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Formulation and Evaluation of Miconazole Nanocapsules

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Abstract

Using the emulsion solvent diffusion technique, the current study's goal was to create and analyze miconazole nanocapsules. Ethyl cellulose as well as HPMC nanocapsules were used to fill the miconazole, which has been produced using the emulsion solvent diffusion method. The FTIR data showed that the miconazole nanocapsules filled with ethyl cellulose nanocapsules were stable and that there was no drug-polymer interaction. To determine whether there is no incompatibility in the formulation, compatibility investigations like FTIR & DSC were utilized. The morphological particle size of miconazole nanocapsules is assessed using SEM. This complete formulation codes for the nanocapsules were F1 to F8. The optimum formulation F6's in vitro dissolution rate was found to be 75.22 percent. A variety of mathematical models, including the zero order, first order, Higuchi matrix, and Korsmeyer peppas model, were fitted to the data on drug dissolution in vitro. The model that the miconazole nanocapsules use has R2 values of 0.937, 0.399, 0.899, and 0.785 and m values of 1593, 0.061, 11409, and 2.560. The Nanocapsules released the medication over 45 minutes. The ethyl cellulose and HPMC nanocapsules that contain miconazole were created under ideal circumstances and exhibit good release properties.

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INTRODUCTION

Nanocapsules are made of polymeric membranes and have an oil-filled core that contains chemicals that can disseminate out in response to environmental, chemical, thermal, or biological stimuli. Colloidal nanocapsules are formed by interfacial deposition of prefabricated polymers. It is suitable for hydrophobic medication delivery. Lipid nanocapsules have been used to treat rat tumour cases that were multi-drug resistant. Although there hasn't been much research on using nanocapsules for drug delivery to RCC, Hureaux et al.'s suggestion Developing a brand-new 180 nm hybrid protein-lipid polymer

nanocapsule as a safe medication for the delivery of the transcription factor p53 and the lipophilic chemical paclitaxel to cause apoptosis in HeLa cells is encouraging [1]

A nanocapsule has a shell and a compartment where desired materials can be inserted. Drug-filled nanocapsules may have antibodies or cell surface receptors on their surface that bind to cancer cells or other target cells and release a biological compound when they come into touch with that particular tissue. Today, polymeric nanocapsules can be produced in a variety of forms and sizes. These can then be made functional by adding molecules with a particular characteristic to the nanocapsules' outer shell. These molecules act as the trigger in a targeted medication delivery system, causing the contents of the nanocapsule to be released in reaction to a specific biomolecule. Due to their controlled release and ability to deliver medications to particular targets, nanocapsules are highly sought-after in drug delivery systems [2]. Nanocapsules range in size from 5 to 1000 nm, although most are between 100 and 500 nm. It is a colloidal medication delivery device that is submicroscopic. You can make nanocapsules out of either synthetic or natural polymers. Drugs are inserted into the core cavity of nanocapsules, which protects them against rapid deterioration. It can be created using several techniques, including layer-by-layer synthesis, double emulsification polymer coating, emulsion diffusion, and nanoprecipitation. It consists of a thin polymer membrane enclosing either an oily or watery core.

Capsules are created from aqueous solutions by sequentially depositing polymer layers onto a sacrifice template. The hollow capsules are created as a result of the sacrificial template dissolving. Similar to a vesicular system, nanocapsules have a hollow that houses the medicine and is surrounded by a polymeric membrane and a liquid core or polymer matrix [3].

The cavity contains the active ingredients as a molecular dispersion in liquid or solid form. These hollow nanocapsules can contain a wide range of materials, including biopolymers including proteins and nucleic acids, medicines, catalysts, colours, and pharmaceuticals. A versatile azole antifungal miconazole also has some efficacy against Gram-positive bacteria. Although intravenous miconazole was no more accessible, a broad spectrum of suppositories, creams, gels, and tablet-based medications are available to treat mucosal yeast infections, including those in the mouth and vagina.

Miconazole's primary mode of action is assumed to be the suppression of fungal CYP450 14-lanosterol demethylase activity [4].

MATERIALS AND METHODS

Miconazole was purchased from Hetero Drug Limited in Hyderabad. Ethyl cellulose, HPMC, Ethanol were purchased from SD Fine Chemical Limited, Hyderabad.

Methodology

Preparation of calibration curve of Miconazole

In a 100 ml standard flask, A pH 7.4 phosphate buffer solution was used to weigh and dissolve 100 mg of miconazole accurately. It offers a concentration of 1 mg/ml.

To make solutions with various concentrations of 5, 10, 15, 20, and 25 g/ml, the stock solutions were thinned out with a pH 7.4 phosphate buffer solution. Each sample was then spectrophotometrically examined at 232 nm [5].

Compatibility studies

IR studies

Drug preformulation research about the drug and polymer interaction becomes unstable since the production of the drug and polymer may interact with one another. They play a crucial role in choosing the right polymer.

To determine whether miconazole and the cellulose polymer were compatible [6].

Differential Scanning Calorimetry

The outcome is a plot of heat flux (rate) vs. temperature at a given temperature rate. It offers details about the sample's physical characteristics. Its natural state is either crystalline or amorphous [7].

According to the thermograms, it illustrates a potential interaction between the medicine and polymers in formulations.

Morphology of the Particles

To determine the morphology, size distribution, and particle size of the Nanocapsules, the following procedures are used [8].

In a mixture of organic solvents and polymers with various ratios, the drug and polymers were simultaneously dissolved. The exterior water phase was stirred as the medication solution was progressively injected there with a syringe. For

Table 1: Formulations of Miconazole Nano capsules

Sl.No	Ingredients	F1	F 2	F 3	F 4	F 5	F6	F 7	F 8
1	Miconazole	2.0	3.0	2.0	3.0	2.0	3.0	2.0	3.0
2	Ethyl Cellulose	1.0	1.5	2.0	2.5	1.0	1.5	2.0	2.5
3	HPMC	1.5	2.0	1.5	2.0	1.5	2.0	1.5	2.0
4	Ethanol	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
5	Distilled water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Table 2: Calibration curve data for Miconazole in pH 7.4 phosphate buffer

S.No	Concentration	Absorbance			Average +SD
		Trail 1	Trail 2	Trail 3	
1.	0	0	0	0	0
2.	15	0.178	0.175	0.175	0.188 ± 0.005
3.	25	0.325	0.330	0.335	0.334 ± 0.008
4.	35	0.505	0.510	0.515	0.511± 0.006
5.	45	0.655	0.670	0.662	0.655± 0.009
6.	55	0.808	0.830	0.810	0.815± 0.015
7.	65	0.965	0.992	0.990	0.982± 0.020
8.	70	0.977	0.932	0.987	0.987±0.023

S.D = Standard deviation

Scanning Electron Microscopy

It is particularly helpful in determining the general morphology and shape of the Nanocapsules. To determine the morphology, size distribution, and particle size of the Nanocapsules, the following procedures are used, the appearance of coated Nanocapsules and Ethyl cellulose Nanocapsules. The particles were freeze-dried, then covered with a 20 nm thick layer of gold-palladium using a sputter coater, and then examined under a microscope [9].

Procedure of Miconazole Nanocapsules

The emulsion solvent diffusion method was used to create the miconazole nanocapsules. In the interior phase, polymers including HPMC and ethyl cellulose are concentrated along with miconazole and ethanol, a suitable solvent.

nearly one hour, the system was continuously agitated at 800 rpm. Additionally, the superior solvent transfers into the inferior solvent [10]. As the droplets progressively solidified, Nanocapsules were created. To remove the Nanocapsules from the preparation system, the system was filtered. The finished product was dried and cleaned with distilled water [Table 1]. The entire procedure took place at room temperature. The medication-to-polymer ratio was displayed.

Evaluation of Nanocapsules

Percentage production yield (PY)

$$\text{PY (\%)} = \frac{Practical\ mass\ of\ Nanocapsules}{Theoretical\ mass} \times 100$$

The PY (%) was calculated after each formulation was performed in triplicate.

Entrapment efficiency

Table 3: Interpretations of FTIR

Observed peak	Characteristic peak	Bond	Functional Groups
	Pure Drug – Miconazole		
3462.22	3300-3500	-N-H-	Amines
3236.55	2700-3300	C-H Stretch	Aromatics
2883.58	2700-3300	C-H Stretch	Aromatics
873.75	800-1200	C-C Stretch	Aromatic
	600-900	C-H Rocking	Alkanes
	DRUG + ETHYL CELLULOSE + HPMC		
3442.94	3300-3600	C=0 Stretch	Hydrogen-bonded
	3000-3700	O-H Stretch	alcohols and phenols
3415.93	3300-3600	C=O Stretch	Hydrogen-bonded
	3000-3700	O-H Stretch	alcohols and phenols
3305.99	2700-3300	C-H Stretch	Aromatics
	3000-3700	O-H Stretch	carboxylic acids or H-bonded alcohols
2972.31	2700-3300	C-H Stretch	Aromatics

Table 4: Percentage drug content determination of Miconazole Nanocapsules

Formulation code	Percentage yield (%)	Entrapment efficiency (%)	Entrapment Loading (%)	Particle size (μm)	Swelling Index (Sec)	Drug content (%)
F1	85.45	55.4	57.8	82	0.7Sec	66.8
F2	83	89.3	88.6	65	0.4 Sec	67.4
F3	75.23	70	85.3	99	0.3Sec	91.6
F4	80.90	64	70.9	54	0.9 Sec	90.9
F5	90.95	66.8	71.4	94	0.5 Sec	76.4
F6	88.57	90.4	69.8	25	1.7 Sec	99.5
F7	82	59.7	65.8	75	0.5Sec	89.7
F8	83.45	61.8	98.7	94	0.3 Sec	88.4

Table 5: *In Vitro* Dissolution Studies

Sl.no	Time	% of Drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	5	1.63	3.08	8.85	8.75	12.62	14.21	18.58	15.40
2	15	4.59	6.91	8.35	13.42	18.53	18.89	20.28	27.08
3	20	6.72	8.53	12.65	15.60	20.27	25.17	26.17	34.80
4	25	7.60	11.65	16.59	25.32	26.22	26.98	29.81	38.74
5	30	11.62	15.55	22.30	28.25	30.07	39.4	42.80	46.45
6	35	30.43	42.42	55.21	56.37	65.72	75.22	69.60	61.82
7	40	27.08	34.15	34.39	42.61	42.38	42.99	47.75	54.25
8	45	15.39	27.12	35.32	38.45	41.09	40.55	42.55	50.35

By using the emulsion solvent diffusion method, the nanocapsules were created. At 10°C, it was centrifuged for 40 minutes at 14,000 rpm.

Table 6: Release order kinetics of zero order kinetics

S.No	Time	% cumulative drug release
1	0	0
2	5	15415
3	10	26077
4	15	33865
5	20	37650
6	25	44310
7	30	52314
8	35	55322
9	40	60877
10	45	87924

Table 7: Release order kinetics of first-order kinetics

S.No	Time	Log cumulative % drug release
1	0	0
2	5	4.167
3	10	4.345
4	15	4.456
5	20	4.462
6	25	4.777
7	30	4.8
8	35	4.744
9	40	4.755
10	45	4.934

Table 8: Release order kinetics of Korsmeyer Peppas

Sl.no	Time	Log cumulative % drug release
1	0	0
2	5	4.112
3	10	4.432
4	15	4.532
5	20	4.456
6	25	4.777
7	30	4.7
8	35	4.622
9	40	4.543
10	45	4.876

Miconazole is contained within the Ethyl cellulose and HPMC. The amount that was detected in the supernatant was less than the sum of the amounts employed to create the Nanocapsules [11]. By using a UV spectrophotometer at 232 nm, the amount of free miconazole in the supernatant was determined. It is determined using the next equation.

$$\%EE=\left(\frac{nitial\ drug-M_{Free\ drug}}{M_{Initial\ drug}}\right)\times 100$$

Where

"$M_{\text{Initial drug}}$" The quantity of the initial medication utilized in the assay.

"$M_{\text{Free drug}}$" The amount of free drug found in the supernatant following centrifugation.

Drug loading efficiency

The leftover sediments (precipitations) were rinsed with distilled water after the drug loading efficiency was eliminated. It is dissolved in a

Table 9: Release order kinetics of Higuchi

Sl.no	The square root of time	% cumulative drug release
1	0	0
2	2.22	14420
3	3.15	26060
4	3.86	33800
5	4.45	37640
6	5	46385
7	5.46	50210
8	5.90	55110
9	6.31	62865
10	6.7s	87910

Table 10: Release kinetics of Miconazole Nanocapsules (F1 to F5)

Model	Equation	F 1		F 2		F 3		F 4		F 5	
		R^2	m	R^2	m	R^2	M	R^2	m	R^2	M
Zero order	Mo-Mt=kt	0.644	68.5	0.940	1124	0.008	15.94	0.203	72.77	0.929	1415
First order	InM=InMo	0.495	0.062	0.541	0.068	0.258	0.038	0.353	0.045	0.439	0.063
Higuchi's Matrix	$M_0 - M_t = kt1/2$	0.517	4509	0.768	7424	0.024	212.0	0.190	515.4	0.804	9619
Korsmeyer-Peppar	$\log (M_0 - M_t) = \log k + n \log t$	0.840	2.355	0.885	2.544	0.573	1.709	0.664	1.812	0.807	2.518

Table 11: Release kinetics of Miconazole Nanocapsules (F6 to F9)

Model	Equation	F 6		F 7		F 8	
		R^2	m	R^2	m	R^2	M
Zero order	Mo-Mt=kt	0.918	15.47	0.948	154.3	0.946	1597
First order	InM=InMo	0.480	0.053	0.464	0.043	0.415	0.062
Higuchi's Matrix	$M_0 - M_t = kt1/2$	0.797	1058	0.847	1054	0.377	0.059
Korsmeyer-Peppar	$\log (M_0 - M_t) = \log k + n \log t$	0.834	2.033	0.826	2.043	0.951	8082

2.5:2.5, v/v solution of chloroform and acetone in a 10 mL volumetric flask. It was sonicated for 30 minutes to achieve complete drug extraction from Nanocapsules. Chloroform was used to dilute the volume to 10 ml. After centrifuging the resultant solution at 14,000 rpm for 30 minutes at 10°C, supernatants were collected and triple-tested for the presence of the loaded medication using a UV spectrophotometer at 232 nm [12].

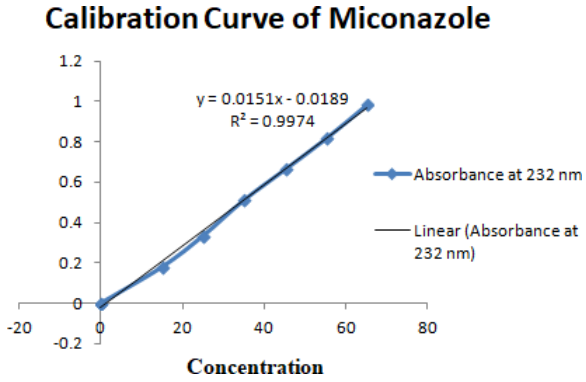

Figure 1: Standard graphs for the calibration curve of Miconazole

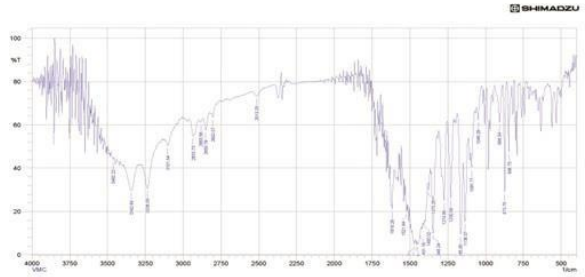

Figure 2: FTIR Spectrum of Pure drug (Miconazole)

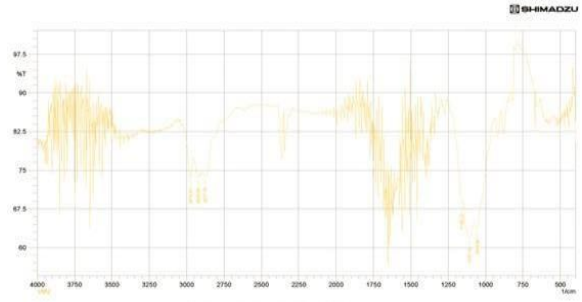

Figure 3: FTIR Spectrum of Ethylcellulose

Particle size determination

Optical microscopy was used to measure the particle size of nanocapsules. For particle size measurements, about 100 Nanocapsules were counted. By suspending it in water, the distribution of particle size was measured [12].

Equilibrium swelling studies of Nanocapsules

Nanocapsules were weighed out and added to phosphate buffer (pH 7.4). It is left to swell while maintaining its weight. The weight variations of the Nanocapsules were measured after they had been taken out and blotted with filter paper. The following formula was used to determine the swelling's degree (a). $\alpha = wg\text{-}wo/wo$

Where

Wo represents the Nanocapsules' initial weight, where

Wg indicates the weight of the Nanocapsules in the medium at equilibrium swelling.

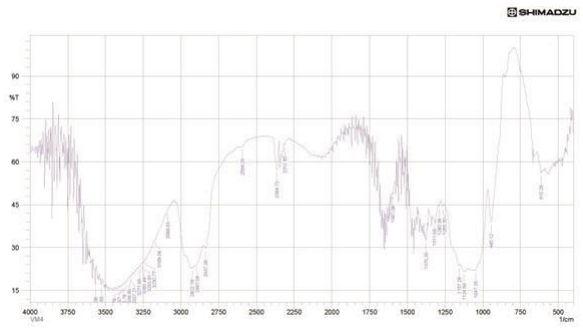

Figure 4: FTIR Spectrum of HPMC

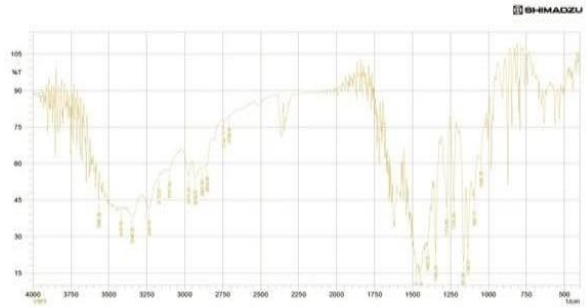

Figure 5: FTIR Spectrum of Drug + Ethylcellulose

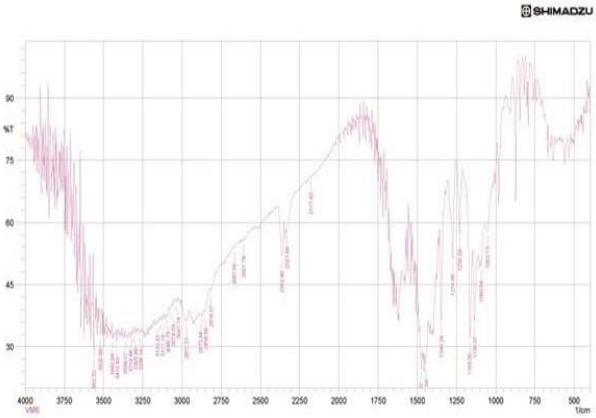

Figure 6: FTIR Spectrum of Drug + EC + HPMC

Drug content

To extract the medication from 50mg of Miconazole Nanocapsules, the Nanocapsules were broken up and suspended in water. After 24 hours, the filtrate's drug content was measured spectrophotometrically at 232 nm using water as the control [13].

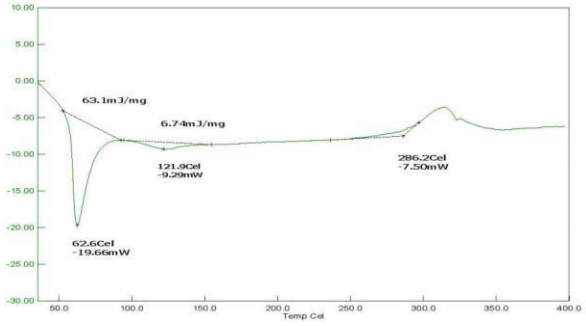

Figure 7: DSC Spectrum of Drug

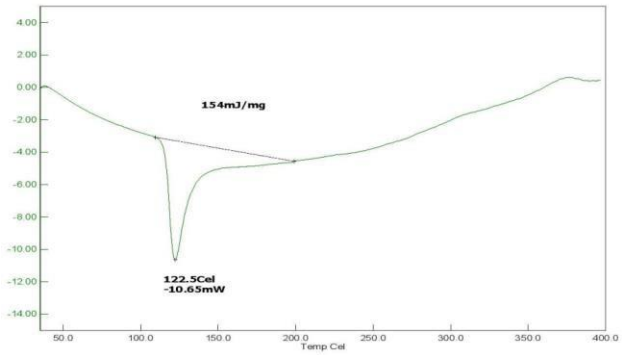

Figure 8: DSC spectrum of Mixtures (Drug + EC + HPMC)

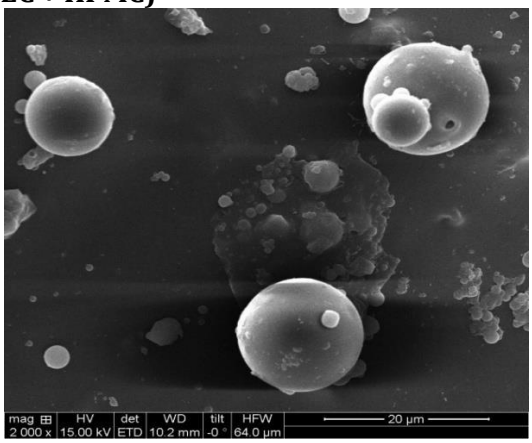

Figure 9: SEM Samples of Best formulations of F6

In-vitro drug release studies

In-vitro drug release studies were carried out utilizing a USP XXIV dissolution apparatus type II and 500ml of dissolution media. It is kept at 50 rpm, 37 0.5 °C, and a pH 7.4 0.2 phosphate buffer as the dissolving media for 45 Minutes [14].

Data Analysis

The data was collected, and it was To investigate the mechanism for the release and release rate kinetics of the dosage form, it was fitted into the Zero order, First order, Higuchi matrix, and Korsmeyer and Peppas models [15]. By contrast, the R-values that were obtained, the best-fit model was discovered.

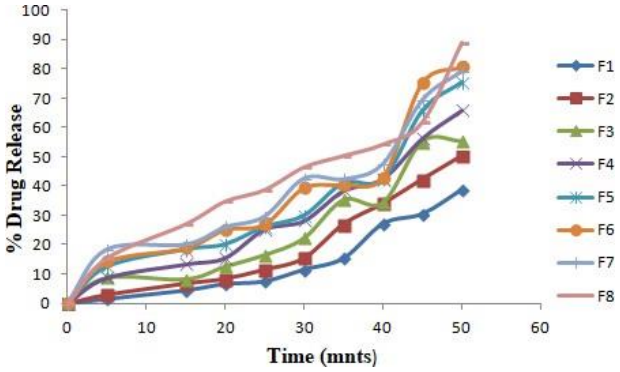

Figure 10: In vitro dissolution studies of Miconazole Nanocapsules

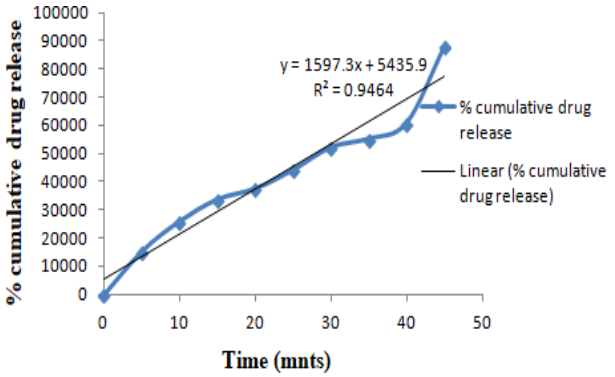

Figure 11: F 6 of In vitro dissolution studies of zero order kinetics

Zero order kinetics

If there is no change in the region and no instances of equilibrium are reached, the medication will be delivered gradually from pharmaceutical dosage forms that do not disaggregate. The following equation serves as a representation of it.

$$Q_t = Q_o + K_o t$$

Where

Q_t = amount of drug dissolved in time t, Q_o = initial amount of drug in the solution, K_o = zero order release constant.

First order kinetics

The data on release rates were fitted to the following equation to analyze the first-order release rate kinetics.

$$\text{Log } Q_t = \log Q_o + K_1 t / 2.303$$

Where

Q_t is the amount of drug released in time t, Q_o is the initial amount of drug in the solution, K_1 is the first-order release constant.

Higuchi model

Several theoretical theories help to construct this concept. to investigate how water-soluble and poorly soluble medicines are released. The equation is they are absorbed into semisolids or solid matrices.

$$Q_t = K_H . t^{1/2}$$

Where, Q_t = Amount of medication (drug) released in time t, K_H = Higuchi dissolving constant.

Korsmeyer and Peppas release model

The release rate data are fitted to the following equation to analyze this model.

$$M_t / M_\infty = K.t^n$$

Where, M_t / M_∞ is the fraction of drug release, K is the release constant, t is the release time, n is the Diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

RESULTS AND DISCUSSION

The standard plot of Miconazole in pH 7.4 phosphate buffer

preparation of a phosphate buffer solution (pH 7.4) containing a 100 mg/ml standard stock solution of the drug miconazole. The standard graph is shown in Figure 1, and the standard plot readings are provided in Table 2.

Compatibility studies

IR studies

FTIR is used to capture the IR spectrum of a pure miconazole sample. This is contrasted with Miconazole's typical functional group frequencies, which are displayed in Table 3. Formula's FTIR spectrum is displayed in Figures 2 to 6.

Differential scanning calorimetry:

The exothermic peak in the DSC sample's spectrum for the pure drug is 122.50 c and -10.65 mw. The drug sample is a mixture of miconazole, ethyl cellulose, and HPMC. The mixture has an endothermic peak of 286.2 ^oC and an exothermic peak of 121.9 ^oC, indicating that there is no compatibility between the excipients and the medication in the formulation. It is appropriate for use in nanocapsule formulation [Figure 7 & 8].

Morphology of the Particles

SEM

Scanning electron microscopy was used to analyze the morphology and structure of nanocapsules, and photomicrographs were acquired at the appropriate magnifications [Figure 9].

Evaluation of Miconazole Nanocapsules

Percentage Yield

The production yield of miconazole nanocapsules utilizing HPMC and ethyl cellulose ranged from 75.23% to 90.95%.

Encapsulation efficiency

Drug entrapment efficiency (%EE)

F1 through F8's percentage entrapment effectiveness ranged from -55.4% to 90.4%. The F 8 demonstrates the effective formulation of the outcomes [Table 4].

Entrapment Loading (%EL)

Formulations F1 to F8 have entrapment loading percentages ranging from 57.8 to 98.7%. The F 8 exhibits excellent formulation and strong effectiveness [Table 4].

Particle size

The particle size distribution of nanocapsules is shown as a range from 25 m to 99 m [Table 4].

Swelling studies

The Nanocapsules were weighed beforehand, and they were given time to expand to their final weight. After being removed, the Nanocapsules were wiped using filter paper. The findings of the weight measurements are displayed in Table 4.

Drug content

Drug content distribution of Nanocapsules represented it indicated that drug content is F 1 (66.8%), F 2 (67.4 %), F3 (91.6%), F4 (90.9%), F 5 (76.4 %), F 6 (86.4 %), F 7 (89.7 %), F 8 (99.5 %). The formula is shown in table 4.

In vitro dissolution Studies

The collected in vitro drug dissolution data was fitted to several mathematical models, such as the zero order, first order, Higuchi matrix, and Korsmeyer Peppas model, to understand the mechanism of drug release rate kinetics of the drug from dosage forms [Table 5]. For various Nanocapsule formulations, the percentage of drug release with data from several kinetic models is shown in Figure 10.

CONCLUSION

The goal of the current effort was to create miconazole nanocapsules for a sustained medication delivery method. According to the results, it appears that formulation F6 was discovered to have excellent morphological properties. The formulation with the highest microsphere production (88.57%), highest entrapment efficiency (90.4%), highest drug loading efficiency (69.8%), highest swelling index (1.7 sec), and highest particle size (25 m) was found to be F6. Numerous Release Kinetic research that used a sustained approach and a consistent pattern over a lengthy period of 45 minutes were fitted with in vitro drug release. The drug content determination of the optimum formulation was discovered to be (99.5). It was found that all of the assessment parameters were strongly impacted by the ethyl cellulose content. As a result, the readymade nanocapsules containing miconazole may be a promising candidate for secure and efficient long-term drug delivery.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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