



Development and *In Vitro* Evaluation of Oteseconazole-Loaded Mucoadhesive Microspheres for Controlled Oral Drug Release

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ABSTRACT

Mucoadhesive microspheres are investigated as multiparticulate carriers intended to prolong contact with mucosal surfaces and modulate drug release. Oteseconazole is an azole antifungal; however, the clinical rationale and intended site of action for an oral mucoadhesive formulation must be established separately from *in vitro* formulation performance. To prepare and characterize oteseconazole-loaded microspheres using an emulsion-based crosslinking approach and to compare six formulations (F1–F6) with different Carbopol 940 levels and crosslinking conditions. According to the supplied study record, microspheres contained oteseconazole, Carbopol 940, chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), and xanthan gum. The reported evaluations included particle size, percentage yield, entrapment efficiency, swelling index, drug content, wash-off retention, *in vitro* release, and antifungal activity against *Candida albicans*. The original experimental record should be consulted to confirm procedural details, replicates, and statistical methods before submission. Reported particle size increased from 182 μm (F1) to 270 μm (F6), and percentage yield increased from 71.5% to 87.1%. Entrapment efficiency increased from 67.2% to 91.6%, swelling index from 88% to 122%, and reported mucoadhesion from 68% to 95%. Drug content ranged from 94.2% to 99.0%. At 12 h, cumulative release ranged from 98% for F1 to 78% for F6. The reported inhibition zone against *C. albicans* increased from 18.2 ± 0.6 mm to 26.3 ± 0.7 mm. F6 had the highest reported entrapment efficiency, swelling index, mucoadhesion, wash-off time, and inhibition-zone diameter, while showing the lowest 12-h drug release. These data suggest a formulation trend toward slower release with higher polymer content. They do not establish improved oral bioavailability, clinical efficacy, or targeted antifungal therapy; such claims require additional validated experiments.

Keywords Oteseconazole, Mucoadhesive microspheres, Controlled release, Carbopol 940, Xanthan gum

INTRODUCTION

Fungal infections range from superficial mucocutaneous disease to invasive infections, and their clinical significance depends on the organism, site of infection, host immune status, and available treatment. Antifungal drug classes include azoles, polyenes, echinocandins, and other agents. Formulation development may influence dissolution, local residence, drug release, and exposure; nevertheless, a delivery system cannot be assumed to overcome resistance or improve clinical outcomes without suitable pharmacological and clinical evidence. Oteseconazole is an azole antifungal developed for recurrent vulvovaginal candidiasis in eligible patients. Its approved clinical use and safety limitations should be checked against the current product

label before the manuscript makes therapeutic claims. The present work describes an experimental oral microsphere formulation, but the intended target site, clinical rationale for oral controlled release, and expected benefit over the approved dosage regimen need to be explained clearly. An *in vitro* formulation study alone cannot establish a new indication or demonstrate clinical effectiveness.

Mucoadhesive drug-delivery systems use polymers that interact with mucus or mucosal tissue, potentially prolonging dosage-form residence and modifying drug release. Mucoadhesion is influenced by polymer chemistry, molecular weight, hydration, chain flexibility, concentration, crosslinking, mucosal characteristics, and the test conditions. Microspheres offer a

multiparticulate format with a relatively high surface-area-to-volume ratio and may be evaluated for particle size, yield, drug loading, swelling, adhesion, and release [1–3]. Carbopol 940 is a crosslinked poly (acrylic acid) polymer commonly used to promote mucoadhesion; chitosan, sodium alginate, HPMC, and xanthan gum can contribute to matrix formation, hydration, viscosity, or release control. Their compatibility and combined effects must be demonstrated experimentally. The use of several polymers also makes it important to specify the composition and crosslinking mechanism precisely. The objective of this study was to compare six oteseconazole-loaded microsphere formulations with varying Carbopol 940 amounts and calcium chloride concentrations. The endpoints reported were particle size, yield, entrapment efficiency, swelling, drug content, wash-off retention, in vitro release, and inhibition of *C. albicans*. The study is presented as a preliminary in vitro formulation evaluation; no in vivo or clinical benefit is inferred.

Table 1. Formulation design

Ingredient	F1	F2	F3	F4	F5	F6
Oteseconazole (mg)	50	50	50	50	50	50
Carbopol 940 (mg)	100	100	200	200	300	300
Chitosan (mg)	100	100	100	100	100	100
Sodium alginate (mg)	50	50	50	50	50	50
HPMC (mg)	50	50	50	50	50	50
Xanthan gum (mg)	50	50	50	50	50	50
Span 80	1%	1%	1%	1%	1%	1%
Liquid paraffin	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Calcium chloride	1%	2%	1%	2%	1%	2%

Preparation of microspheres

The supplied method describes an emulsion-crosslinking approach. The drug and polymers were reportedly dispersed or dissolved in an aqueous phase, which was added gradually to liquid paraffin containing Span 80 under mechanical stirring to form droplets. Calcium chloride was then added to promote hardening of alginate-containing droplets. The microspheres were separated, washed to remove the oil phase, dried, and stored in a desiccator. This description is not yet sufficiently reproducible for journal submission. The authors should insert the actual quantities and volumes of aqueous and oil phases; order of addition; pH; stirring speed and duration; temperature; calcium chloride concentration, volume, and exposure time; washing solvent and number of washes; drying temperature and duration; and final storage conditions. If chitosan was crosslinked using glutaraldehyde, the method must state whether it was used and its concentration. If calcium chloride alone was used, the authors should explain the proposed crosslinking mechanism for the complete polymer mixture. Do not retain steps that were not actually performed.

Preformulation studies

The supplied record lists organoleptic examination, solubility, melting point, pH, partition coefficient, and powder-flow testing. The reported organoleptic observations were white to off-white, odourless crystalline powder, with a slightly bitter taste. Solubility was qualitatively described in water, ethanol, methanol, and buffers at pH 1.2, 6.8, and 7.4. The reported

MATERIALS AND METHODS

Materials

Oteseconazole was the active pharmaceutical ingredient. Carbopol 940, chitosan, sodium alginate, hydroxypropyl methylcellulose (HPMC), xanthan gum, Span 80, liquid paraffin, and calcium chloride were listed as formulation materials. The supplier, grade, batch number, and country of origin for each material were not included in the supplied record and should be added from laboratory records. The grade and concentration of the crosslinking agent and the identity of any solvent used to prepare each polymer phase should also be specified.

Formulation design

Six formulations (F1–F6) were described (Table 1). Each contained 50 mg oteseconazole, 100 mg chitosan, 50 mg sodium alginate, 50 mg HPMC, 50 mg xanthan gum, and 1% Span 80. Carbopol 940 was listed at 100 mg in F1–F2, 200 mg in F3–F4, and 300 mg in F5–F6. Calcium chloride was listed at 1% for F1, F3, and F5 and 2% for F2, F4, and F6. Liquid paraffin was added in a quantity sufficient.

melting point was $152.4 \pm 1.2^\circ\text{C}$, pH 6.18 ± 0.08 , and log P 3.48 ± 0.12 . These measurements should be reported only if supported by laboratory records and validated methods. A pH value for a drug solution is meaningful only when the solution concentration and preparation conditions are stated. Powder-flow parameters reportedly included angle of repose, bulk density, tapped density, Carr index, and Hausner ratio. Carr index is calculated as $[(\text{tapped density} - \text{bulk density}) / \text{tapped density}] \times 100$; Hausner ratio is tapped density divided by bulk density. The supplied values were $27.85 \pm 0.45^\circ$, $0.44 \pm 0.03 \text{ g/cm}^3$, $0.53 \pm 0.02 \text{ g/cm}^3$, $16.98 \pm 0.62\%$, and 1.20 ± 0.03 , respectively. Because the materials and measurement replicates were not specified, these results need verification (Table 1).

Particle size and morphology

Particle size was reportedly measured by microscopy and expressed in micrometres. The number of particles measured per batch, calibration procedure, magnification, and whether the reported value represents a mean, median, or range should be added. Scanning electron microscopy was listed in the study plan, but no numerical morphology results or images were supplied; therefore, SEM findings should not be claimed unless images and acquisition conditions are available.

Percentage yield

Percentage yield was calculated as: percentage yield = (practical mass of dried microspheres / theoretical total mass of solids) $\times$ 100. The authors should define which solids were included in

the theoretical yield and state whether the yield was determined for independent batches.

Entrapment efficiency and drug content

Entrapment efficiency was defined as (measured amount of drug entrapped / theoretical amount of drug added) $\times$ 100. Drug content was reportedly determined by dissolving or extracting a known quantity of microspheres and measuring absorbance by UV spectrophotometry. The solvent, wavelength, calibration curve, extraction recovery, specificity, dilution procedure, and blank correction must be provided. A validated analytical method is required to distinguish oteseconazole from polymer or medium interference (Table 2).

Swelling index

The swelling index was calculated using: swelling index (%) = $[(W_t - W_0) / W_0] \times 100$, where W_0 is the initial dry mass and W_t is the mass after immersion for a defined time. The supplied record mentions simulated gastric fluid at pH 1.2 and simulated intestinal fluid at pH 6.8, but does not provide separate time-course results. The incubation time, medium volume, temperature, blotting procedure, and replicate number should be reported.

Mucoadhesion and wash-off test

The supplied method describes a modified balance method or texture analyser using excised intestinal mucosa and a wash-off test under continuous buffer flow. The detachment force and wash-off retention time are different endpoints and should be reported separately. Tissue source, ethical or institutional oversight where applicable, tissue preparation, contact force and duration, buffer composition, flow rate, temperature, and number of replicates are required. The reported percentage mucoadhesion method was not defined; this calculation must be added.

In vitro drug release

The study record describes a USP Type I basket apparatus at $37 \pm 0.5^\circ\text{C}$ and 50–100 rpm. The medium was stated to be 0.1 N HCl for the first 2 h followed by phosphate buffer at pH 6.8, with samples collected at 1, 2, 4, 6, 8, 10, and 12 h and replaced with fresh medium. The authors should report the dissolution volume, drug-equivalent amount, selected rotation speed, sink-condition justification, sampling volume, correction for withdrawn drug, analytical wavelength, and number of independent replicates. A single, prespecified rotation speed should be reported rather than a range (Table 4).

Antifungal assay

The supplied results report inhibition-zone diameters against *Candida albicans*. The organism strain and source, inoculum density, culture medium, incubation conditions, test-sample concentration, amount applied per well or disc, positive control, negative control, and replicate number were not provided. The assay should follow a validated antifungal susceptibility or diffusion protocol, with controls and a clear description of whether the test material was a drug solution, microsphere suspension, or release sample. Zone diameters alone do not establish clinical antifungal efficacy.

Statistical analysis

The supplied record does not identify the number of independent batches or replicate measurements, nor the statistical tests or software used. Values reported as mean $\pm$ standard deviation should be supported by replicate-level data. The authors should state the sample size for each endpoint, how data are summarised, the statistical test and assumptions, significance threshold, and software version. If no inferential analysis was performed, results should be presented descriptively and no claims of statistical significance should be made.

RESULTS AND DISCUSSION

The reported inhibition-zone diameter increased from F1 to F6, with the largest value for F6. Interpretation is limited because the assay protocol, controls, test concentration, strain identifier, and replicate number were not supplied. Differences in diffusion of the free drug and polymeric particles can affect zone size; therefore, these data should not be interpreted as proof that F6 is clinically more effective. The supplied dataset shows a consistent descriptive pattern: increasing Carbopol 940 content across the formulation series coincided with larger microspheres, higher production yield, higher entrapment efficiency, greater swelling, longer wash-off retention, and slower drug release. A more viscous polymer phase may generate larger droplets during emulsification, while an increased polymer fraction may reduce drug escape during preparation. These are plausible explanations, not confirmed mechanisms; they require direct process observations and appropriate controls. The reported entrapment efficiency rose from 67.2% in F1 to 91.6% in F6. A higher polymer-to-drug ratio can increase matrix capacity or reduce drug diffusion into the external phase during particle formation. However, entrapment efficiency should be verified with a validated extraction method and a full mass balance. Drug content values of 94.2–99.0% also need a clearly defined denominator and analytical recovery to establish what “drug content” represents.

The swelling index increased from 88% to 122%, consistent with increased water uptake by hydrophilic polymer components. Swelling can facilitate polymer-chain mobility and contact with mucin, but excessive hydration may also weaken the matrix or reduce adhesion. Because the reported swelling values are not separated by medium or time point, they cannot yet describe pH-dependent behaviour or the swelling mechanism. The wash-off time increased from 5.2 to 9.0 h and the reported mucoadhesion percentage increased from 68% to 95%. These results are directionally consistent with improved retention in the reported in vitro test. Nevertheless, ex vivo wash-off behaviour does not directly predict residence time in the human gastrointestinal tract, where mucus turnover, motility, food, enzymes, and fluid volume can alter performance. The method should distinguish adhesive force, percentage retained, and time to detachment rather than treating them as interchangeable measures [1–3]. The 12-h release results ranged from 98% for F1 to 78% for F6. The slower release from higher-polymer formulations may reflect increased diffusion path length, viscosity, matrix tortuosity, or crosslinking. To support a controlled-release claim, the authors should report replicate curves with variability and compare appropriate kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas where applicable. Model selection should be based on fit diagnostics and justified assumptions, not on the highest correlation coefficient alone.

Table 2. Preformulation and flow properties.

Parameter	Reported result
Colour / appearance	White to off-white crystalline powder
Odour / taste	Odourless / slightly bitter
Solubility observations	Water: slightly soluble; ethanol: soluble; methanol: freely soluble; pH 1.2 buffer: slightly soluble; pH 6.8 buffer: moderately soluble; pH 7.4 buffer: soluble
Melting point	152.4 ± 1.2°C
pH	6.18 ± 0.08
Log P	3.48 ± 0.12
Angle of repose	27.85 ± 0.45°
Bulk density	0.44 ± 0.03 g/cm ³
Tapped density	0.53 ± 0.02 g/cm ³
Carr's index	16.98 ± 0.62%
Hausner ratio	1.20 ± 0.03

These are the values supplied by the authors and have not been independently verified. The solvent-specific solubility observations are qualitative; quantitative equilibrium solubility values would be more informative for a formulation study.

Table 3. Physical characteristics, yield, entrapment, swelling, and mucoadhesion.

Parameter	F1	F2	F3	F4	F5	F6
Particle size (µm)	182	190	218	228	256	270
Yield (%)	71.5	74.8	78.2	81.6	84.3	87.1
Entrapment efficiency (%)	67.2	71.4	78.6	82.5	88.3	91.6
Swelling index (%)	88	92	102	108	116	122
Mucoadhesion (%)	68	72	79	84	90	95
Drug content (%)	94.2	95.3	96.1	97.5	98.2	99.0
Wash-off time (h)	5.2	5.8	6.4	7.1	8.3	9.0

Across the reported formulations, particle size, yield, entrapment efficiency, swelling index, mucoadhesion percentage, drug content, and wash-off time increased from F1 to F6. The formulation design changes Carbopol 940 concentration in three steps and calcium chloride concentration in paired formulations; therefore, the trend is consistent with a formulation-composition effect but cannot isolate the independent contribution of either variable without a suitable factorial design and statistical analysis (Table 3).

Table 4. *In vitro* drug release.

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
1	18	15	12	10	8	7
2	30	26	22	20	16	14
4	52	48	43	39	34	31
6	70	65	58	54	48	44
8	83	78	71	66	60	56
10	92	88	82	76	71	66
12	98	95	90	86	81	78

Cumulative release increased with time in all formulations. At 12 h, F1 had the highest reported release (98%) and F6 the lowest (78%) (Table 4). The intermediate formulations showed a progressive reduction in release as the Carbopol 940 amount increased, with paired differences also present between the two calcium chloride levels. These descriptive data suggest that the composition may retard release; release kinetics should be examined using the complete replicate-level dataset and appropriate models before assigning a mechanism.

Table 5. Antifungal activity.

Formulation	Zone of inhibition (mm)
F1	18.2 ± 0.6
F2	20.1 ± 0.5
F3	21.4 ± 0.7
F4	23.2 ± 0.6
F5	24.6 ± 0.5
F6	26.3 ± 0.7

The increase in inhibition-zone diameter from 18.2 to 26.3 mm is potentially interesting but cannot be interpreted without assay

details. Larger zones may result from differences in drug loading, sample concentration, release during incubation, or diffusion

through agar. Appropriate controls should include the free drug at an equivalent dose, blank microspheres, solvent or vehicle, and a validated antifungal positive control (Table 5). MIC or another validated susceptibility endpoint would provide a more interpretable comparison than diffusion zones alone. A major translational limitation is that the study reports only in vitro tests. It does not assess gastrointestinal stability, pharmacokinetics, bioavailability, in vivo mucosal retention, safety, or clinical outcomes. The title and conclusion should therefore avoid implying demonstrated targeted therapy or improved treatment. The indication and intended target site for oteseconazole should be justified from current authoritative prescribing information and relevant pharmacology literature. The present formulation concept should be considered exploratory until that rationale is supported. Additional limitations include incomplete method details, absence of sample sizes and statistical tests, no reported microscopy/SEM images, no batch-to-batch reproducibility data, no stability study, and no evidence that the measured physicochemical properties were validated. The supplied reference list contains many studies on floating or gastroretentive systems that do not directly support claims about oteseconazole or this specific microsphere formulation. The final reference list should prioritise directly relevant and verifiable sources.

CONCLUSION

Based on the supplied in vitro dataset, formulation F6 showed the highest reported yield (87.1%), entrapment efficiency (91.6%), swelling index (122%), mucoadhesion percentage (95%), wash-off time (9.0 h), drug content (99.0%), and *C. albicans* inhibition-zone diameter (26.3 ± 0.7 mm), alongside the lowest 12-h cumulative drug release (78%). These findings identify F6 as the leading formulation within the reported series for further investigation. The results should be regarded as preliminary until the methods, replicate data, controls, and statistical analysis are verified. In vivo performance, oral bioavailability, safety, clinical efficacy, and suitability for a particular antifungal indication remain unestablished.

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CONFLICT OF INTERESTS

In this Manuscript the authors declare no conflict of interest

ETHICS APPROVAL

Not applicable to the supplied in vitro formulation data. If excised animal or human tissue was used, provide the relevant ethics approval or institutional determination and tissue source.

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on based on their request

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