Next-Generation Antifungal Therapy: Miconazole Nitrate-Loaded Microspheres for Prolonged and Enhanced Drug Action

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Abstract

The current research focused on developing and characterizing sustained-release microspheres of miconazole nitrate (MCN) with different polymers to optimize drug entrapment efficiency and manage drug release. Microspheres were produced with an optimized method and examined for particle size, surface topography, yield percentage, drug content, entrapment efficiency, and in vitro drug release kinetic. Optical microscopy and scanning electron microscopy (SEM) validated the spherical microspheres with a size of 140–210 µm. The entrapment efficiency of the drug ranged from 72.06 ± 6.09 to 89.45 ± 5.18 %, and the percentage yield was between 72.09 ± 5.22 and 92.60 ± 7.76 %. The in vitro dissolution studies revealed sustained drug release over 12 h, with cumulative release percentages of 81.80 ± 8.43 to 93.60 ± 8.77 %. Release kinetics showed that drug release was in accordance with the Higuchi matrix model, indicating a diffusion-controlled process, and the Peppas model with a combination of diffusion and erosion. IR spectroscopic compatibility studies proved to be devoid of any significant chemical interactions between the excipients and the drug. It was successfully demonstrated in this study that MCN microspheres can show a controlled and sustained drug release profile and can emerge as a promising alternative for better antifungal therapy.

Keyword: *Miconazole Nitrate, Peppas Model, Microspheres, Entrapment Efficiency, Sustained Release, Excipients.*

1. INTRODUCTION

Fungal diseases have become a significant emerging public health problem, especially among the immunocompromised patients, including HIV/AIDS, cancer patients, and recipients of organ transplantation. The prevalence of increased drug resistance by fungi and the restrictions imposed by traditional antifungal drugs have pushed the research agenda to introduce innovative drug delivery systems with higher efficacy, increased compliance in patients, and lesser side effects. Among these approaches, microsphere-based drug delivery systems have been extensively explored because of their potential to deliver drugs with sustained release, enhance bioavailability, and promote therapeutic efficacy (1, 2).

Miconazole nitrate (MCN), an antifungal compound of the imidazole class, is extensively employed in the treatment of superficial and systemic mycotic infections such as candidiasis and dermatophytosis (3). Nonetheless, traditional miconazole preparations like creams and oral gels need to be taken too often, which results in lower patient compliance and poor therapeutic effects (4). In addition, systemic side effects and inadequate solubility restrict its drug-like performance (5). To overcome such challenges, the incorporation of MCN into microspheres holds great promise as a method of prolonged and controlled release of drugs, providing maintained therapeutic concentrations at the site of infection while restricting systemic exposure (6).Microspheres, especially biodegradable polymer-based microspheres like poly(lactic-co-glycolic acid) (PLGA), chitosan, and alginate, have shown extensive potential in terms of drug retention and targeting of fungal infections better (7). These polymeric carriers shield miconazole from enzymatic degradation, regulate its release over a long period, and enhance its solubility, resulting in improved antifungal activity (8). Microsphere-based formulations have also been demonstrated to decrease the risk of antifungal resistance by ensuring a constant-state concentration of the drug at the site of infection, avoiding fungal adaptation to subtherapeutic levels of the drug (9)

This research investigates the development, characterization, and therapeutic application of MCN-loaded microspheres as a new generation antifungal drug. The controlled release provided by microspheres can transform antifungal therapy by improving drug bioavailability, extending the duration of action, and enhancing patient compliance. The results of this research could lead to the creation of more efficient antifungal therapies, alleviating the worldwide fungal infection burden.

Experimental

2. MATERIALS

Miconazole nitrate (MCN) was received as a gift sample from Micro Labs limited, Hosur, tamil Nadu, India. Eudragit RS100 obtained from CDH Fine Chemical, New Delhi, India and Hydroxypropyl Methylcellulose (HPMC K4M) from Otto Chemie Pvt Ltd, Mimbai, India. Isopropyl alcohol, Dichloromethane, span 80 was purchased from Loba Chemie, Mumbai, India. n-hexane and liquid paraffin was purchased from Merck (Sigma-Aldrich), Bangalore, India. This study made use of internally produced double distilled water, analytical grade chemicals, and reagents.

Preformulation Study

Preformulation testing is the initial step in dosage form development of a drug substance. It can be described as an examination of physical and chemical properties of a drug substance in isolation and when it is mixed with excipients. The aim of preformulation testing is to provide information to the formulator to develop stable and bioavailable dosage forms that can be manufactured on a large scale (10-16).

Melting Point Determination

MCN melting point was established by the capillary fusion technique. A small amount of the drug was placed in a capillary tube in such a manner that one end of the capillary tube was partially closed. The capillary tube containing the drug was then inserted into Thiel's melting point apparatus, and the temperature at which the drug began to melt was noted. Melting point indicates the purity and thermal stability of the drug substance (17, 18).

Solubility Studies

The solubility of MCN was assessed in various solvent systems to establish its solubility profile. An excess quantity of the drug was placed in 10 mL of each of the solvents in a

screw-capped test tube or glass tube and mixed well. The solutions were checked visually for the absence or presence of undissolved drug particles. This research assists in choosing suitable solvents and excipients during formulation development (19,20).

Drug-Excipient Compatibility Study

Excipients are an important part of the formulation of pharmaceutical dosage forms as they maintain stability, enhance bioavailability, and facilitate drug release. Excipient compatibility of MCN with Eudragit RS 100 and HPMC was analyzed through fourier transform infrared spectroscopy (FTIR). FTIR spectral examination was conducted to identify any probable interactions between excipients and drug by monitoring characteristic peak shifts. Potassium bromide (KBr) disc pellet technique was employed to make samples ready for IR analysis (21-24).

Calibration Curve

To prepare a calibration curve for MCN by UV-Visible spectrophotometry, a set of standard solutions with known concentrations are prepared and their absorbance is determined at a particular wavelength. In this process, MCN has a maximum absorbance at around 232 nm. A stock solution is made by dissolving a precisely weighed quantity of MCN in an appropriate solvent, e.g., ethanol, to give a concentration of 1000 µg/mL. Dilutions are then made to provide a series of concentrations, usually between 2 and 10 µg/mL. The absorbance of each solution is determined at 232 nm using a UV-Visible spectrophotometer against a blank solution. Graphing the absorbance values (Y-axis) versus the respective concentrations (X-axis) gives a calibration curve.

Preparation of MCN-loaded Microspheres

MCN-loaded microspheres were prepared by the emulsion-solvent evaporation method, using Eudragit RS100 and HPMC as polymers. 1 g of the chosen polymer was first dissolved in a solvent mixture containing equal volumes of ethanol, isopropyl alcohol, and dichloromethane (10 mL each), and then sonicated for 5 min to form a uniform solution. Independently, 1 g of MCN was dissolved in 10 mL of hydrochloric acid and then added to the polymer solution, with additional sonication for 20 min until clarity was achieved, creating the aqueous phase. The mixture was added to 200 mL of liquid paraffin with 1% w/v Span 80, via a 20-gauge needle, and stirred at 1000 rpm at 75–85 °C for 3 h to allow solvent evaporation and solidification of microspheres. Then, 10 mL of n-hexane was added to solidify the microspheres, and stirring was carried out for another h. The obtained microspheres were filtered, washed with petroleum ether to remove excess oil, and dried at 50 °C for 30 min. six batches (F-1 to F-6) were formulated with different drug-to-polymer ratios: F-1 to F-3 used Eudragit RS100, whereas F-4 to F-6 used HPMC. This approach is in line with the solvent evaporation methods outlined in the literature for preparing controlled-release microspheres (25-28).

Table 1. Various Formulation of MCN-Loaded Microspheres

S. No	Ingredients	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Drug (mg)	200	200	200	200	200	200
2	Eudragit RS100(mg)	200	400	600	-	-	-
3	HPMC (mg)	-	-	-	200	400	600
4	Ethanol (mL)	2	2	2	2	2	2
5	Isopropyl alcohol (mL)	2	2	2	2	2	2

6	Dichloromethane (mL)	2	2	2	2	2	2
7	Span- 80 (mL)	0.5	0.5	0.5	0.5	0.5	0.5
8	n- hexane (mL)	2	2	2	2	2	2
9	Liquid paraffin (mL)	40	40	40	40	40	40
10	HCl (mL)	2	2	2	2	2	2

Particle Size and Surface Morphology

Optical microscopy is a direct technique for measuring microsphere size. A small amount of microspheres is placed on a glass slide. Calibration is done using a stage micrometer (a microscopic scale) to obtain precise size measurements. Microspheres are placed under the objective of an optical microscope and are measured for diameters using an eyepiece micrometer. The mean particle size is determined from several readings (29, 30).

Scanning Electron Microscopy was employed to identify the particle size distribution, surface topography, texture and to study the morphology of fractured or sectioned surface. SEM is most widely utilized technique for describing drug delivery systems, largely due to ease of sample preparation and ready availability. Dry microspheres were mounted on an electron microscope brass stub and gold-coated in an ion sputter. Photograph of microspheres was captured using random scanning of the stub (31-33).

Percentage Yield

MCN-loaded microspheres equal to the weight of MCN were sonicated after being diluted with 2 mL of ethanol. For additional dilutions, double-distilled water was utilized, and UV absorbance was measured. The material balance was calculated in relation to the drug content, which was measured using a standard calibration curve at 232 nm (33). The percent yield of each of the sample was calculated from the equation.

$$\% \text{ Yield} = \frac{\text{weight of microparticles}}{\text{weight of solid starting materials}} \times 100$$

Drug Content

Accurately weighed 100 mg MCN-loaded microspheres were ground in glass mortar and pestle; powder microspheres were dispersed in 100 mL of appropriate solvent. Solution was filtered after 12 h and filtrate was scanned for the drug content by UV-Visible spectrophotometer (34).

Percentage Entrapment Efficiency (%EE)

The supernatant obtained during the microsphere formulation was used to calculate the MCN % encapsulation efficiency (%EE) in MCN-loaded microspheres. After centrifugation at 6000 rpm for 15 min, the clear supernatant was collected, and UV-visible spectroscopy at 232 nm was used for analysis. The drug percentage EE was determined using equation (35).

$$\%EE = \frac{\text{Practical drug content}}{\text{theoretical drug content}} \times 100$$

In Vitro Dissolution Study

The in vitro release profile of MCN-loaded microspheres was evaluated with the help of a USP Type II (paddle) dissolution apparatus to mimic physiological conditions. The dissolution experiment was performed in 900 mL of phosphate buffer (pH 7.4) at 37 ± 1°C, with the stirring speed maintained constant at 50 rpm for uniform dispersion of the drug.At 1-h fixed intervals, 5 mL aliquots were taken from the dissolution medium, filtered on Whatman filter paper, and then scanned by a UV-Visible spectrophotometer at 232 nm to

calculate the released concentration of MCN. For maintaining sink condition, the same volume of fresh dissolution medium was replaced after each sampling.

Mechanism of MCN Release

The release data were then studied to ascertain the mechanism and kinetics of drug release. Cumulative drug release data were used to fit some mathematical models. Zero-order kinetics (cumulative drug release, Q, versus time, t); first-order kinetics (log of drug remaining, log (Q_o-Q), vs. time, t); Higuchi model (cumulative drug release, Q, vs. the square root of time, $t^{1/2}$); Korsmeyer-Peppas model (logarithm of cumulative drug release, Log Q, vs. Log t) (36-38)

3. RESULTS AND DISCUSSION

Melting point of MCN was 179 ± 0.78 °C, ascertaining purity and crystalline in nature. Narrow melting range reflects the low level of presence of impurities in the compound. The observation is in confirmation with expected thermal stability of MCN to be favorable for formulation development. MCN's solubility pattern in various solvents was also investigated. It was sparingly soluble in water and could pose difficulties in water-based formulations. MCN was soluble in chloroform, soluble in acetone, and almost insoluble in ethanol and methanol. Findings indicate organic solvents would be better to improve the solubility and formulation of MCN.

Compatibility Study by IR Spectra

The IR spectra of the physical mixture of MCN, the polymer, and their mixture were examined for potential interactions. The typical MCN peaks of C=N stretching, C–H bending, and N–O asymmetric stretching was preserved in the mixture, with no disappearance of peaks or major shift (Figure 1). There were also no new peaks or peak broadening observed, which means there are no strong chemical interactions between the polymer and MCN.

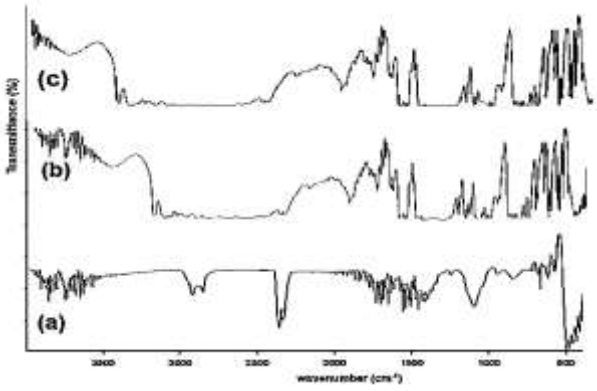

Figure 1. FTIR Spectra of (A) Pure MCN (B) PM, and (C) MCN-Loaded Microsphere

These findings justify the polymer's compatibility with MCN, implying that the formulation is chemically stable. Non-interaction ensures MCN will not lose its structure while formulating with the polymer, thereby possible for further development of formulation

MCN Calibration Curve

The calibration curve for MCN was built by correlating concentration (µg/mL) with absorbance at 232 nm. The standard curve was linear with the equation y = 0.0575x - 0.005 and had a very good correlation coefficient (R^2 = 0.9989), which shows super linearity.

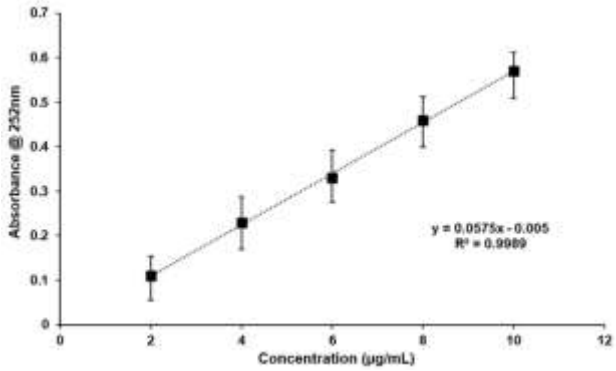

Figure 2. Standard Calibration Curve of MCN from 2-10 Mg/Ml

The extremely high R^2 value indicates close linear relationship between absorbance and concentration, proving the reliability and validity of the technique to be applied for the quantitative estimation of MCN. The absence of variability in absorbance values, indicated by error bars, also indicates the accuracy of the analytical procedure. The above-mentioned confirmed method can conveniently be employed for the quantitative estimation of MCN in pharmaceutical products.

Evaluation of MCN-loaded Microspheres

Particle Size Analysis of MCN-Loaded Microspheres

Particle size distribution of microspheres loaded with MCN in various formulations (F1–F6) is illustrated in the bar graph (Figure 3). The results reflect variation in particle size among formulations with varying particle sizes from 150 to 210 µm. F3 exhibited the largest particle size, and therefore parameters like polymer concentration or stirring rate affected microsphere growth. F4 had the smallest particle size, and this indicates that some of the formulation conditions may have resulted in the production of smaller particles. The other formulations (F1, F2, F5, and F6) had intermediate particle sizes, indicating equilibrium between formulation ingredients and processing conditions.

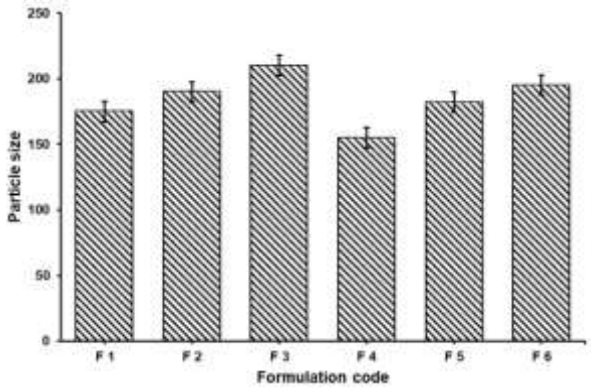

Figure 3. Average Particle Size of MCN-Loaded Microspheres from F1 to F6 Formulation.

Particle size variations observed may affect the bioavailability, drug encapsulation efficiency, and drug release rate. Controlled release of the drug is possible with big particles, and dissolution and absorption are increased in small particles. The results point towards the significance of optimization in formulation to establish the desired features of microspheres for controlling drug delivery.

Scanning Electron Microscopy (SEM)

SEM micrographs of MCN are presented in Figure 3, revealing the surface morphology and particle properties. Figure 4a illustrates that MCN particles are spherical with a porous and rough surface of the F1. The porosity can be beneficial for drug loading and release behavior in drugs. Figure 4b is a deformed and aggregated surface, and it is perhaps due to processing conditions or interactions with excipients of the F2. The remaining morphology remains unaltered, indicating structural stability. The SEM study verifies that MCN has a well-defined spherical morphology, which is desirable for controlled drug delivery systems. The porous surface could potentially increase drug entrapment, and the observed aggregation could be reduced by proper formulation techniques.

Scanning electron microscopy was performed to characterize the surface of the formed microspheres. Particles from F1, F3 and F5 were rough surfaced but spherical, whereas F2, F4 and F6 are found to be spherical, smooth and discrete

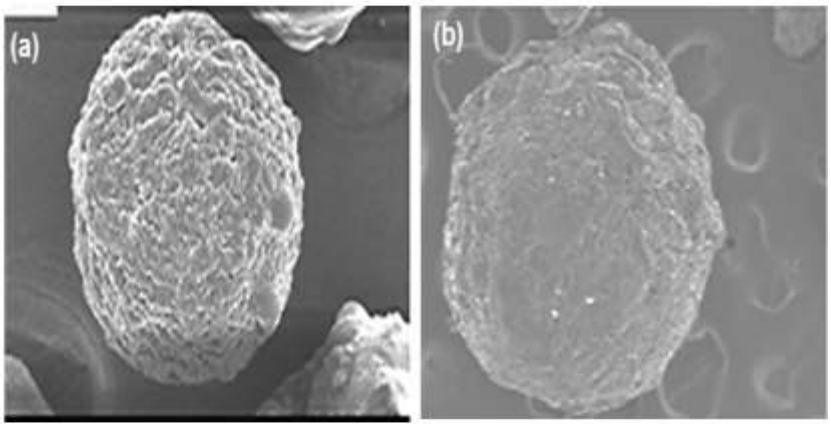

Figure 4. SEM Image of MCN-Loaded Microspheres of (A) F1 and (B) F4

% yield, Drug Content, and %EE

The entrapment efficiency, drug content, and yield of MCN-loaded microspheres for different formulations (F1–F6) are presented in the table. The results indicate that microsphere performance was influenced to a large extent by formulation parameters. The yield ranged from 72.09 ± 5.22 % (F4) to 92.60 ± 7.76 % (F3). The maximum yield was for F3, which suggests optimal conditions for microsphere formation. F4 provided the minimum yield, and it could be due to polymer loss during processing.

The drug content was between 79.56 ± 6.21 % (F4) and 90.45 ± 6.09 % (F3). F3 had the highest drug content, reflecting effective drug incorporation. The comparatively lower drug content in F4 reflects potential drug loss during the formulation process.

Entrapment efficiency varied from 72.06 ± 6.54 % (F4) to 89.45 ± 7.89 % (F3). F3 had the highest entrapment efficiency, reflecting improved drug-polymer interaction and least drug leakage. F4 contained least EE, whose cause may be low polymer content or drug diffusivity in the process of preparation of microspheres. F3 exhibited maximum yield (92.60 ± 7.76 %), drug content (90.45%), and entrapment efficiency (89.45 ± 7.89 %) and thus is the ideal formulation for MCN microspheres. Difference between these parameters of entrapment efficiency and drug content depicts the need for optimizing formulation parameters for increasing the drug loading as well as drug release properties.

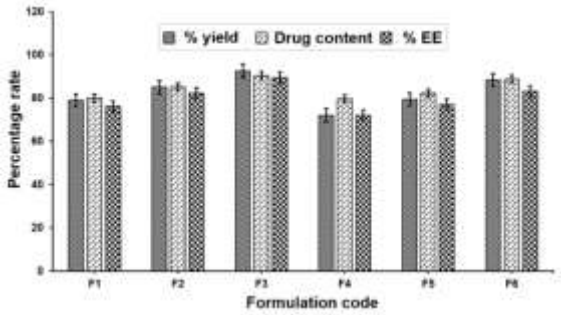

Figure 5. Various Evaluation of % Yield, Drug Content, and %EE on MCN-Loaded Microspheres.

***In Vitro* MCN Release**

In vitro release studies of drugs were carried out employing a USP-II dissolution apparatus to study the release profile of MCN from various formulations (F1 to F6). Cumulative drug release percentage was determined over 12 h for each of the formulations**.** The drug release profiles indicate a gradual increase in drug release over time for all formulations. The release patterns suggest differences in drug release rates among formulations, with some formulations exhibiting faster release than others. The initial phase (0-2 h) of all formulations showed a rapid increase in drug release, reaching approximately 20-30% of cumulative drug release. Intermediate phase (2-8 h) of drug release continued at a steady rate, with some variations among the formulations. F5 (yellow) exhibited a slightly higher release compared to others, while F3 (purple) appeared to have a slower release at this stage. The final phase (8-12 h) of cumulative drug release reached around 80-100% for all formulations, with F3 showing the highest release at 12 h. The error bars indicate slight variability in the data, but overall, all formulations followed a similar release pattern shown in Figure 6.

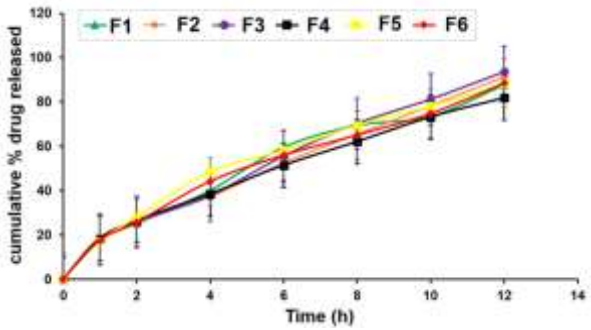

Figure 6. In Vitro MCN Release from MCN-Loaded Microspheres from F1 to F6.

The in vitro drug release study demonstrated that all formulations exhibited a controlled and sustained release profile over 12 hours. The differences in drug release rates could be attributed to variations in formulation composition, including polymer concentration, excipients, and drug-polymer interactions. F5 exhibited the fastest release, suggesting that its formulation may have a lower polymer concentration or a more hydrophilic matrix, facilitating faster drug diffusion. F3 showed a slightly slower release, which may indicate a higher polymer concentration or stronger drug-polymer interactions, leading to a more controlled release profile. The similarity in the overall trend among formulations suggests that the release mechanism follows a diffusion-controlled process, possibly governed by matrix erosion or swelling behavior. The presence of error bars indicates some variability in release rates, which may be due to differences in formulation properties, batch-to-batch variations, or experimental

conditions. Overall, the study confirms that the formulations successfully achieved sustained drug release over 12 h, which is desirable for controlled drug delivery applications.

Release Kinetics

Release data were processed based on four mathematical models to characterize the release kinetics. The results of in vitro release studies for all six formulations are given in Table 2 below and depicted in Figure 7. Moreover, the graphical presentations of various kinetic models are given in Tables and Figures. Kinetic parameters derived for different formulations are listed in below Table. The Korsmeyer-Peppas model (0.9650 ± 0.011 to 0.9983 ± 0.027) provided a better explanation for the in vitro release of MCN from MCN-loaded microspheres compared to the first-order (0.993 ± 0.07) release kinetics, as displayed in

Table 2. Regression Co-Efficient (R^2) Values of Different Kinetic Models and Diffusion Exponent (N) of Peppas Model for MCN-Loaded Microspheres.

Formulation code	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2 value	n value
F1	0.9669 ±0.024	0.9449 ±0.045	0.9932 ±0.043	0.9932 ±0.078	0.6245 ±0.002
F2	0.9854 ±0.014	0.9169 ±0.067	0.9650 ±0.098	0.9650 ±0.011	0.6436 ±0.008
F3	0.9848 ±0.035	0.9116 ±0.076	0.9683 ±0.034	0.9983 ±0.027	0.6231 ±0.004
F4	0.9830 ±0.091	0.9683 ±0.025	0.9951 ±0.022	0.9951 ±0.045	0.5955 ±0.007
F5	0.9782 ±0.088	0.9492 ±0.076	0.9926 ±0.045	0.9926 ±0.019	0.6242 ±0.001
F6	0.9658 ±0.061	0.9500 ±0.057	0.9974 ±0.076	0.9974 ±0.088	0.646 ±0.002

Diffusion and others were implicated in the complex release mechanism. Release rate is intermediate between case II and Fickian transport. This can be advantageous for controlled-release systems to balance rapid and long-term release. Figure 7, MCN release from MCN-loaded microspheres could be better diffusion regulated with extended release than free CuR. It correlates a release exponent (n) and time with the amount of drug released. This exponent tells us about the drug release mechanism. For $0.5 < n < 1.0$ (0.5955 ±0.007 to 0.646 ±0.002), anomalous diffusion is indicated. Fickian diffusion and other mechanisms, such as relaxing the cross-linking complex with MCN by HPMC chains, occur concurrently to release the drug from MCN-loaded microspheres.

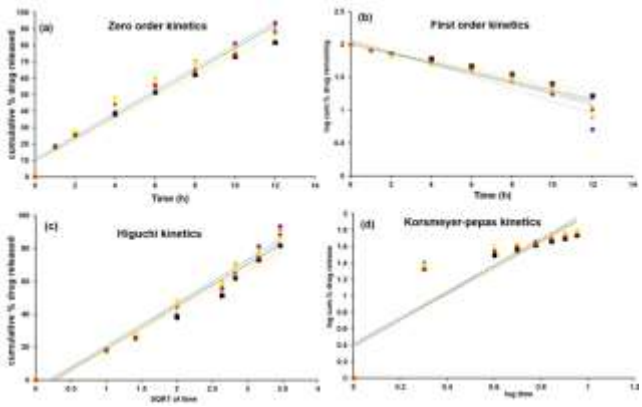

Figure 7. Mechanism of MCN Release Kinetics of Various Models Such as (A) Zero-Order, (B) First Order, (C) Higuchi Model, (D) Korsmeyer-Peppas Model, Release from MCN-Loaded Microspheres.

4. DISCUSSION

The formulated MCN microspheres were effectively tested for particle size, surface texture, drug content, entrapment efficiency, and in vitro drug release. Microscopy using light and SEM proved that the microspheres were spherical in shape with different surface textures, and their mean particle diameters were 140–210 µm in different formulations. The efficiency of drug entrapment ranged from 72.06% to 89.45%, reflecting good capacity for drug loading, and the percentage yield ranged from 72.09% to 92.60%, indicating effective formulation. The in vitro study of drug release revealed a sustained release pattern, with cumulative drug release at 12 h from 81.80% to 93.60%. Release kinetics analysis revealed that drug release according to the Higuchi matrix model (r^2 = 0.9650–0.9974) confirmed diffusion-controlled release of the drug. The Peppas model reflected n-values in the range 0.5945–0.6439, reflecting non-Fickian (anomalous) diffusion, i.e., a mixed diffusion and erosion mechanism. The results thus attest that the synthesized MCN-loaded microspheres display good encapsulation efficiency, drug release control, and stable compatibility with excipients. The optimized formulations show promise for sustained-release drug delivery, providing enhanced therapeutic effects in antifungal therapy.

5. CONCLUSION

This research successfully formulated and evaluated Miconazole Nitrate (MCN)-loaded microspheres as a new antifungal drug with extended and sustained drug action. The in vitro drug release experiment showed a controlled and sustained release pattern within 12 h, which is sufficient to prove that the microsphere system can significantly prolong the therapeutic window of MCN. The differences in drug release rates among the formulations mirror that the release kinetics is greatly influenced by polymer composition and formulation parameters. The optimal formulation exhibited an excellent balanced release profile, preserving sustained drug action and minimizing burst release. Sustained release mechanism is predicted to enhance antifungal effectiveness, lower the frequency of dosing, and improve patient compliance. In summary, the results validate the effectiveness of MCN-loaded microspheres as a sophisticated drug delivery system for antifungal therapy. Kinetic modeling, stability tests, and in vivo tests are proposed for future studies to verify its clinical use and therapeutic action.

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