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Research Paper

Design, Development and Evaluation of Ornidazole Microspheres

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ABSTRACT

The present study aimed to develop and optimize Ornidazole-loaded microspheres using a spray-drying technique and to investigate the influence of hydroxypropyl methylcellulose (HPMC) concentration and feed flow rate on particle size and in-vitro drug release. Ornidazole was subjected to preformulation studies including organoleptic evaluation, solubility assessment, melting-point determination, UV spectrophotometric analysis, Fourier-transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD). Microspheres were prepared using HPMC, polyvinylpyrrolidone K-30 and maltodextrin as carrier materials. A 3^2 full factorial design was applied using Design-Expert® version 13, with HPMC concentration (150–175 mg) and feed flow rate (1–3 mL/min) as independent variables and particle size and 12-h drug release as responses. The formulations were evaluated for particle size, zeta potential, morphology, drug content, entrapment efficiency, in-vitro drug release, release kinetics and accelerated stability. The optimized formulation, batch M4, had a mean particle size of 2560.5 nm, zeta potential of -11.3 mV, drug content of 48.7% and entrapment efficiency of 73.28%. Cumulative drug release at 12 h was 91.71%. FTIR showed retention of the characteristic functional groups of Ornidazole without evidence of new chemical interactions, while XRD indicated reduced crystallinity after spray drying. The particle-size model was significant ($F=152.26$, $p=0.0008$; $R^2=0.9961$), and the drug-release model was significant ($F=444.08$, $p=0.0002$; $R^2=0.9987$). Release data for M4 showed the highest correlation with the Higuchi model ($R^2=0.9877$), suggesting diffusion-controlled release. Accelerated storage of M4 at $40\pm 2^\circ\text{C}/75\pm 5\%$ RH for 6 months showed no major change in appearance, particle size or 12-h drug release.

INTRODUCTION

Oral drug delivery remains an important route because of its convenience and patient

acceptability; however, conventional immediate-release dosage forms may require repeated administration and can produce fluctuations in drug exposure. Novel drug delivery systems have

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therefore been investigated to modulate the rate and duration of drug release. Microspheres are particulate carriers in which a drug can be dispersed, entrapped or encapsulated within a polymeric matrix and can be designed for sustained or controlled release.[1-4]

Microspheres can provide advantages such as reduced dosing frequency, improved control of drug release and protection of the incorporated drug. Their performance is influenced by polymer characteristics, drug-to-polymer ratio, processing conditions and particle size. Spray drying is particularly useful for producing dry particulate systems because atomization of a feed solution followed by rapid solvent evaporation can generate free-flowing particles in a single processing step.[5-7]

Ornidazole is an antimicrobial drug for which a modified-release particulate system may be useful when prolonged drug release is desired. In the present work, HPMC was selected as the principal release-controlling polymer, with PVP K-30 and maltodextrin incorporated as carrier materials. A systematic factorial design was used to examine the effects of HPMC concentration and spray-dryer feed flow rate on particle size and drug release. The study was designed to identify a formulation region providing small particle size together with high drug release over 12 h.

MATERIALS AND METHODS

Materials

Ornidazole was used as the active pharmaceutical ingredient. HPMC, PVP K-30 and maltodextrin were used as carrier materials. Ethanol, phosphate-buffer components and other analytical reagents were of analytical-reagent grade. The source and supplier information were recorded in the dissertation; the present manuscript retains the experimental composition and processing conditions reported there.

Preformulation studies

Organoleptic properties were evaluated for colour, odour, taste and physical appearance. Solubility was assessed qualitatively and quantitatively in distilled water, phosphate buffer pH 7.4, ethanol, methanol and selected solvents. For equilibrium solubility, excess Ornidazole was added to 10 mL solvent and shaken at 100 rpm for 24 h at $25 \pm 2^\circ\text{C}$. Samples were filtered through a 0.45- μm membrane and analysed at 317 nm. Measurements were performed in triplicate.

The melting point of Ornidazole was determined by the open-capillary method using a Thiele tube. The UV absorption maximum was determined over 200–400 nm using a UV–Visible spectrophotometer. Calibration curves were prepared over 2–10 $\mu\text{g/mL}$ in phosphate buffer pH 7.4 and ethanol at 317 nm. The regression equations reported in the source dissertation were $y=0.098x-0.0041$ ($R^2=0.9945$) for phosphate buffer and $y=0.0989x+0.0046$ ($R^2=0.9986$) for ethanol.

FTIR spectra of Ornidazole and the selected excipients were recorded using a Jasco FT/IR-4600 spectrometer. Compatibility was assessed by comparing characteristic functional groups of the drug with spectra of the excipients and physical mixture. XRD was used to evaluate the crystalline characteristics of the pure drug and optimized microspheres.

Preparation of Ornidazole-loaded microspheres

Ornidazole-loaded microspheres were prepared by spray drying. HPMC was dissolved in distilled water under continuous magnetic stirring. PVP K-30 and maltodextrin were subsequently added and dissolved. Ornidazole was separately dissolved in ethanol and incorporated slowly into the polymeric solution under continuous stirring. The feed was sonicated for 10 min to remove entrapped air and then spray dried using a Labultima LU-222



Advanced Spray Dryer equipped with a 0.7-mm two-fluid stainless-steel nozzle and cyclone separator. Atomization pressure was 2.0 bar, inlet temperature 120°C, outlet temperature 70±5°C,

feed flow rate 1–3 mL/min and aspirator capacity 35 m³/h. The dried microspheres were collected from the cyclone separator and stored in a desiccator.

Table 1. Spray-drying conditions used for preparation of Ornidazole microspheres.

Parameter	Condition
HPMC concentration	150–175 mg
Drug:polymer ratio	300:150–175 (approximately 2:1)
Nozzle	Two-fluid nozzle, 0.7 mm
Feed flow rate	1–3 mL/min
Inlet temperature	120°C
Outlet temperature	70±5°C
Aspirator	35 m ³ /h or maximum
Atomization pressure	2.0 bar

Experimental design and optimization

A 3² full factorial design was generated using Design-Expert® version 13. HPMC concentration (X1) was studied at 150, 162.5 and 175 mg, while feed flow rate (X2) was studied at 1, 2 and 3 mL/min. The dependent variables were particle size (Y1) and cumulative drug release at 12 h (Y2). Nine formulations (M1–M9) were prepared. A second-order polynomial model was used to assess linear, interaction and quadratic effects. Model significance was evaluated by ANOVA at $p < 0.05$, together with R^2 , adjusted R^2 , predicted R^2 and adequate precision. Contour, response-surface, perturbation and normal-probability plots were used to visualize the design space.

Evaluation of microspheres

Particle size and zeta potential were measured by dynamic light scattering using a Horiba Scientific NanoParticle SZ-100. Surface morphology of the optimized batch was examined by scanning electron microscopy. Drug content and entrapment efficiency were determined by solvent extraction. Microspheres equivalent to 10 mg Ornidazole were dispersed in 100 mL ethanol, sonicated for 15 min and stirred for 30 min. The extract was

filtered, suitably diluted and measured at 317 nm. Results were expressed as mean±SD ($n=3$).

In-vitro drug release was evaluated for 12 h using phosphate buffer pH 7.4 maintained at 37±0.5°C and 100 rpm. The dissertation reports that preliminary solubility assessment provided adequate sink conditions in this medium. Samples were withdrawn at predetermined intervals and analysed spectrophotometrically at 317 nm. The release profiles were fitted to zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models.

Stability study

Accelerated stability testing of optimized batch M4 was performed according to ICH Q1A(R2) at 40±2°C/75±5% relative humidity. The microspheres were stored in airtight HDPE containers. Appearance, particle size and 12-h in-vitro drug release were evaluated initially and after 1, 3 and 6 months. The source study reports one-way ANOVA for statistical comparison and no statistically significant difference ($p > 0.05$).



RESULTS AND DISCUSSION

Preformulation characterization

The drug exhibited the expected organoleptic characteristics and a melting-point range of 86–90°C, with an observed value of approximately 88°C. Ornidazole showed measurable solubility in the tested solvents, supporting preparation of an ethanolic drug solution for spray drying. The UV maximum was 317 nm. The calibration curves in phosphate buffer pH 7.4 and ethanol showed good linearity over 2–10 µg/mL, with R^2 values of 0.9945 and 0.9986, respectively.

FTIR analysis showed the characteristic functional groups of Ornidazole. The physical mixture with excipients did not show evidence of a new characteristic peak attributable to chemical interaction. XRD of the pure drug confirmed its crystalline character. In the optimized formulation,

the XRD pattern showed reduced crystallinity after spray drying without formation of an additional crystalline phase. DSC was not performed in the study and is therefore not reported as a characterization result.

Particle size, zeta potential and morphology

Particle size of formulations M1–M9 ranged from 2560.5 to 7856.4 nm. Batch M4 showed the smallest mean particle size (2560.5 ± 22 nm). The source study describes spherical microspheres with smooth surfaces in SEM images. Zeta potential values ranged from -7.5 to -17.6 mV, with M4 showing -11.3 ± 0.50 mV. The relatively small absolute zeta-potential values indicate that electrostatic stabilization alone would not be expected to provide high colloidal stability; the dried formulation was nevertheless physically evaluated during the reported stability study.

Table 2. Particle size and zeta potential of Ornidazole microspheres.

Batch	HPMC (mg)	Flow rate (mL/min)	Particle size (nm)	Zeta potential (mV)
M1	150	1	2825.6 ± 12	-7.5 ± 0.25
M2	150	2	3600.7 ± 15	-12.4 ± 0.62
M3	150	3	4928.2 ± 67	-17.6 ± 0.29
M4	162.5	1	2560.5 ± 22	-11.3 ± 0.50
M5	162.5	2	3287.2 ± 56	-13.9 ± 0.84
M6	162.5	3	3523.7 ± 35	-15.2 ± 0.43
M7	175	1	7232.2 ± 72	-9.7 ± 0.27
M8	175	2	7495.3 ± 17	-12.8 ± 0.92
M9	175	3	7856.4 ± 57	-15.7 ± 0.55

Drug content and entrapment efficiency

Drug content ranged from 40.5 to 93.6%, while entrapment efficiency ranged from 66.26 to 92.88% across M1–M9. Batch M6 had the highest drug content ($93.6 \pm 0.41\%$) and entrapment efficiency ($92.88 \pm 0.48\%$). Batch M4, selected by

the factorial optimization, showed $48.7 \pm 0.26\%$ drug content and $73.28 \pm 0.58\%$ entrapment efficiency. The observed variation indicates that polymer concentration and spray-drying conditions affected incorporation of Ornidazole into the dried matrix.



Table 3. Drug content and entrapment efficiency of Ornidazole microspheres.

Batch	Drug content (%)	Entrapment efficiency (%)
M1	43.9±0.12	82.47±0.24
M2	65.7±0.45	77.57±0.46
M3	89.3±0.61	76.89±0.31
M4	48.7±0.26	73.28±0.58
M5	76.3±0.33	72.76±0.16
M6	93.6±0.41	92.88±0.48
M7	40.5±0.23	66.26±0.27
M8	71.2±0.72	70.95±0.82
M9	87.9±0.83	73.45±0.51

In-vitro drug release

All formulations showed gradual release over 12 h. The 12-h cumulative release values ranged from 63.55% for M9 to 91.71% for M4. M4 therefore provided the highest reported 12-h release among the nine factorial formulations. Increasing HPMC

concentration and feed flow rate generally reduced the 12-h drug release within the studied design space. This behavior is consistent with the role of polymer concentration and processing conditions in determining matrix density and mass transfer during release.

Table 4. Cumulative drug release at 12 h.

Batch	12-h drug release (%)
M1	88.04±0.29
M2	82.53±0.32
M3	74.26±0.48
M4	91.71±0.93
M5	86.20±0.90
M6	80.08±0.83
M7	75.48±0.09
M8	70.28±0.67
M9	63.55±0.56

Factorial design analysis

For particle size, the fitted quadratic model was significant, with an F-value of 152.26 and $p=0.0008$. The coefficient of determination was $R^2=0.9961$, adjusted $R^2=0.9895$ and predicted $R^2=0.9617$, with adequate precision of 29.3821. HPMC concentration, feed flow rate and their interaction were significant contributors to particle size within the model. The coded-factor equation was: Particle size = $3106.00 + 1871.57A + 615.00B - 369.60AB + 2532.60A^2 + 26.70B^2$.

For 12-h drug release, the fitted model was also significant ($F=444.08$, $p=0.0002$), with $R^2=0.9987$, adjusted $R^2=0.9964$, predicted $R^2=0.9854$ and adequate precision of 63.5031. The coded-factor equation was: Drug release = $86.54 - 5.92A - 6.22B + 0.4625AB - 10.31A^2 - 0.8167B^2$. The negative coefficients for the principal linear terms indicate that increasing HPMC concentration and feed flow rate decreased the predicted 12-h drug release within the experimental region.



Table 5. Statistical characteristics of factorial-design models.

Response	Model F-value	p-value	R ²	Adjusted R ²	Predicted R ²	Adequate precision
Particle size	152.26	0.0008	0.9961	0.9895	0.9617	29.3821
Drug release at 12 h	444.08	0.0002	0.9987	0.9964	0.9854	63.5031

Optimization and release kinetics

Numerical optimization was performed with the objectives of minimizing particle size and maximizing 12-h drug release while keeping HPMC concentration and feed flow rate within their experimental ranges. The optimization procedure identified batch M4 as the selected formulation. M4 contained 162.5 mg HPMC and was produced at a feed flow rate of 1 mL/min. The

reported desirability for the selected design space was 1.000.

Release data from M4 were fitted to different kinetic models. The Higuchi model produced the highest correlation coefficient ($R^2=0.9877$), compared with 0.9181 for zero-order, 0.9610 for first-order, 0.8528 for Hixson–Crowell and 0.3930 for Korsmeyer–Peppas models. On the basis of the highest R^2 , the source study interpreted the release as predominantly diffusion controlled.

Table 6. Kinetic analysis of optimized batch M4.

Kinetic model	m	C	R ²	Interpretation
Zero order	9.5854	8.0748	0.9181	Lower fit
First order	-0.0607	1.971	0.9610	Lower fit
Higuchi	0.0431	0.0171	0.9877	Best fit
Hixson–Crowell	-0.2412	4.5144	0.8528	Lower fit
Korsmeyer–Peppas	1.9854	0.7291	0.3930	Lower fit

Stability study

The optimized M4 microspheres remained white during accelerated storage. Mean particle size was 2560.5 ± 0.27 nm initially and 2561.9 ± 0.42 nm after 6 months. Twelve-hour drug release was

$91.71 \pm 0.25\%$ initially and $89.81 \pm 0.57\%$ after 6 months. The reported statistical comparison showed no significant difference ($p > 0.05$), indicating that the measured attributes remained comparatively stable under the tested accelerated condition.

Table 7. Accelerated stability data for optimized batch M4 at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$.

Time	Appearance	Particle size (nm)	12-h drug release (%)
Initial	White	2560.5 ± 0.27	91.71 ± 0.25
1 month	White	2563.7 ± 0.53	89.02 ± 0.57
3 months	White	2565.6 ± 0.38	90.65 ± 0.31
6 months	White	2561.9 ± 0.42	89.81 ± 0.57

DISCUSSION

The present work demonstrates the feasibility of producing Ornidazole-loaded microspheres by

spray drying with HPMC as the principal release-controlling polymer and PVP K-30 and maltodextrin as carrier materials. The preformulation results supported the analytical



methods used for subsequent characterization, particularly the linear UV response at 317 nm.

The factorial study showed that both formulation and process variables influenced the measured responses. Particle size was strongly associated with HPMC concentration and feed flow rate, as reflected by the high model R^2 and significant model F-value. The response-surface analysis reported in the source dissertation showed that particle size changed substantially across the design space, whereas drug release decreased as HPMC concentration and feed flow rate increased. These effects allowed simultaneous consideration of particle size and drug release during numerical optimization.

Although M6 produced the highest drug content and entrapment efficiency, M4 was selected as the optimized formulation because the predefined optimization objectives emphasized minimum particle size and maximum 12-h drug release. This distinction is important because the optimized formulation should be selected from the complete response profile rather than from a single response alone.

FTIR and XRD results provided evidence that the characteristic chemical groups of Ornidazole were retained after processing and that spray drying reduced crystallinity without producing an additional crystalline phase. The absence of DSC data should be recognized as a limitation of the present characterization package. Similarly, the in-vitro release experiment used phosphate buffer pH 7.4 alone; therefore, the reported release profile primarily represents the selected intestinal-phase test condition rather than a sequential gastrointestinal transit simulation.

The accelerated stability data support physical retention of the measured attributes over the six-month test period under $40\pm2^\circ\text{C}/75\pm5\%$ RH. However, the study did not include in-vivo pharmacokinetic or bioavailability evaluation, and therefore improvements in systemic

bioavailability, plasma half-life or clinical performance cannot be concluded from the present data. Further work should address these endpoints together with a more biorelevant dissolution protocol and expanded solid-state characterization.

CONCLUSION

Ornidazole-loaded microspheres were successfully prepared by spray drying using HPMC, PVP K-30 and maltodextrin as carrier materials. A 3^2 full factorial design effectively quantified the influence of HPMC concentration and feed flow rate on particle size and 12-h drug release. Batch M4, prepared with 162.5 mg HPMC at a feed flow rate of 1 mL/min, was selected as the optimized formulation, with a particle size of 2560.5 nm, zeta potential of -11.3 mV, entrapment efficiency of 73.28% and 12-h drug release of 91.71%. The drug-release profile of M4 showed the highest correlation with the Higuchi model. Accelerated stability testing indicated no significant change in the evaluated attributes over 6 months. These findings support further development of the Ornidazole microsphere system, while additional biorelevant dissolution, pharmacokinetic and in-vivo studies are required before claims concerning enhanced bioavailability or therapeutic benefit can be established.

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CONFLICT OF INTEREST

The author declares no conflict of interest.



FUNDING

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ETHICAL STATEMENT

No human participants or experimental animals were used in the formulation, characterization, in-vitro release and accelerated stability studies reported in this manuscript; therefore, no human or animal ethics approval was required for these experiments.

DATA AVAILABILITY

The experimental results and formulation data supporting the findings are contained in the present manuscript and the underlying dissertation records.

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