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Developing and Analyzing Polymeric Microparticles with Agomelatine-loaded Mesoporous Silica Nanoparticles for Controlled Drug Delivery

Praveena R.[1], Mitali Danu[2], Jeevan M. Ghormade[3],Shalini K. S.[4], Vijay Dhondiram Wagh[5],Suhas Narayan Sakarkar[6], Bhavesh Akbari[7], Nazim Uddin[8*]

[1]Associate Professor, QCPRL-CRF/chemistry, Bannari Amman Institute of Technology, Sathyamangalam, Erode, 638401, Tamil Nadu, India

[2]Assistant Professor, Amrapali University, Nainital, Uttarakhand, 263139, India

[3]Professor, Pharmaceutics, Dr. Rajendra Gode College of Pharmacy, Amravati - 444602, Maharashtra, India

[4]Associate Professor, Department of Chemistry, Maharani Cluster University, Palace Road, Bengaluru - 560001, Karnataka, India

[5]Professor and Principal, NGSPMs College of Pharmacy, Nashik, Maharashtra, 422 213, India

[6]Professor, Maharashtra Institute of Pharmacy BetalaBramhapuri,mChandrapur, Maharashtra, 441206, India

[7]Principal & Professor,School of Pharmacy,P P Savani University, Nr. Biltech, Dhamdod, Kosamba, Surat- 394125, Gujarat, India

[8]Research Scholar, Chandigarh University, Mohali, Punjab, 140413, India

***Corresponding author:**Nazim Uddin,Research Scholar, Chandigarh University, Mohali, Punjab, 140413, India

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ABSTRACT

An effective method to enhance the solubility of a medicine is by utilizing mesoporous silica nanoparticles, which transform the drug's crystalline structure into an amorphous state.The solvent impregnation method was used to add the drug. As independent variables, tetraethyl orthosilicate, CTAB, and NaOH 2 M were chosen to see how they affected the dependent variable. Agomelatine, a medicine, was enclosed in mesoporous silica nanoparticles. Then, using a method called double emulsification liquid evaporation, these nanoparticles were mixed into ethyl cellulose polymeric microparticles. The improved mesoporous silica nanoparticles had a mean particle size in the nanometer range, a low polydispersity index (PDI), and a zeta potential that was good. FE-SEM, DSC, and XRD were used to test the improved mesoporous silica nanoparticles. The polymeric microparticles were tested for drug release in vitro, looked at under a microscope, and their sizes were measured. The microparticles made of polymers had a regression coefficient (R2) of 2 and behaved according to the Higuchi model. They released 16% of their mass in a burst and then kept releasing over 10 hours.The polymeric microparticles with mesoporous silica nanoparticles loaded with agomelatine were made to make the drug more bioavailable when taken by mouth and to control how fast it releases.

Keywords: Mesoporous silica, nanoparticles, controlled release, polymeric microparticles.

INTRODUCTION:

At the moment, most drugs are taken by mouth because they are easier for patients to take and cost less to make. To meet the goals of being available in the therapeutic range at the target area and having a pharmacological effect, the drug needs to be able to dissolve in the right amount before it is absorbed [1-3]. Many of the drugs that are brought to market through fast drug development and finding don't dissolve well in water, according to reports. This makes them less bioavailable and makes it harder for them to reach a steady concentration in the bloodstream. Medications that don't dissolve well in water can be made to dissolve better in a number of different ways. In these ways, different types of a substance are used, solid mixtures are made, molecules are bound together, crystalline products are made, and a self-emulsifying system is used [2-4].

Nanoparticles of mesoporous silica (MSN) are a good way to make drugs that don't dissolve easily dissolve better. MSN can change a medicine from a solid form to an amorphous form. As the name suggests, mesoporous silica is an inorganic material with well-organized structures that lets pore sizes be changed from 2 to 100 nm [3-5]. Surfactants from different forms of silica, like sodium silicate, TMOS, and tetraethyl orthosilicate, are used to make this substance. The silica species goes through polycondensation while it is being made. Mesoporous silica nanoparticles are very popular in nanotechnology right now because they have unique properties like a large surface area, whole sizes that can be changed, and the ability to withstand high temperatures, changing pH levels, and chemical breakdown [4-6].

Mesoporous silica nanoparticles have a large surface area that lets different medicinal chemicals and functional groups stick to them. The drugs in mesoporous silica nanoparticles don't crystallize because they have an irregular structure. This makes them easier to dissolve. The current study project's goal is to make agomelatine more bioavailable and better at dissolving by creating a controlled release formulation [5-7]. To do this, agomelatine will be mixed into polymeric microparticles that have mesoporous silica nanoparticles inside them. We used polymeric microparticles with agomelatine-loaded mesoporous silica nanoparticles to study how drugs for depression are released in a controlled way [6-8]. These were used as part of a statistical scheme. After that, the nanoparticles were tested by measuring their particle size and how well they released drugs in a controlled setting.

MATERIAL AND METHODS:

Materials:

A free taste of agomelatine was given out by the company. Sodium hydroxide, cellulose, and CTAB were all provided by Loba ChemiePvt. Ltd. Everywhere else in the study, only analytical-grade chemicals were used.

Methods Preparation of MSN:

With a few changes, the sol-gel method was used to make the best lot of mesoporous silica nanoparticles. The silica source is broken down and condensed in the sol-gel process, which is also called the chemical solution coating method. During this step, CTAB was mixed with milli-Q water, and a 2 M NaOH solution was used to raise the pH of the resulting alkaline solution. Following its transfer to a round-bottom flask, the solution was kept at 80°C for 30 minutes. To make a mix of nanoparticles, TEOS was slowly added to the solution that was already mentioned. The mixture was then stirred constantly for two hours at an 80°C temperature [7-9].

Loading of a drug into MSN:

A solvent impregnation method was used to get a medicine into the holes of mesoporous

silica nanoparticles. After measuring out 25 mg of agomelatine, it was mixed with 25 mL of ethanol. In a hot air oven, the mesoporous silica nanoparticles were cooked to 120°C for one hour. After that, mesoporous silica nanoparticles were added to an ethanolic solution of agomelatine and stirred around at a speed of 180 revolutions per minute. After 1, 3, 8, 15, 24, and 72 hours, 50 milliliters of distilled water were added to the mix each time. A vacuum filter was used to separate the solution into mesoporous silica nanoparticles, which were then washed with pure water. In addition, a vacuum desiccator was used to dry out the leftover substance [8-10].

Experimental Design:

The Box-Behnken design was used to make the mesoporous silica nanoparticles' features better. The statistical and experimental analysis was done with the Box-Behnken design in Design Expert program. The trial design was made using the Box-Behnken method. We used the processes of TEOS (A1), CTAB (A2), and NaOH 2 M (A3) to find out the particle size (B1), PDI (B2), zeta potential (B3), and entrapment efficiency percentage (B4). Based on the statistical design shown in Table 1, 9 batches should be used, with 3 center points in each block for each batch [9-11].

Table 1: Statistical design for the formulation of batch codes and factor quantities

Batches	TEOS (A1)	CTAB(A2)	NaOH2 (A3)
B1	5.00	500	2..5
B2	2.5	500	5.0
B3	5.00	350	3.50
B4	3.50	350	4.00
B5	5.00	600	3.50
B6	3.50	300	3.50
B7	3.50	300	3.50
B8	3.50	600	5.00
B9	2.5	400	3.50

Polymeric microparticles Preparation:

We made polymeric microparticles with agomelatine-loaded mesoporous silica nanoparticles using the twofold emulsification liquid evaporation method. Table 2 shows the steps that were taken to make the batches of polymeric microparticles. By soaking the cellulose in dichloromethane, a solution was made of ethyl cellulose and mesoporous silica nanoparticles that were loaded with agomelatine. The earlier mentioned polymeric slurry was added drop by drop to a PVA solution in order to get rid of the dichloromethane. Then, a homogenizer was used to mix it well for about five minutes, and a magnetic mixer was used to stir it all night. In addition, the microparticles were made by centrifuging the sample at 2800 spins per minute for about 15 minutes. After that, they were freeze-dried and cleaned three times with water to get rid of any remaining PVA. To keep the agomelatine-loaded mesoporous silica nanoparticles in a dried polymeric microparticle form for future study, they were kept at a temperature range of 2 to 8°C [10].

Table 2: Formulation's excipient quantities and batch code

S. No	Batches	Excipients	
		Ethyl	PVA

		Cellulose(mg)	(mL)
1.	F1	200	100
2.	F2	300	100
3.	F3	400	100

Evaluation:

Evaluation of MSN:

We used polarizing and field emission-scanning electron microscopy to look at the shape of the improved mesoporous silica nanoparticles. Several methods were used to study the improved mesoporous silica nanoparticles, such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), zeta potential measurement, entrapment efficiency determination, mean particle size determination, and polydispersibility index measurement [11].

Particle size, PDI, and zeta potential:

We used the Horiba SZ-100 particle size analyzer to find out the zeta potential, polydispersibility index, and hydrodynamic particle size of the best amounts of agomelatine-loaded mesoporous silica nanoparticles. The dynamic light scattering method was used to figure out the particle size. The scattering angle was set to 90°, and the temperature was kept at 25°C. The cup holder was 25°C hot or cold. The zeta potential of the improved agomelatine-loaded mesoporous silica nanoparticles was used to test how stable the nanoparticle solution was [12].

DSC analysis of MSN:

We used differential scanning calorimetry to do their work, and indium was used to calibrate the instrument. The materials that were looked at included the drug itself, CTAB, a physical mixture, mesoporous silica nanoparticles that had been optimized, and mesoporous silica nanoparticles that had agomelatine loaded on them. A standard-quality metal pan was filled with a sample that weighed between 3 and 6 mg, and the lid was then crimped shut. A thermogram was made of the samples by scanning them at a rate of 20°C/min over a temperature range of 50°C to 300°C [13].

% Entrapment efficiencyand drug loading:

We were able to measure how well the sample was entrapped and how much drug was loaded into the holes of mesoporous silica nanoparticles by mixing it with 5 ml of ethanol and leaving it alone for 24 hours. A solution that had been spread out was also centrifuged, and the liquid that came out on top of the sediment was measured using a UV spectrophotometer to find its wavelength of 229 nm. How many lots of mesoporous silica nanoparticles have been fine-tuned for entrapment [14].

Agomelatine-loaded mesoporous silica nanoparticle polymeric microparticle evaluation

Determination of particle of microparticles:

The Malvern Mastersizer was used to measure the particle size of polymeric microparticles that contained agomelatine-loaded mesoporous silica nanoparticles. To find out the size of polymeric microparticles that contain agomelatine-loaded mesoporous silica nanoparticles, milli-Q water was used to make a good suspension of the microparticles [15].

Morphological evaluation:
The Malvern Mastersizer was used to measure the particle size of polymeric microparticles that contained agomelatine-loaded mesoporous silica nanoparticles. To find out the size of polymeric microparticles that contain agomelatine-loaded mesoporous silica nanoparticles, milli-Q water was used to make a good suspension of the microparticles [16].

In-vitro drug release:
Using a low-pressure ultrafiltration method with a stirred cell ultrafiltration machine and a polyethersulfone ultrafiltration membrane on its base plate, pharmaceuticals were freed from polymeric microparticles in a lab setting. A certain number of polymeric microparticles carrying a release medium were added to a cell that was being stirred at a speed of 100 turns per minute. It was possible to get samples by slowly adding nitrogen at a low pressure to a stirred cell at set times. In order to keep the sink state, 5 ml of aliquots were taken out and replaced with the same amount of fresh medium. A UV spectrophotometer set to a frequency of 229 nm was used to look at the sample and figure out how much drug was released [17].

RESULTS AND DISCUSSION:
Optimization of MSN:
The experiment results were put through statistical analysis with design expert tools to figure out what properties the final formulation should have. TEOS, CTAB, and NaOH 2 M were some of the independent factors that were optimized. These factors had ranges of 3–6 mL, 300–500 mg, and 2.5 mL, in that order. The smallest particle size, the lowest polydispersity index (PDI), the needed zeta potential, and the entrapment efficiency were chosen as the response parameters for evaluation. The design expert program came up with a lot of different ideas, all of which were good in their own way. The best formulation was chosen as the one with the highest draw, which was 0.778. After that, mesoporous silica nanoparticles filled with agomelatine were made. It was established that the given design's entrapment efficiency followed the quadratic model. On the other hand, the particle size, PDI, and zeta potential followed the linear model. Real numbers were used to make a polynomial equation that showed how the formulation factors were connected (see figure 1) [18].

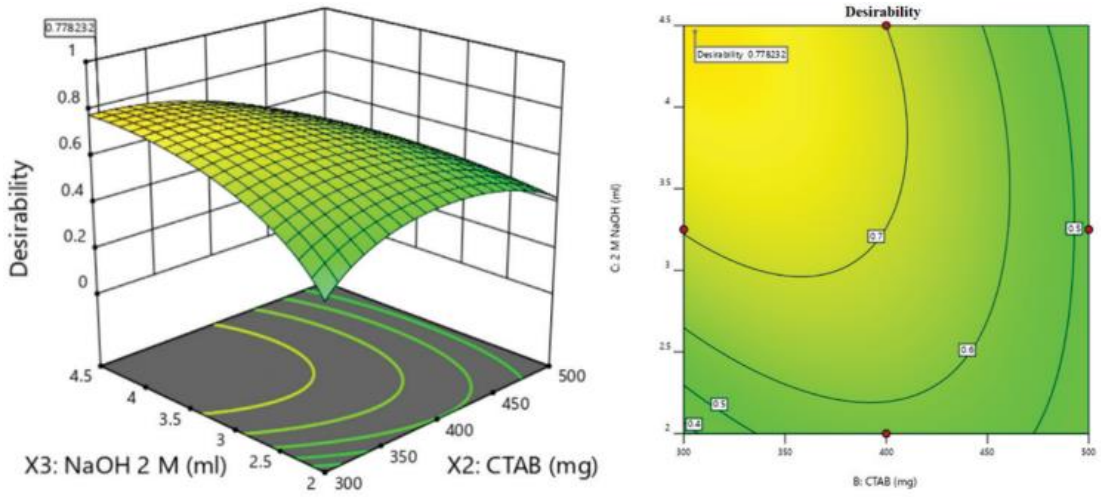


Figure 1:The MSN's response surface and contour plot

The reaction surface graph shows that the size of mesoporous silica nanoparticles is negatively related to the concentration of CTAB. This means that as the concentration of

CTAB goes up, the size of the nanoparticles goes down. The graph also shows that there is a positive relationship between the concentration of TEOS and the size of the nanoparticles. This means that as the concentration of TEOS rises, so does the size of the nanoparticles. CTAB stops particles from sticking together and makes a covering layer on their surface, which lowers surface energy and stops particles from touching each other. This is very important for making particles smaller. Because CTAB is a quaternary ammonium surfactant with a positive surface charge, its zeta potential goes up as its content goes up. On the other hand, because TEOS and NaOH have negative charges, the zeta potential goes down as their amounts rise. This shows how long the mesoporous silica nanoparticles will stay spread out. To fit the drug inside the holes of mesoporous silica nanoparticles, they need to have a large surface area [19].

Zeta potential, polydispersibility index, and particle size:

The polydispersibility index and zeta potential of particle size are very important for how particles stick together and interact with each other during cellular absorption. We found that the best mesoporous silica nanoparticles were 168.2 nm in size and had a particle density index of 0.358. The improved mesoporous silica nanoparticles were very stable, as shown by the 42.5 mV zeta potential, which also shows that the suspension is stable. Figure 2 is a graph that shows the tailored mesoporous silica nanoparticles and how big each one is. Notes are written down in Table 3 [20].

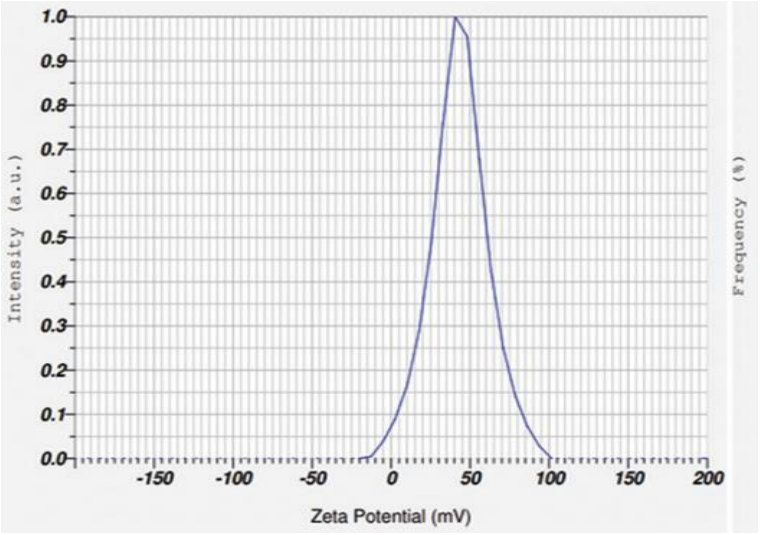


Figure 2: Particle size analysis of the formulation

Table 3: Measured response of statistical design

Batches	Particlesize(A1)	PDI (A2)	ZP(A3)	EE%(A4)
B1	470.4±0.82	0.413	45.25	44.12±0.15
B2	248.0±0.71	0.437	42.46	76.00±0.08
B3	549.2±0.61	0.568	36.82	40.72±0.13
B4	205.4±0.61	0.431	41.72	55.34±0.86
B5	340.1±0.80	0.389	45.85	65.22±0.46
B6	380.5±0.40	0.375	43.96	65.33±0.44
B7	380.5±0.42	0.362	42.34	65.33±0.22
B8	306.6±0.63	0.388	48.78	48.60±0.34
B9	107.6±0.32	0.301	38.13	59.23±0.14

Entrapment efficiency % and loading of drug:
High drug molecule loading capacity and high entrapment rate are two good things about mesoporous silica nanoparticles. The mesoporous silica nanoparticles that were loaded with agomelatine had an entrapment efficiency of 76.00% and a drug loading of 44.12%, as shown in Table 3.

DSC study of optimized mesoporous silica nanoparticles:
We did a DSC study on the pure drug sample, CTAB, physical mixture, optimized mesoporous silica nanoparticles, and agomelatine-loaded mesoporous silica nanoparticles to find out whether they were crystalline or amorphous. The DSC test on the pure drug sample shows that the drug powder is there in its crystal form. The fact that an endothermic peak was seen at 107°C, which is the drug's melting point, shows this. There is a clear, sharp rise in both the physical combination and CTAB. In the differential scanning calorimetry (DSC) test, the mesoporous silica nanoparticles don't show any peaks. The medicine was enclosed in the mesoporous silica nanoparticles, which could be seen because the particles that contained agomelatine did not have a solid peak. So, the DSC thermograph didn't show an endothermic peak. This suggests that the drug-loaded mesoporous silica nanoparticles in Figure 3 were not crystalline agomelatine but rather amorphous agomelatine [21-24].

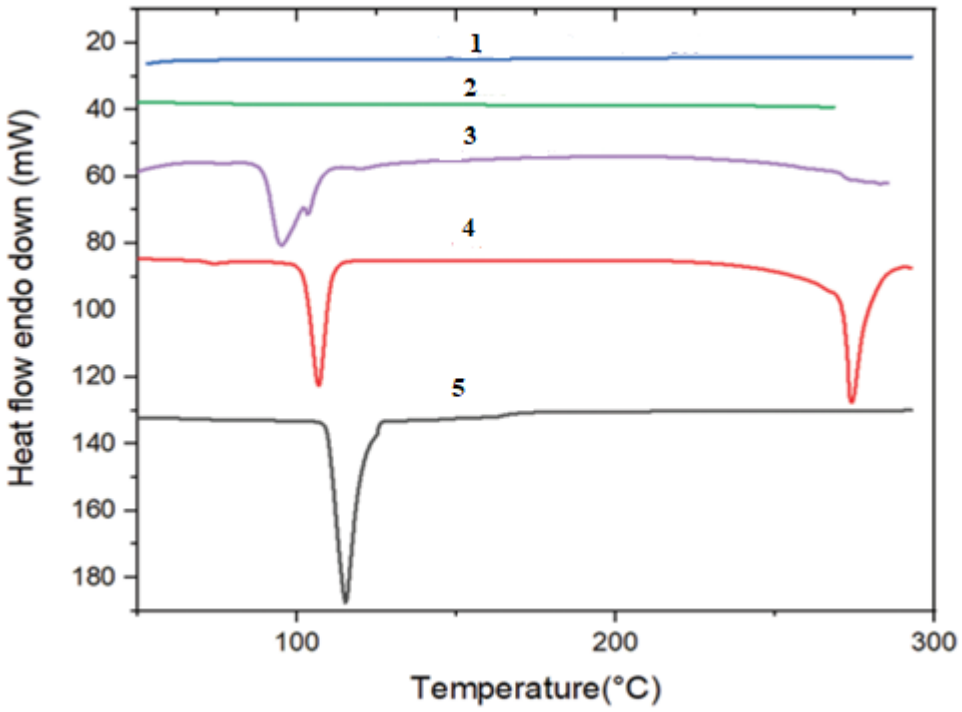


Figure 3: DSC analysis overlay 1: Agomelatine loaded MSN 2: MSN 3: Mixture 4: CTAB 5: Agomelatine

Particle size and PDI of polymeric microparticles:
The Malvern Mastersizer was used to measure the particle size of the polymeric microparticles that contained agomelatine-loaded mesoporous silica nanoparticles. It was found that the particle sizes in all three groups were between 30 and 75 µm. The amount of ethyl cellulose used to make polymeric microparticles has a direct effect on how big they are. It makes the polymeric film layer bigger when the concentration of ethyl cellulose goes up. This makes the microparticles bigger. Table 4 shows the particle sizes of the polymeric microparticles made up of mesoporous silica nanoparticles that have agomelatine placed on

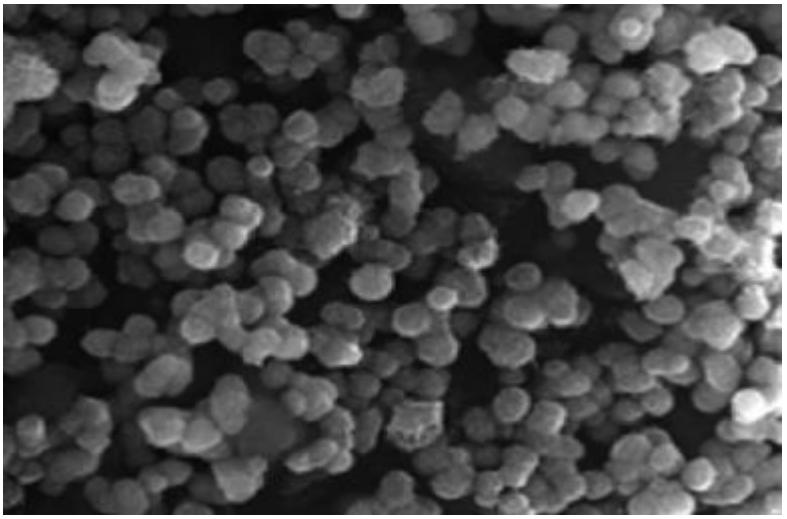
them [25-29].

Table 4: Formulation batch code and polymeric microparticle size

S. No	Batches	Particlesize
1.	F1	32.538
2.	F2	58.579
3.	F3	61.486

Morphological of polymeric microparticles:

The FE-SEM picture shows that the optimized mesoporous silica nanoparticles are spread out evenly in the form of circles. Mesoporous silica nanoparticles are easy to spot because they have this round form. These tiny things are between 80 and 265 nm in size. The polarized microscope method was used to find out what the shape of the polymeric microparticles was. In the microparticle picture (figure 4), there are no crystals and the surface is smooth. This suggests that the optimized agomelatine-loaded mesoporous silica nanoparticles are fully integrated into the polymeric microparticles [30-35].



Figures 4:Morphological of polymeric microparticles

In vitro drug release:

A phosphate buffer solution with a pH of 7.4 was used to release drug-filled polymeric microparticles in a lab setting. How the polymeric microparticles with agomelatine-loaded mesoporous silica nanoparticles released their drugs was affected by how much ethyl cellulose was present. When the quantity of ethyl cellulose goes up, the rate at which polymeric microparticles leak goes down. If you raise the quantity of ethyl cellulose from F1 to F3, the rate of release goes down over time. We looked into how polymeric microparticles containing agomelatine-filled mesoporous silica nanoparticles released drugs in a lab setting. The graph made it possible to look at how quickly the drugs were released from the polymeric microparticles that were made. The formula shows a fast release at first, followed by a steady release pattern. This means that F3's regression coefficient and release rate constant are in line with the Higuchi model. In addition, it has the highest regression coefficient (0.9154) of all the release kinetics plots.

Table 5: Total percentage of polymeric microparticles released with drugs

Time (min)	% CDR (F1)	% CDR (F2)	% CDR (F3)
0	0	0	0
15	21.75±0.65	15.89±0.60	10.88±0.33
30	34.25±0.58	25.20±0.30	21.79±0.55
60	45.21±0.33	46.21±0.46	45.33±0.28
120	48.00±0.30	49.51±0.70	58.32±0.50
240	55.80±0.50	55.78±0.60	60.40±0.40
360	61.40±0.19	69.40±0.98	66.40±0.60
480	68.70±0.50	72.89±0.50	67.29±0.61
600	82.88±0.80	80.11±0.39	68.89±0.22

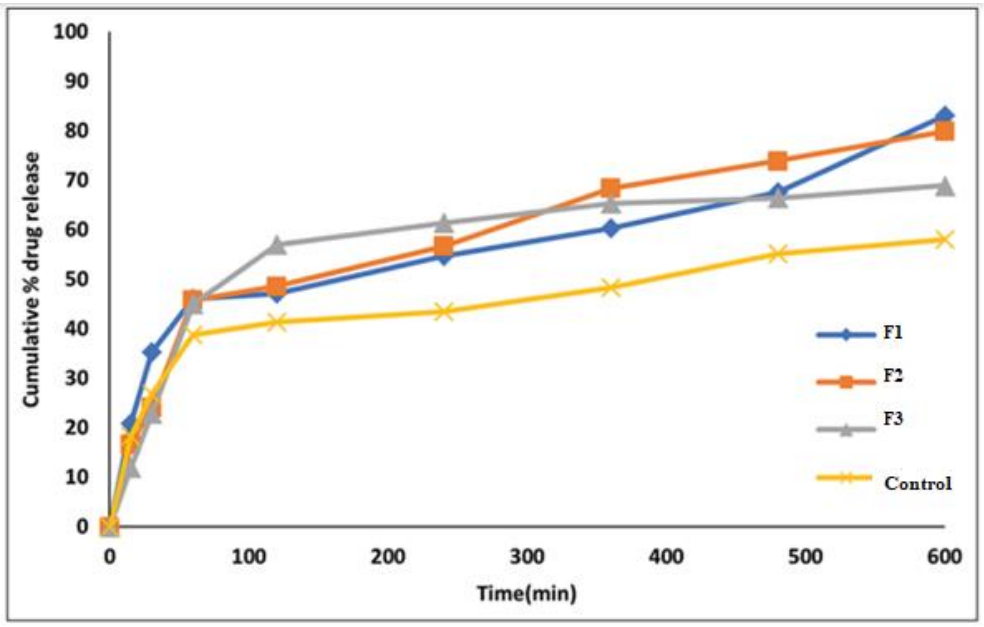


Figure 5: Drug release from polymeric microparticles *in-vitro*

CONCLUSION:

Mesoporous silica nanoparticles are popular in nanotechnology. Scientists created polymeric microparticles using mesoporous silica nanoparticles loaded with agomelatine to overcome its bioavailability and dissolution issues. Polymeric microparticles with mesoporous silica nanoparticles speed up medication release for depression treatment. Ethyl cellulose and PVA were used to make agomelatine-loaded mesoporous silica nanoparticle polymers. We examined polymeric microparticles for particle size, drug release in vitro, and microscopic examination. Polymeric microparticles release in two phases: burst and steady. According to the latest study, mesoporous silica nanoparticles coated with the medicine in polymeric microparticles can make agomelatine more accessible when taken orally. This will create a controlled drug release pattern, reducing the number of doses needed to treat long-term depression.

Funding:
None

Conflict of Interest:
None

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