** and **drug rotation** was observed in de-ionized water and **phosphate buffered saline (PBS).** Biofilm assays and **SEM (Scanning electron microscopy)** were utilized.	Included.
(3)	Shinoga and Anita	2012 Full Text	In vitro exp	Acrylic resins were used to fabricate disc specimens.	**Silver** and **Fluorine** ions were incorporated in the resin using **Plasma-based ion implantation**.	Ion implantation was confirmed by **X-ray photoelectron spectroscopic analysis**. Antibacterial activity of Silver and Fluorine ions was evaluated by **luminescent microbial cell viability assay** (enzyme luciferase).	Included.
(4)	Sun et al	2011 Full Text	In vitro exp	**Methacrylic acid (MAA)** co-polymerized with acrylic denture base resins were used.	**Miconazole 2% aqueous solution**.(Specimens were immersed in it)	Modified resins demonstrated **recharging ability** and they had higher capability to bind the antifungal drug miconazole. Drug quenching was observed using **Ethylene diamine tetra-acetic acid (EDTA) solutions.** Flexural strength was also evaluated. It was observed that concentrations up to 10% did not affect the flexural strength; however conc. greater than 20% affected it.	Included.

(5)	Cao et all	2011 Full Text	In vitro exp	Self-cure resins were used in P/L ratio of **5g/3mL** .Disc specimens of 3.8 mm diameter and 1 mm thickness were fabricated.	**Chlorhexidine digluconate** (Powder form: **10% w/w**)	**High Performance Liquid Chromatography (HPLC)** was used for drug elution. **SEM** images of biofilm revealed characteristic zone of inhibition.	Included.
(6)	Amin et al	2010 Full Text	In vitro exp	PMMA resin specimens were fabricated.	**Titanium Dioxide (TiO_2) was used for surface coating.** Titanium isopropoxide was used for the development of titanium sol which was plasma treated.	**Atomic force microscopy (AFM**) revealed a well-defined film of Titanium dioxide. These film-coated samples were immersed in a bacterial suspension containing E.coli and S.Aureus and decrease in the **Colony forming units (CFU**) counts was observed.	**EXCLUDED.** Surface modification was not included.
(7)	Brook et al	1991 Full Text	**In vivo study**	PMMA resins modified with semi-permeable membrane (SPM) were used.	**Hydrocortisone sodium succinate.(HSS)**	Volunteers wore the drug-delivery devices for a week. Saliva was also collected from them. Initial high release of drug was observed in both cases.	Included.
(8)	Koide et al	1990 Full Text	In vitro exp	Denture base resins.	**Fluoride ions**	Fluoride release was observed.	Included.
(9)	Bertolini et al	2014 Full Text	In vitro exp	Resin discs were prepared from denture liner materials. C.albicans strains were used.	**Chlorhexidine diacetate** salt.	Dose-related inhibitory effects were visible on the strains placed on agar plate.	**EXCLUDED.** Only denture base resins were included in the materials of study.
(10)	Salim et al	2012 Full Text	In vitro exp	Materials of study were soft denture liners , particularly Self-cure **poly ethyl methacrylate (PEM)** and **tetra hydro-furfuryl methacrylate (THFM).**	**Chlorhexidine digluconate** And **Fluconazole** (Powder and capsule form)	Antifungal activity and Drug elution profiles were observed for a period of 28 days.	**EXCLUDED.** Acrylic liners and tissue conditioners were kept in the exclusion criteria.
(11)	Salim et al	2012 Full Text	In vitro exp	Self-cure soft denture liners.	**Chlorhexidine digluconate** And **Fluconazole**	In this study, bonding characteristics were observed.	**EXCLUDED.** Soft denture liners were excluded.
(12)	Yamamo to et al	2009 Full Text	In vitro exp	A modified tissue conditioner was used.	Lyophilized cation was used to modify the resins, so as to make it capable of binding to protein.	It was observed that microbial protein lactoferrin binded with the modified specimens.	**EXCLUDED.** Only denture base materials were included.
(13)	Nazirkar et al	2014 Full Text	In vitro exp	45 heat-cured acrylic specimens were used. C.albicans strains were used.	**Titanium dioxide (TiO_2) nanoparticles**.	Surface modification was done and flexural strength was evaluated.	**EXCLUDED.** Surface modification was not included in this search.

(14)	Lamb and Douglas	1988 Full Text	**In vivo study**	Drug containing palatal dentures were fabricated. A hole of approximately 3 cm was cut in the centre of the denture and miconazole nitrate base mixed with PMMA and MMA resins was placed in the void.	**Miconazole nitrate base**	10 patients who were suffering from Recurrent denture stomatitis were selected. They were made to wear modified dentures. Candida was eliminated from the mouth of 5 patients, over a period of 3 months.	Included.
(15)	Lamb D et al	1983 Full Text	**Animal experiment in rats**.	Self-cure PMMA resins were used to fabricate palatal acrylic plates.	**Chlorhexidine acetate (7.5%)**	Ten rats were fixed with palatal acrylic plates. After 5 weeks palatal candidiasis was established, then acrylic plates were replaced with plates containing the drug to check the effects.	Included.
(16)	Monteiro et al	2012 Abstract	In vitro exp	Denture resins to which nanoparticle suspension was added.	**Silver nanoparticles**. These were made available by the reduction of silver nitrate with sodium citrate.	It was observed, using an **Atomic absorption spectrophotometer** that dissemination of nanoparticles decreased when using lower concentrations.	Included.
(17)	Al-haddad et al	2014 Full Text	In vitro exp	30 **single-edge-notched (SEN)** samples were prepared.	**Chlorhexidine (10%** by mass) and **Fluconazole** (**4.5%** by mass).	Use of bioactive compounds in denture bases was discussed. Addition of Chlorhexidine resulted in decreased fracture toughness whereas Fluconazole had no effect on it.	Included.
(18)	Cae et al	2009 Abstract	In vitro exp	Modified specimens were prepared by co-polymerizing acryloyl sulfadiazine with MMA and sequentially treating the copolymers with dilute silver nitrate aqueous solutions. E.coli , S.aureus and C.tropicalis strains were used.	**Silver sulfadiazine.**	**Kirby-Bauer (KB)** method indicated 100% inactivation (contact kill) of the E.coli and S.aureus within 10 mins, and C.tropicalis within 30 mins.	Included.
(19)	Kamika wa et al	2014 Full Text	In vitro exp	Sheets of heat-cured acrylic resins were fabricated. C.albicans strains were used.	**Silver nitrate solution.** (Gaps were cut in sheets, in which silver nitrate coatings were embedded)	**Adhesion assays** were analyzed using yeast culture solutions. Potent antifungal effects were observed by the inhibition of adhesion of Candida species.	Included.
(20)	Kamijo et al	2009 Abstract	In vitro exp	PMMA denture base resins.	**S-PRG (Surface pre-reacted glass monomer)** for fluoride release, 20% by wt.	Initial amount of fluoride release was greater and it had anti-cariogenic effects against strains of S.mutans.Recharging of fluoride was done by immersing in a solution containing 9000 ppm fluoride, for 8 hrs.	Included.

(21)	Silva et al	2008 Full Text	In vitro exp	Heat-polymerized and Microwavable PMMA resin specimens were used.	**Fluconazole** and **Nystatin**	Use of antifungal drugs in denture bases is discussed. Surface roughness was also characterized.	Included.
(22)	Cao et al	2010 Full Text	In vitro exp	Modified denture discs were prepared by co-polymerization of **Methacrylic acid(MAA)** and **Diurethane dimethacrylate (DUDMA)** in aluminum molds	Ethanol solutions of **Miconazole 5%** and **Chlorhexidine digluconate 10%**	Modified resins were capable of drug recharging. **Drug releasing** and **quenching** was tested in artificial saliva and distilled water using **HPLC**. It was observed that drug releasing was greater at acidic concentrations.Miconazole was present in the specimens even after 60 days. Biofilm activity was tested by **Kirby Bauer (KB**) method.	Included.
(23)	Yamamoto et al	2011 Full Text	In vitro exp	Self-cure resins were used to fabricate disc shaped specimens.	**Fluconazole** (Powder form: **10% w/w**)	**HPLC-UV (Ultra Violet)** revealed that the rate of release was greater for the first four days, by sustained release for four weeks. Rate of release was higher in artificial saliva as compared to water.	Included.
(24)	Amin et al	2009 Full Text	In vitro exp	15 specimen discs of PMMA resin (3.8 mm in diameter and 1mm in thickness) were prepared.	**Fluconazole (5% by wt**.), **Chlorhexidine (10% by wt.**) and a combination of two (**5% by wt. each**) were incorporated in the specimens.	**HPLC** was used to observe drug elution in distilled water.Chlohexidine was released in greater amounts than Fluconazole. Biofilm activity was tested using **Agar Well diffusion** method.	Included.
(25)	Lin et al	2003 Full Text	In vitro exp	**Ethylene vinyl acetate co-polymer (EVA**) was used to make thin square specimens of 1mm.	**Tetra-hydrochloride (TTH), doxycycline hydrochloride (DOH)** and **Chlorhexidine diacetate (CDA).**	Elution of drugs was done in water and water/ethanol in(4:1)	**EXCLUDED.** Novel approach for denture bases but does not include denture bases.
(26)	Jayaseel et al	2013 Full Text	In vitro exp	Standard agar plates were used.	**Gold silver nanoparticles** obtained from aqueous seed extracts from plant source.	**Agar-well diffusion** method was used and relative zones of inhibition were measured. **UV-visible spectroscopy** was also used.	**EXCLUDED**. Denture base resins were not used as materials.
(27)	Riggs et al	2000 Full Text	In vitro exp	**Dimethyl-p-toluidine DMPT** monomer were used with PMMA powder.	**Chlorhexidine diacetate (CDA)**	**Nuclear magnetic resonance spectroscopy** showed that Chlorhexidine was being released from the polymer.	Included.

(28)	Acosta-Torres et al	2012 Full Text	In vitro exp	Discs of dimensions 20 mm by 2 mm were created from PMMA and MMA. The volume ratio of MMA monomer to silver nanoparticles was kept as **3:1.** C.albicans strains were used.	**Silver nanoparticles.** These were synthesized using a natural green infusion from a plant source, as a reducing agent.	**SEM analysis** demonstrated fairly good dispersion of silver nanoparticles in the polymer matrix. Significant reduction in the adherence of fungal strains was observed using a **luminescent microbial cell viability assay.**	Included.

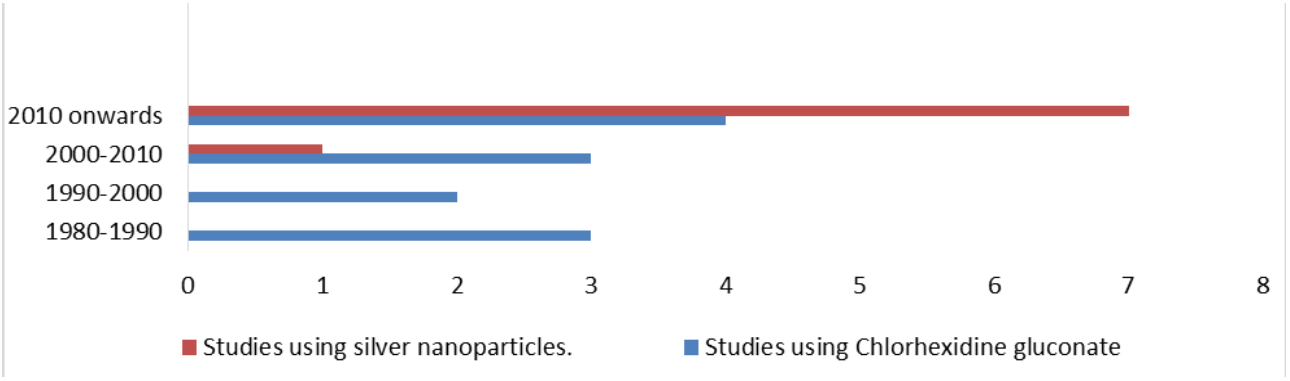

Figure 2: Trend of therapeutic agent incorporated in denture bases.

weeks.[5,23] In another study, 15 containers in a thermostatically controlled water bath with 60ml of distilled water were used to see the drug release. It was found out that Chlorhexidine was released in a higher amount than Fluconazole and the surface initial release was rapid followed by a slower and sustained release for up to four weeks.[24] Various extraction mediums used include de-ionized water,[2] distilled water,[24] phosphate-buffered saline PBS[2] artificial saliva[23] and water: ethanol in 4:1 ratio.[24]

Apart from drug-releasing, drug-recharging and drug quenching was also evaluated. In a study using PVP monomers, the drug-depleted resins could be recharged with the same or a different class of antifungal drug to further extend antifungal duration. If needed, drugs on the PNVP-grafted denture materials could be "washed out" (quenched) by treating with PNVP aqueous solutions to stop drug release.[2] Other agents for drug quenching include 5% EDTA solution.[4,22] Drug rotation was also tested. After 60 days of Miconazole release; the specimens were quenched with PNVP aqueous solution, and recharged with chlorhexidine. Similarly, after 14 days of chlorhexidine release, the discs were quenched again and then recharged with Miconazole.[2]

Anti-microbial effects were mainly assessed using Agar Well Diffusion method.[15,23,24,26] Stock cultures of C. albicans were used in most cases.[1,9,18,26] Inoculated agar was poured on assay plates and wells were cut from in it which 10 to 20ul of therapeutic agent was placed. Characteristic zone of inhibition was observed which pointed towards the anti-microbial tendency.[23] Another method commonly used is the Kirby Bauer (KB) technique.[17,22] The discs were rinsed with Phosphate-buffered saline (PBS) and placed onto surface of agar plate containing a culture of C.albicans and zone of inhibition was measured with a ruler.[22] Scanning electron microscopy (SEM) was also employed in many studies.[2,4,5] SEM images of biofilm also revealed a characteristic zone of inhibition. Diameter of the zones was measured by PBI Read biotic measuring device.[5] In one study, Nuclear magnetic resonance spectroscopy was used; it showed that chlorhexidine was being released from the polymer.[27]

For silver nano particles, The XTT reduction and crystal violet assays were used which indicated that the bioactivity and biomass of C. albicans biofilms decreased successively with increasing Nano-silver suspension concentration.[1] Biofilm architecture was severely destroyed in the presence of silver nanoparticles. Confocal scanning laser microscopy (CSLM) demonstrated that silver nanoparticles get wrapped around C.albicans and caused fungal membrane disruption and inhibition of the normal budding process.[1] UV-visible spectroscopy was also used.[26]

An antibacterial activity test was also performed by the adenosine-50-triphosphate luminescence method, using an enzyme luciferase. ATP is an indicator of biomass content. ATP luminescence method can determine the quantity of live bacteria on the sample quickly and

accurately. It was found antibacterial activity was remarkably enhanced in the F and Ag dual-ion implanted and deposited PMMA which was also hydrophobic after the modification.[3] The antifungal effect was assessed using a luminescent microbial cell viability assay and significant reduction in the adherence of C. albicans to sample disks was observed.[28]

In one study, ten rats were fixed with acrylic palatal plates. After 5 weeks palatal candidiasis was established, then acrylic plates were replaced with plates containing the drug to check the effects.[15] In 2 vivo studies in humans were also done. In one study, ten patients suffering from recurrent denture stomatitis were selected and Candida was eliminated from the mouth of five patients.[14] In the second study, five volunteers offered saliva collection and the results were compared in those who wore the drug delivery devices and those who did not and the drug release was evaluated.[7]

Drug-based delivery is an alternative approach to conventional systemic and topical anti-microbial treatment methods. Chlorhexidine gluconate is one most commonly used agent for oral diseases. It was found that duration of inhibition of adhesion of pathogens lasted longer when Chlorhexidine was used as compared to Nystatin. The problem is that most of the drug-delivery based denture devices are not suitable for long term use. The current approaches of implementation cannot incorporate enough quantity of the therapeutic agents to maintain the necessary concentration on or near the denture surfaces, for extended use, ranging from years to months. Dentures are worn for years and Candida-Associated Stomatitis is a recurring disease. Newer studies therefore focus on rechargeable denture-base resins to overcome this problem. Rechargable resins serve for a longer release of drugs to match the recurrence potential. Silver nanoparticles incorporation is also a well-documented concept. Release of fluoride offers anti-cariogenic benefits for the abutment teeth. Future laboratory investigations should target the elution profiles of therapeutic agents in artificial saliva so that the effect is comparable with clinical scenarios. Most studies have been done in vitro and results compared with a control group. In vivo studies are necessary to gauge the beneficial effects of the drug-supplemented polymeric devices. Apart from antifungals, sialagogues incorporation for the treatment of xerostomia conditions is also a newer area for studies. Similarly drug-based delivery in nylon and polyamide dentures also needs to be explored.

Conflict of interest: None declared.

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