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Formulation and Optimization of Miconazole-Loaded Microspheres for Enhanced Bioavailability and Sustained Drug Release

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Abstract:

Objective:

The aim of this study was to develop and improve Miconazole-encapsulated microspheres to enhance drug absorption, reduce dosage requirements, minimize potential side effects, and prolong drug efficacy.

Methods:

Miconazole-infused polymeric microspheres were created through the process of ionotropic gelation. The compatibility of Miconazole with the chosen polymers was assessed using techniques such as Fourier transform-infrared spectroscopy and differential scanning calorimeter.

Results:

Among different batches tested, the F2 batch exhibited the highest drug encapsulation efficiency of 90.25% and a production yield of 70.21%. The average size of the microspheres was determined to be 150.50 micrometers. The release profile demonstrated a consistent and gradual release pattern, with a remarkable release rate of 98.80%, indicating enhanced bioavailability.

Conclusion:

The developed Miconazole-encapsulated microspheres showed promising results in terms of drug encapsulation efficiency, production yield, particle size, and release profile. These findings suggest the potential of these microspheres to improve drug absorption, reduce dosage requirements, and extend drug efficacy, thus offering a valuable therapeutic option for fungal ailments.

Key words: *Miconazole, Fourier Transform Infrared (FTIR) analysis, Sodium Alginate, Ionotropic Gelation method, In vitro medication release investigations.*

1. INTRODUCTION:

Pharmaceutical delivery is an expanding domain, concentrating on enhancing the accessibility of medications at precise body locations for prolonged durations. Techniques in nano-medicine, such as the use of nano-structured apparatus like microcapsules or nanospheres, strive to boost drug accessibility and direct delivery to designated locations. In the present era, there is a substantial focus on the creation of sustained-release drugs, drawing considerable interest from both commercial and scholarly sectors.

Numerous products on the market claim sustained or controlled drug delivery, formulated for oral and injectable routes. The strength of drug delivery lies in its capacity to modify drug pharmacokinetics and bio-distribution. Nanotechnology holds promise in improving drug delivery and targeting, potentially increasing efficacy while reducing toxicity. This advancement not only benefits patient but also creates new market opportunities for pharmaceutical and drug delivery companies.

Drug delivery strategies often aim to overcome barriers like the blood-brain barrier or find alternative routes for delivering proteins. Novel drug delivery systems offer diverse solutions, including oral and implant systems, pulmonary and nasal delivery, and transdermal and topical applications. Lipid or polymer-based nanoparticles have shown enhanced pharmacological actions, particularly in novel drug delivery systems.

Achieving optimal therapeutic efficacy necessitates delivering agents to target tissues in precise amounts and timeframes, minimizing toxicity and side effects. Various approaches, such as using microspheres as drug carriers,

facilitate sustain controlled release. Well-designed drug delivery systems can address conventional therapy limitations and enhance therapeutic outcomes significantly.

Microspheres, defined as small spherical particles in the micrometer range, are utilized for controlled drug release, including vaccines, antibiotics, and hormones. They offer advantages like enhanced solubility, prolonged therapeutic effects, reduced doses, and toxicity, along with protecting drugs from degradation. Microsphere morphology allows controlled variability in degradation and drug release.

However, microsphere technology also presents challenges, including higher material costs, environmental impact concerns, and reproducibility issues. Different types of microspheres cater to specific needs, such as bio-adhesive, magnetic, floating, or radioactive microspheres, each offering distinct advantages in drug delivery.

In the realm of microspheres, polymeric types take precedence, falling into two main categories: biodegradable and synthetic. Each category has its distinct uses and advantages. Synthetic polymers, such as poly (lactic acid) and poly (glycolic acid), provide properties of sustained release, while natural polymers, including albumin and gelatin, are utilized for targeted drug delivery.

Microspheres are prepared using a variety of methods such as single and double emulsion techniques, polymerization, phase separation, and solvent extraction. Each of these methods presents unique benefits and difficulties in obtaining the desired characteristics of the particles and the profiles of drug release

The latest developments in microsphere technology have seen the application of chitosan polymers in a variety of areas such as orthopaedics, cosmetics, dental medicine, and wound healing. The distinctive attributes of chitosan, including its biocompatibility and muco-adhesiveness, make it an adaptable material for use in drug delivery and tissue engineering applications.

In conclusion, microspheres represent a promising avenue in drug delivery, offering tailored solutions for controlled release and targeted therapy across various medical domains. Ongoing research and innovation in this field continue to expand the possibilities for improving therapeutic outcomes and patient care.

2. MATERIALS AND EQUIPMENT :

2.1. MATERIALS

1. Miconazole, crafted by HETERO DRUGS LTD in Hyderabad.
2. Sodium alginate, meticulously formulated by Syn Pharma Research Lab, also situated in Hyderabad.

2.2. EQUIPMENT

S No	Equipment	Name
1	A digital weighing machine with a sensitivity of 0.001mg.	The Sartorius TE 124S
2	A Precision balance CB-Series. (sensitivity : 10 mg).	Contech
3	Stirrers	Remi motors, Mumbai
4	Hot Air Oven	Cintex Ind. Corporation
5	UV-Visible Spectrophotometer	Lab India
6	Sonicator (sonica ultrasonic cleaner-2200MH)	Spinotech Pvt. Ltd, India

3. METHODOLOGY :

Color, odor, taste and the appearance

Descriptive terminology was used to document the drug's color, smell, and flavor.

The determination of melting point

The melting point of the drug sample was ascertained using a capillary method with a melting point apparatus.

The Determination of solubility

The solubility of Miconazole was assessed by introducing an abundant quantity of the drug into the solvent. The equilibrium solubility was then determined by extracting the supernatant and analyzing it using a double beam spectrophotometer from Lab India.

$$\% \text{ solubility} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times \text{Dilution factor} \times 100$$

Developing analytical methods for miconazole.

Prior to the preparation of Miconazole Microspheres, a standard curve of Miconazole was established in various media to measure the samples. All solutions were made fresh immediately before they were needed.

0.2 M potassium dihydrogen phosphate solution

A 27.218 gm of potassium dihydrogen phosphate was dissolved in some amount of water and diluted with water to 1000 ml.

0.2 M sodium hydroxide solution preparation

An 8 gm of sodium hydroxide was dissolved in some amount of water and diluted with water to 1000 ml.

Phosphate Buffer pH 7.4 preparation

A 250 ml of 0.2 M potassium dihydrogen phosphate was poured to a 1000 ml volumetric flask, which was followed by 195.5 ml of 0.2 M sodium hydroxide. The volume was filled with water, and the pH was adjusted to 7.4 with the addition of 0.2M potassium dihydrogen phosphate/sodium hydroxide.

Setting up a Standard Miconazole Solution

the stock solution I

A 10 ml volumetric flask was filled with 10 mg of precisely weighed miconazole. Phosphate buffer was used to increase the volume to 10 ml, yielding a 1000 mcg/ml solution.

The stock solution II

To achieve 100 mcg/ml, 1 ml of the stock solution I was aliquoted, put in a 10 ml volumetric flask, and diluted with 10 ml of phosphate buffer.

the Stock solution III

To get 10mcg/ml, an aliquot of 1ml was prepared up to 10ml from stock solution II.

From stock solution I, comparable dilutions were made in other media, such as pH 7.4 buffer solutions.

Finding the miconazole absorption maximum (λmax)

Using a double beam spectrophotometer, a 10 mcg/ml standard solution of miconazole was scanned against corresponding media blanks. For every solution, an absorption maximum (λmax) of 280 nm was found, and this value was chosen to create the standard curve.

Constructing a Miconazole standard curve

Miconazole standard curves were acquired in water and 7.4 pH buffers. Miconazole standard solution (stock solution-II) containing 100 mcg/ml was divided into aliquots of 10, 20, 30, 40, and 50 ml. The aliquots were then diluted using the appropriate medium to achieve concentrations ranging from 10 to 50 mcg/ml. At 280 nm, the absorbance of the solutions was measured using the corresponding medium as a blank. For every buffer, the experiment was conducted six times, and the mean value was used to create a calibration curve.

Drug and the excipient compatibility study

Studies on the compatibility of drug excipients with drugs under expedited settings were conducted. A uniform combination of excipients and drug was prepared for the investigation, and the mixture was then placed into both HDPE and LDPE bags. For four weeks, glass vials were exposed to 600 C and 400 C/75% RH, while LDPE bags were subjected to 400 C±75% RH. Periodically, samples were checked for any physical changes.

Miconazole microsphere preparation and assessment

Polymer selection for microsphere preparation

Drug formulations have included polymers as excipients, and the formulation of microspheres also makes use of cellulose derivatives. For the purpose of creating Miconazole microspheres in this investigation.

Procedure for Microsphere Preparation
The process of ionotropic gelation was utilized to create microspheres using Miconazole as the core ingredient.

Composition table:

Table: 3.1. Miconazole Microspheres preparation

Composition	F-1	F-2	F-3	F-4
Drug	100	100	100	100
Sodium alginate	500	1000	-	-
HPMC	-	-	500	1000

Evaluation of the Microspheres

The developed microspheres have been evaluated for a number of factors, including yield, particle size, drug entrapment effectiveness, assessment of the drug in vitro, and the impact of various formulation and process variables, including drug to polymer ratio, polymer type, speed, and polymer combination.

A. The yield of Microspheres

The yield of microspheres was determined by dividing the quantity of microspheres produced by the total quantity of non-volatile components.

$$\% \text{ Yield} = \frac{\text{Actual weight of the Microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

B. Size and shape of the particle

Optical microscopy was used to measure the microspheres' particle sizes. Using a stage micrometer, the ocular micrometer was calibrated, and the calibration factor was then used to the computation of microsphere size. The microspheres were used with an ocular micrometer to see them under an optical microscope after being finely dispersed on a slide. A sample of around fifty readings was randomly selected, and the mean ± standard deviation was computed. With the use of a binocular microscope, the Microspheres' form was seen and pictures were visualized.

C. Microsphere surface morphology
A scanning electron microscope (SEM) was used to examine the Microspheres' surface morphology.

D. The drug entrapment efficiency (DEE)

By repeatedly extracting the drug with aliquots of 7.4 pH buffer and crushing 50 mg of Microspheres using a crusher and pestle, the amount of drug entrapped was calculated. After the extract was moved into a 100 ml volumetric flask, 7.4 pH buffer was used to adjust the volume. After being put in a beaker, the solution was sonicated for two hours in a

bath sonicator. Following adequate dilutions, the solution was filtered, and absorbance was measured spectrophotometrically at 280 nm against a suitable blank.

The following calculation was used to determine how much medication was entrapped in the microspheres.

$$DEE = \frac{\text{The amount of drug actually present}}{\text{The theoretical drug load expected}} \times 100$$

E. Investigation of drug release in vitro

All formulations were subjected to in vitro pharmacological testing using Franz diffusion cells. To maintain sink conditions, microspheres containing 10 mg of miconazole were added to 1 ml aliquots, which were then removed at prearranged intervals and replaced with an equal volume of dissolving media. The 7.4 pH buffer was used to make the requisite dilutions, and the solution was then spectrophotometrically examined at 280 nm using a UV-Visible spectrophotometer (Lab India) against a suitable blank to determine the drug concentration. Every formulation was tested three times. To examine the drug pattern, the cumulative proportion of drugs was computed and plotted against the function of time.

F. Studies of stability

Stability studies are the sole way to assess if a formulation is successful. For a duration of three months, the produced Miconazole Microspheres were kept at ambient temperatures, such as room temperature (40±2oC) and refrigerator temperature (2–8oC), on plastic tubes that included desiccant.

4. THE RESULTS AND DISCUSSION:

Four formulations with varying polymer concentrations were made for this investigation and assessed for stability, in vitro release, and physic-chemical characteristics.

The preformulation studies

a) The organoleptic evaluation

Table:- 4.1. The organoleptic properties of Miconazole

Properties	Results
State	Powder
Taste	tasteless
Odor	Odorless
Color	White

b) Determination of the melting point

Miconazole's melting point was discovered to be between 159 and 1630 °C, which is consistent with the standard and suggests that the medication sample was pure.

c) Solubility of the formulation

It has been determined that miconazole is soluble in water, methanol, and ethanol as well as DMSO.

Preparing a Miconazole standard curve

Miconazole's standard curve has been developed by graphing the absorbance V/s concentration at 280 nm. using a pH 7.4 solution that was produced at 280 nm. It also complies with Beer's law. The value of R 2 is 0.998.

Table-: 4.2. Miconazole calibration curve in 7.4 phosphate buffer

S. No	Concentration (µg/ml)	Absorbance
1	10	0.128
2	20	0.226
3	30	0.332
4	40	0.452
5	50	0.561

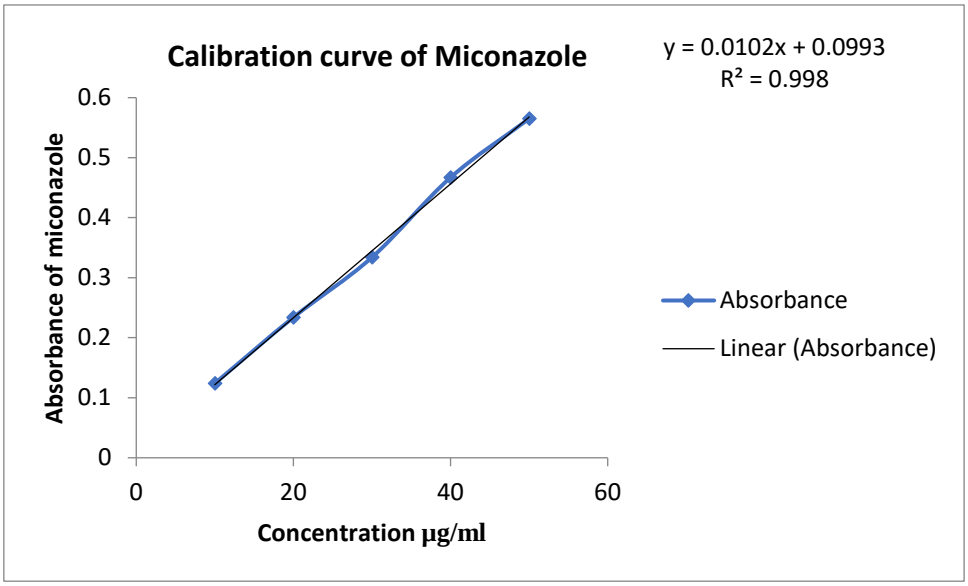

Fig-: Calibration curve of Miconazole

Studies on the drug-excipient compatibility (FT-IR)

Using the FTIR peak matching approach, the drug's compatibility with the chosen lipid and other excipients was assessed. The drug-lipid combination did not exhibit any peaks that appeared or vanished, indicating that there was no chemical interaction between the drug, lipid, and other substances.

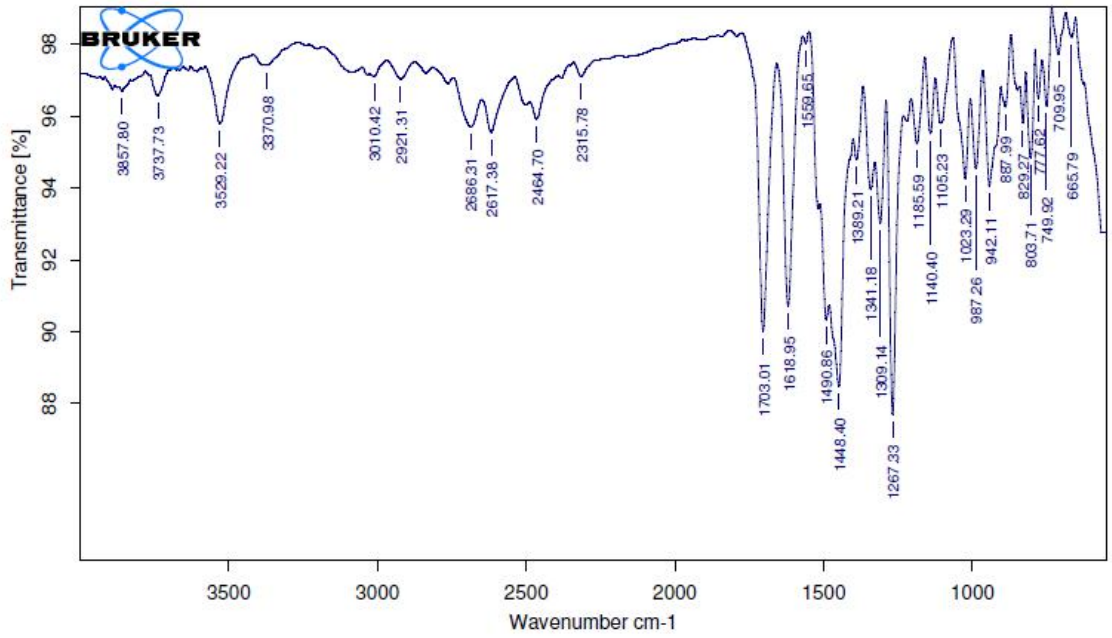

Fig-: The FT-IR Sample for Miconazole

Table-: 4.3. the characteristic Peaks and frequency of Miconazole

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	3887-3737	3500
2	OH Bending	2342-2421	2100
3	C-H stretching	2464-2315	2500
4	C-N stretching	1750-1653	1650

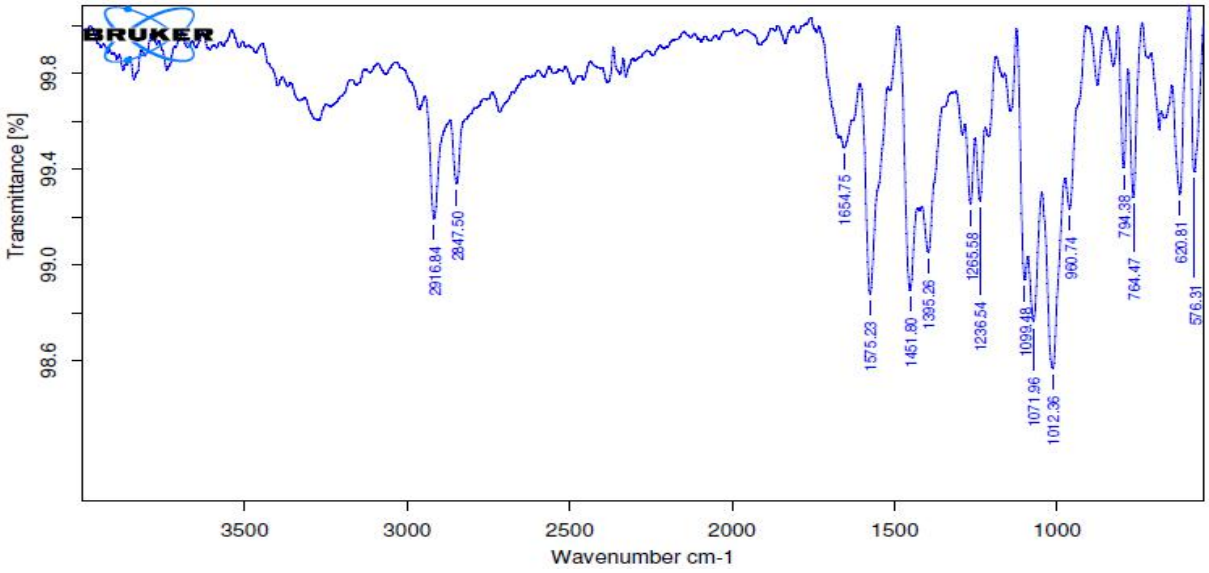

Fig-: The FT-IR Sample for Optimized Formulation

Table-: 4.4. The characteristic Peaks and frequency of Mixture

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	2916-2847	3000
2	OH Bending	1575-1421	1500
3	C-N stretching	1395-1236	1600

Developing and Assessing Sustained Release Miconazole microspheres

Formulation variable optimization

Consequently, the following were the ideal circumstances for the development of sustained release microspheres:

The results of the sustained release microspheres' formulation assessment parameters

The manufactured sustained release microspheres were assessed based on a number of factors, including in vitro drug release, yield, and drug entrapment efficiency. Additionally, the effects of process and preparation variables on particle size, yield, entrapment effectiveness, and in vitro release of miconazole from sustained microspheres were investigated. These variables included drug polymer ratio, speed, type of polymer, and combination of polymers.

Microsphere Characterization

A. Scanning electron microscopy (SEM) surface topography:

the optimized microspheres at 100 and 1000 magnifications are shown in the SEM shot. SEM images revealed distinct, spherical microspheres. Additionally, SEM images demonstrated the presence of drug crystals on the microspheres'

surface, indicating that some of their surfaces were rough. The presence of unentrapped drug in the dispersion media might be the cause of the drug crystals on microspheres.

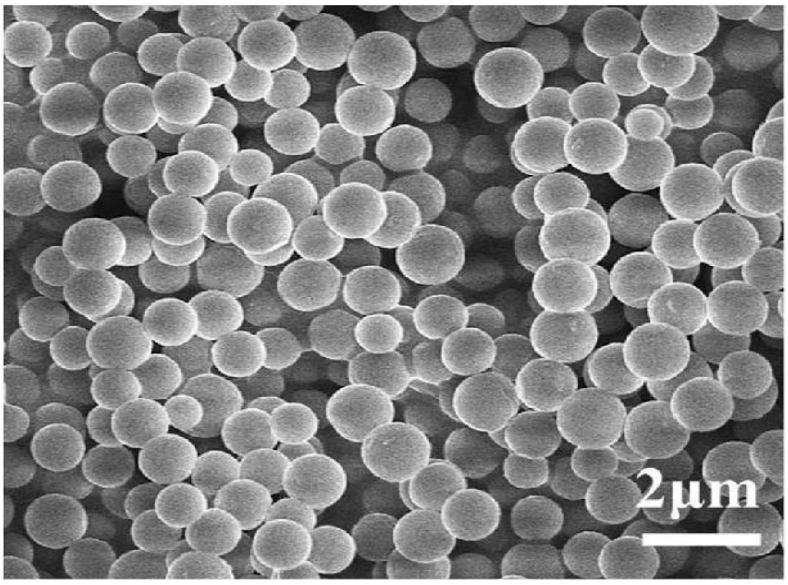

Fig-: SEM Analysis of Microsphere

Table-: 4.5. The evaluation parameters of microspheres

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	64.23	140.7	91.8
F2	69.37	142.8	87.5
F3	70.25	139.6	86.7
F4	68.67	147.4	84.2

In vitro drug release studies

Table-: 4.6. The cumulative % drug release

TIME (Hours)	F1	F 2	F3	F4
0	0	0	0	0
1	14.52	14.22	13.16	12.25
2	26.32	24.70	26.98	36.40
3	36.25	39.86	45.86	48.55
4	49.85	47.96	52.68	58.75
5	58.35	59.45	67.85	68.38
6	68.56	70.25	71.25	74.86

7	80.95	81.26	80.45	84.32
8	95.60	94.80	94.60	92.45

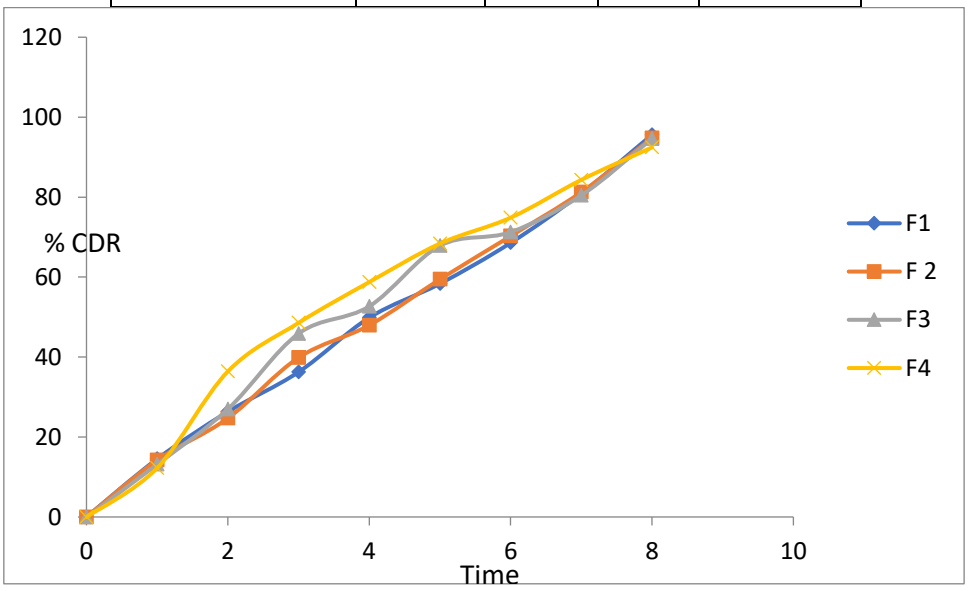

Fig-: The cumulative percentage drug released Vs Time Curves of microspheres F1–F 4 in P^H 7.4 buffer.

Here, the interaction between the disperse phase and dispersion medium, which impacts the size distribution of the particle, is influenced by maintaining a constant drug ratio and varying the polymer ratio as the polymer concentration increases viscosity. Furthermore, when compared to other formulations, the F1 formulation performs well.

In conclusion, the graph above suggests that the F1 formulation's drug release percentage exhibits superior drug release in comparison to other formulations.

Study of Stability

After three months, the formulation F-1's chemical and physical characteristics did not significantly alter. Displayed were parameters measured at different time periods.

Table-: 4.7. The results of stability studies of optimized formulation F-1

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-1	**25^0C/60%RH % Release**	95.60	95.55	94.85	93.99	**Not less than 85 %**
F-1	**30^0C/75% RH % Release**	95.60	95.52	94.82	93.57	**Not less than 85 %**
F-1	**40^0C/75% RH % Release**	95.60	95.50	94.80	93.50	**Not less than 85 %**

5. CONCLUSION :

A novel approach of medication administration, miconazole It functions as an antifungal. The treatment of fungal infections involves its use. It is put into microspheres made of polymeric materials, such as tragacanth and sodium alginate, to create polymeric microspheres that decrease GI side effects and improve the drug's controlled and targeted bioavailability. Using the ionotropic gelation procedure, microspheres with miconazole as the core material were created. Microspheres had a good yield and trapping efficiency. The kind of polymer, polymer concentration, stirring speed, and polymer mixture all affected particle size, entrapment efficiency, and manufacturing yield. Various polymer compositions designed for in vitro dissolution at pH 7.4 are releasing the drug up to 8hrs. F1 formulation is considered to be the most optimized one with high concentration of sodium alginate.

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