Review Article

Bioadhesive polymer in antifungal drug delivery for therapeutic treatment of candidiasis

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Abstract

Candida species are the primary cause of candidiasis, a common yeast infection, with *Candida albicans* being the most prevalent pathogen. These infections often infiltrate the body through cutaneous and vaginal routes. Given the potential severity of some Candida infections, particularly invasive cases, there is a critical need for effective antifungal treatments. Controlled drug delivery strategies have been developed to achieve optimal release kinetics and precise targeting of active agents, especially in fungal infection therapeutics. Consequently, significant attention has been focused on exploring and utilizing bioadhesive polymers to enhance the performance of drug delivery systems for antifungal medications. Bioadhesive drug delivery systems aim to sustain the release of therapeutic agents, reducing the need for frequent dosing. This article provides a comprehensive review of scientific investigations into the use of antifungal drugs within bioadhesive drug delivery systems for treating candidiasis, locally and systemically. The evaluation covers the efficacy of these systems against candidiasis, factors affecting prolonged contact at the application site, and the underlying mechanisms of drug delivery.

Key words: Antifungal drug delivery, bioadhesive polymer, *Candida albicans*, candidiasis, fungal infection

INTRODUCTION

Bioadhesion, a crucial aspect of drug delivery systems, enhances drug bioavailability by prolonging residence time and facilitating drug permeation.[1] Candidiasis, caused by Candida species, is a global health concern, with *Candida albicans* as the predominant pathogen.[2] Although antifungals are the mainstay treatment for candidiasis, conventional formulations struggle with maintaining drug concentrations and retention in affected areas.

Bioadhesive polymers offer diverse options based on their origin, solubility, charge type, and bioadhesive forces. First-generation bioadhesive polymers such as carbomers, chitosan, and cellulose derivatives are widely used, while second-generation materials such as thiomers and lectins demonstrate specific binding capabilities.[3] Polymers interact with mucin glycoproteins through various mechanisms, including electrostatic interactions, hydrogen bonds, van der Waals contacts, and covalent bonds [Figure 1].[4] In addition, bioadhesion is regulated by both the inherent properties of the adhesive polymer and the environment under which adhesion takes place.

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This study conducted a comprehensive literature search utilizing databases of Science Direct Freedom Collection, PubMed, Linking Hub Elsevier, Springer Link, Wiley Online Library, Scopus, and Google Scholar. The search used keywords such as "antifungal drug delivery," "mucoadhesive polymer," "bioadhesive polymer," and "candidiasis" to identify English-language articles published between January 2011 and December 2023. The selected research papers underwent meticulous assessment and review.

BIOADHESIVE POLYMERS FOR THE TREATMENT OF CANDIDIASIS

Chitosan

Chitosan, derived from chitin found in crustacean exoskeletons, possesses mucoadhesive properties due to its hydroxyl and amino groups, favoring hydrogen, and covalent bonding with mucin.[1] The antimicrobial efficacy varies based on molecular weight and degree of acetylation, impacting its interaction with Gram-negative and Gram-positive bacteria.[5,6] Studies by Lo *et al*. suggest that lower molecular weight chitosan exhibits notable antifungal effects when combined with fluconazole.[7]

Regarding drug release, chitosan's combination with fluconazole showed rapid release and high bioavailability, attributed to significant swelling on the tablet surface.[7,8] Another study focused on clotrimazole release from chitosan with a drug-free pectin layer, prolonging release through ionically interacting polymer chains.[9] In addition, ketoconazole incorporation into chitosan/gellan gum gel flakes slowed release due to electrostatic interactions.[10] Varying release efficiencies for nystatin were observed in chitosan-based therapeutic formulations, with propolis enhancing efficiency.[11]

Chitosan incorporation in formulations improved adhesion and drug absorption. The combination of itraconazole with chitosan demonstrated superior mucoadhesion and prolonged drug residence time in vaginal candidiasis treatment.[12] Despite chitosan's impact on gel viscosity, it did not significantly affect the release profiles of miconazole and econazole, providing a sustained release for up to 8 h.[13,14] Chitosan-hydrogel formulations containing nystatin and propolis exhibited significant inhibition of *C. albicans* growth within a synthetic vaginal environment.[11]

Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC) is a cellulose derivative widely used in controlled-release formulations due to its biocompatibility, water solubility, and moldable nature when heated. The polymer concentration in HPMC formulations influences drug release rates, with higher concentrations leading to slower release due to increased gel viscosity.[13] In terms of mucoadhesion, HPMC contributes to prolonged adhesion through hydrogen bonding with mucin glycoprotein.[15] Mucoadhesive buccal discs and tablets containing HPMC exhibited extended residence times in the oral cavity.[12,13,16] However, the mucoadhesive strength may decrease at higher HPMC proportions.[17] Introducing polyethylene glycol 400 to HPMC films also reduced mucoadhesive strength. Despite challenges such as film disintegration in vaginal mucoadhesive formulations,[17] HPMC incorporation has demonstrated promising results in improving drug release and mucoadhesion in various pharmaceutical applications.

Carboxymethylcellulose

Carboxymethylcellulose (CMC), a water-soluble polysaccharide, offers exceptional solubility and versatility in various applications due to its carboxylate and hydroxyl groups.[18] Formulations containing CMC exhibited controlled release profiles, such as nystatin films for vulvovaginal candidiasis treatment, achieving complete drug release within 5 h.[19] The mucoadhesive buccal discs with fluconazole showed slower release rates with sodium CMC/HPMC compared to sodium alginate/HPMC formulations. Regarding mucoadhesion, films containing nystatin displayed longer residence time on vaginal mucus surfaces, promoted by CMC's hydrophilic and swelling characteristics.[19]

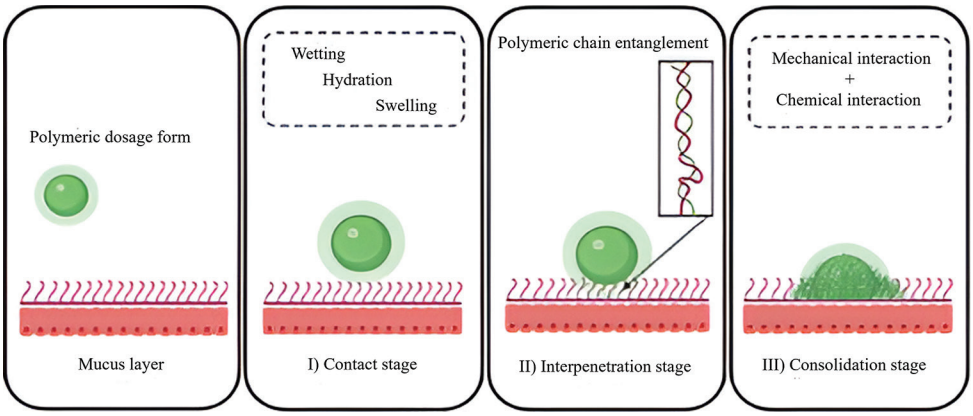

Figure 1: Phases of the mucoadhesive polymer's interaction with mucin glycoproteins. Adapted from Ahmady *et al*.[4]

Table 1: Antifungal drug delivery utilizing bioadhesive polymers in the treatment of candidiasis

Types of polymer	Disease	Findings	References
Chitosan	*C.albican* infection	Chitosan and fluconazole have synergistic fungicidal effects against *C. albicans*	[7]
	Vaginal candidiasis	Chitosan hydrogel formulations incorporating both nystatin and propolis efficiently inhibited fungal growth	[11]
		Vaginal gels formulated with medium molecular weight chitosan may offer advantages, including favorable retention in the vagina and excellent mucoadhesive, mechanical, and release properties	[28]
		The carrier containing ketoconazole effectively coats and distributes across the vagina, exhibiting free-flowing properties. It adheres to the interior of folded vaginal epithelia, enabling sustained release over an extended period and enhanced penetration to deep-seated infections	[10]
	Oral candidiasis	Liquid crystalline system containing 0.5% chitosan exhibited improved mucoadhesive properties and effectiveness against strains of *C. albicans*	[29]
		The use of buccal mucoadhesive chitosan-coated fluconazole nanoparticles resulted in reduced side effects in the treatment of oral candidiasis	[30]
HPMC	*C.albican* infection	An optimized gel formulation incorporating itraconazole was developed utilizing an HPMC gel base. The resulting gels demonstrated favorable characteristics, including excellent spreadability, appropriate pH, and satisfactory drug content	[31]
	Vaginal candidiasis	The *in situ* vaginal gel, employing a combination of gelling agents with HPMC, demonstrated a prolonged residence time exceeding 8 h and achieved a drug release of 99.76%, leading to increased drug retention in vaginal tissue	[12]
PVP	Vaginal candidiasis	Fluconazole diffusion rate from the PVP hydrogels loaded with the drug was notably higher in the final phase compared to the initial phases, indicating a sustained release pattern as opposed to an initial burst release at the commencement of the experiment	[32]
CMC	Oral candidiasis	The combination of miconazole and urea in the bioadhesive CMC film inhibits *C. albicans* with a significantly lower minimum inhibitory concentration value	[33]
Carboxymethyl derivative	Vaginal candidiasis	The release mechanisms of the vaginal film prepared from a carboxymethyl derivative of fenugreek gum involve a combination of diffusion and swelling. The formulation was nonirritating, nontoxic to the vaginal mucosa, and possesses antifungal properties	[19]
Chitosan and guar gum	Vaginal candidiasis	The formulation comprising a chitosan/guar gum ratio of 2:1, containing fluconazole, exhibited robust initial drug release at 90.97%, accompanied by a sustained release profile	[8]
Chitosan and pectin	Oral candidiasis	Clotrimazole incorporated into a multilayer system comprising chitosan and pectin demonstrated an extended drug release, coupled with potent antifungal efficacy and a favorable safety profile	[9]
Chitosan and HPMC	Vaginal candidiasis	*In vitro* testing revealed the efficacy and safety of the formulation, exhibiting a time-to-kill value of 3 min against *C. albicans* and no observed cytotoxic effects	[17]
HPMC and polyacrylic acid	Oral candidiasis	The mucoadhesive bilayered buccal tablets facilitated unidirectional drug release into the oral cavity, providing an extended-release profile	[13]
HPMC and SCMC	Oral candidiasis	The direct compression of HPMC/SCMC buccal disc yields a mucoadhesive disc with favorable adhesion time, prolonged residence time (>8 h), and complete drug release within 360 min	[21]
Glycogen and gelatine	Candida infection	The nanocomposite-based biopolymers demonstrated a 69.2% rate of inhibition against biofilm formation	[21]

HPMC: Hydroxypropyl methylcellulose, PVP: Polyvinylpyrrolidone, CMC: Carboxymethylcellulose, SCMC: Sodium CMC, *C. albicans: Candida albicans*

Gelatine

Gelatine, derived from collagen, exists in Type A and Type B forms and boasts nonimmunogenic, nonantigenic, and biocompatible properties.[20] Its hydrophilicity, swelling rate, and ability to form electrostatic contacts and hydrogen bonds make it a promising bioadhesive material. Gelatine-based nanocomposites demonstrated inhibitory and antibiofilm activity against candida strains, suggesting potential for controlled drug release.[21] Cross-linked gelatine and combining gelatine with other polymers enhances its mucoadhesive strength, mechanical stability, and hydration characteristics, offering potential in various drug delivery applications.[4]

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a biocompatible polymer known for its mucoadhesive and nonimmunogenic properties, making it suitable for mucosal drug delivery applications.[22] PVP's crosslink density impacts hydrogel characteristics, such as pore size and swelling, with higher concentrations leading to increased crosslink density.[23] In drug release studies, mucoadhesive tragacanth gum-PVP-based hydrogels showed pH-dependent release of fluconazole, with higher

release rates in acidic compared to alkaline buffer solutions.[24] Despite no initial bursts, these hydrogels delivered extended drug release over a 24-h period.

Polyacrylic acid (carbomer/carbopol)

Carbomer is a pH-dependent polymer with exceptional mucoadhesive characteristics, maintaining solubility in acidic pH and transforming into a low-viscosity polymer in alkaline pH.[25] Carbomer microgels, sparingly soluble in water, undergo significant swelling during gel neutralization, resulting in three-dimensional crosslinked microgels.[26] Carbomer-based mucoadhesive formulations offer improved mucoadhesive characteristics, allowing for prolonged drug release. Carbomer was utilized in the mucoadhesive layer of bilayered buccal tablets containing natamycin, showcasing sustained drug release and resistance to salivation, tongue movement, and swallowing.[13] In addition, carbomer-based nystatin films demonstrated prolonged drug release in the oral cavity, with mucoadhesive film attachment for at least 4 h.[27]

Table 1 provides a concise summary of the use of bioadhesive polymers for delivering antifungal drugs in the treatment of candidiasis.

CONCLUSIONS

The importance of bioadhesion is evident in achieving optimal residence time for antifungal drugs at the absorption site. While first-generation polymers such as carbomers, chitosan, and cellulose derivatives have demonstrated notable advantages, exploration of second-generation bioadhesive polymers remains limited in scientific studies and necessitates further investigation for their role in antifungal drug delivery. Novel second-generation polymers, such as thiolated polymers, lectins, and lecithins, hold promise as they can specifically bind to chemical structures on cell or mucus membranes. Furthermore, the degree of bioadhesion in antifungal drug formulations proves to be adaptable through the utilization of diverse dosage forms, including hydrogels, films, and micro/nanoparticles.

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Conflicts of interest

There are no conflicts of interest.

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