JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

OFLOXACIN LOADED MICROSPHERES RECONSTITUTABLE SUSTAINED RELEASE SUSPENSIONS: FORMULATION AND EVALUATION

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ABSTRACT- Background: The objective of this work was to develop and evaluate controlled released reconstitutable suspensions of Ofloxacin loaded microspheres. **Results**: The resulting microspheres obtained from emulsion solvent diffusion method were with good % yield and mean particle size of microspheres ranged from 52.37±1.54µm to 72.45±1.44µm and the encapsulation efficiencies ranged from 83.53±1.42 to 95.25±2.04%. The encapsulation efficiency was also found to be dependent on amount of polymer used in the formulation. The FTIR and DSC spectra confirmed that Ofloxacin and the polymers used in the formulations have no interaction. The microspheres were porous, smooth, round, and somewhat aggregated, according to scanning electron microscopy. The sustaining impact of microspheres was shown to be dependent on the polymer concentration and amount of cross-linking agent utilised in the formulation, according to in-vitro dissolution investigations. The amount of xanthan gum in the suspension changed the volume of sedimentation and redispersibility. **Conclusion**: This study suggested that stable suspensions of Ofloxacin loaded microspheres could be formulated with 0.6 % W/V xanthan gum by the addition of 20% D-sorbitol.

KEYWORDS: Ofloxacin, microspheres, Suspension, Xanthan gum and D-sorbitol.

INTRODUCTION:

Per oral sustained or controlled release dose forms have been the focus of most of the research in creating innovative drug delivery methods. Multi-unit formulations, such as micro particles, have grown more common among oral dosage forms due to their benefits over single-unit dosage forms. They may be dispersed more regularly throughout the gastrointestinal tract because to their simplicity of ingesting and versatility in dosing calculation, resulting in more uniform drug absorption, decreased local discomfort, and optimal administration for paediatric and geriatric patients[1]. In addition to the classic form, sustained release suspensions can be created to cause prolonged action by attaining and sustaining a desirable blood drug concentration at a steady level for an acceptable period of time. A sustained release pharmaceutical delivery system's main purpose is to ensure patient safety while also enhancing drug efficiency and

decreasing dose frequency, resulting in greater patient compliance.[2] Traditional oral suspensions can be given right away, but an important class of oral solutions and suspensions that must be mixed before being given is more palatable and stable. These are dry mixes or syrups that must be diluted with water before being dispensed. When medication stability is a primary concern, reconstituted systems are the formulation of choice. These systems have acceptable drug stability during the shelf life after reconstitution. It also decreases the weight of the finished product by eliminating the aqueous carrier, potentially lowering shipping costs.[3]

METHODS

Preparation of Ofloxacin Microspheres [4]

Ofloxacin microspheres were made using the emulsion solvent diffusion approach. Table 1 shows the medication to carrier ratios for various formulations. At room temperature, 500 mg of Ofloxacin was weighed and dissolved in a small amount of dichloromethane, and the polymer, Ethyl cellulose, was added to the drug solution. Using a mechanical stirrer with a four-blade "butterfly" propeller, this mixture was prepared to 200ml of water that contains 0.5 percent surfactant (PVA) and spun continuously at 900 rpm for 6 hours until the dichloromethane was completely evaporated. The resulting microspheres were vacuum filtered before being rinsed four times with distilled water to remove any non-encapsulated drugs and excess PVA. Microspheres were recovered and dried at 500°C for 6 hours before being kept in desiccators. The parameters utilised were as follows:

- Amount of Ofloxacin (500mg)
- Stirring speed (900 rpm)
- Time of stirring (6 hours)
- Concentration of PVA Solution (0.5%)
- Volume of PVA Solution (200ml)

Table 1 Formulations of Ofloxacin Microspheres

SI.NO	Ethyl Cellulose(mg)	Drug (Ofloxacin in mg)
OF_1	500	500
OF_2	1000	500
OF_3	1500	500

Preparation of Reconstitutable Suspensions

In the suspension formulations, xanthan gum was used as a dispersing agent. To improve palatability, D-sorbitol is now used as a polyol. D-sorbitol was added according to the geometric dilution method. Table no. 2 lists representative formulae for the manufacture of dry mixes. To produce the reconstituted suspension, 10ml of water was added in two stages to the dried suspended flour and blended with a spoon until it was homogenous.

Table 2 Compositions of reconstitutable suspensions containing Ofloxacin microspheres

Formulation Code	Microspheres (Each 5 ml contain 50 mg of Ofloxacin)	Xanthan gum (mg)	D-sorbitol (ml)	Citric acid (mg)	Sodium citrate (mg)	Sodium benzoate (mg)
SHM1	1000	150	2.5	360	180	50
SHM2	1000	150	3.75	360	180	50
SHM3	1000	150	5	360	180	50

Compatibility studies Compatibility studies were conducted using FTIR and DSC.

Fourier Transform Infra-Red Spectroscopy (FT-IR) [5]

The FT-IR spectroscopy of the unadulterated drug and drug additives combinations were acquired using an FTIR spectrophotometer (Shimadzu IR-345, Japan). 2–3 mg samples were mixed with 400 mg powdered potassium bromide and crushed at 10.000–15.000 pressure into transparent discs. With a resolution of 4 cm-1 and a sweeping range of 500–4000 cm-1, the IR spectra were recorded.

Differential Scanning Calorimetry (DSC) Analysis [6]

Thermal characteristics may be inferred from DSC data, which can be used to infer polymer structural morphology. The DSC analysis was utilised in this investigation to determine if the medication and chosen polymer components were compatible. For Ofloxacin and the physical combination of the formulation, DSC thermograms were obtained. Examples of 5 milligrams clear Ofloxacin and its physically mixtures with numerous adjuvants being properly sealed in flat top aluminium pans and warmed in the DSC instrument (Shimadzu, Japan) in a nitrogen atmosphere to eliminate the oxidative and pyrolytic effects. The heating rate was 50 C/min in a maximum temperature of 25–3000 C. The DSC thermograms were kept track of. Thermo grammes were acquired and analysed in order to ascertain the drug's and formulation's thermal transitions and Tgs.

Physico-Chemical characterization

Evaluation of Microspheres

Percentage yield [7]

Percentage Practical yield is computed to determine the percentage yield or efficiency of any process, which aids in the selection of the most appropriate production method. The weight of Ofloxacin microspheres recovered from each batch in respect to the total of starting material was used to determine practical yield. The following formula may be used to compute it:

The percentage yield can be calculated by using formula

$$\%\ \boldsymbol{yield} = \frac{\boldsymbol{Practical\ yeild}}{\boldsymbol{theortical\ yeild}} \times \mathbf{100}$$

Drug loading and encapsulation efficiency [7]

When it comes to release characteristics, drug loading is crucial. In general, increasing drug loading causes drug release to be accelerated. The fraction of the original quantity of drug that has been integrated into microspheres is known as drug entrapment efficiency. 10mg of Ofloxacin Assessing the microspheres and transferring them to a 10ml volumetric flask carrying one little quantity of methanol which was then filled with buffers to the desired volume. A U.V spectrophotometer was used to test the absorbance of 1 ml of solution was diluted to 10 ml using pH 1.2 & pH 7.4 buffers., respectively (Shimadzu 1800). The formula was used to compute the percent drug loading.

$$\%\ \boldsymbol{drug\ loading} = \frac{\boldsymbol{amount\ of\ drug\ in\ microspheres}}{\boldsymbol{number\ of\ microsphere}} \times \mathbf{100}$$

$$\boldsymbol{Entrapment\ efficiency\ (percentage)} = \frac{\boldsymbol{Real\ drug\ content}}{\boldsymbol{Calculated\ drug\ content}} \times \boldsymbol{100}$$

Particle size of microspheres [8]

The optical microscopic approach was used to conduct the size study. The average diameter was computed after the size distribution data was gathered using a calibrated eye piece micrometre. The microsphere was disseminated in liquid paraffin and viewed at a magnification of 10X under a microscope. Using a calibration factor, the sizes of 100 particles were calculated at random.

Surface Morphology [9]

It gives important details regarding the porosity and microstructure of these drug delivery devices. Scanning electron microscopy is the most common technique used (SEM). Because a vacuum field is required for image creation in SEM, the material prepared for this approach should be dried. To take a photomicrograph. The samples are therefore wrapped using electron dense protective coatings including gold, palladium, or a combination of the two. The surface can be sprayed via sputter coating or heated suction evaporation. Before photographing the findings, they set microsphere samples on aluminium stages and used a Hummer sputter coater to paint each using 10m of gold/palladium.

In-vitro drug release studies [10]

The standard USP dissolving technique was used to look into the discharge of Ofloxacin via microspheres in vitro.

The amount of microsphere corresponding to 100mg of Ofloxacin was put in a basket of dissolution test device containing 900ml of dissolution medium, pH 1.2 buffers solution, and the temperature was kept at 37°C with stirring at 50 rpm using a basket type apparatus. Dissolution proceeded in pH 7.4 after 2 hours. After each sampling, aliquots of 5ml were removed at predetermined intervals and an equal quantity of new medium was added to replace the withdrawn liquid. The disintegration lasted for 12 hours. By diluting the medication appropriately and the amount of pharmaceutical dispersed was determined by measuring the absorbance with a UV spectrophotometer. For each product, three trials were conducted, and an average value was computed.

EVALUATION OF SUSPENSION

Physical stability and redispersibility of suspension [11]

The physical stability of the formed suspension was determined by measuring the sedimentation volume. A 50ml graduated measuring cylinder was used to collect 50ml of each suspension. The suspension was dispersed by turning three times upside down. After allowing the suspension to settle and recording the amount of sediment, the cylinder was left undisturbed for 7 days. This is the first sample volume (i.e., Ho). The ultimate volume of sediment was calculated using the volume of sediment measured on the seventh day (i.e., Hu). The sedimentation volume F was calculated using the formula.

$$F = \frac{Hu}{Ho} \times 100$$

Where, Hu is the final volume of sediment.

Ho is the original sample volume

The suspension then permitted to stay in a measuring cylinder. To count the number of reversals necessary to re-establish a homogeneity suspension, the cylinder's opening was sealed and inverted 1800 times. If the homogeneity of the suspension could be attained with just one inversion, it was rated 100 percent easily redispersible. The proportion of ease of redispersibility reduces by 5% for each subsequent inversion.

Determination of drug content [12]

5 mL of produced solution containing 200 mg equivalent microspheres (50 mg Ofloxacin) was dissolved in 40 mL methanol and diluted to 100 mL using 1.2 pH buffers. This mixture was stirred for 1 hour to allow the medication to diffuse completely from the microspheres (stock-1). 5 mL stock-1 solution diluted to 100 mL with pH 1.2 buffers solution Polymers were removed using millipore filters with a pore size of 0.45m. The absorbance of Ofloxacin was measured using a UV-vis spectrophotometer to determine its content. Using pH 7.4 phosphate buffer solutions, a similar calculation was performed. It was determined how much Ofloxacin was used.

The assessment of pharmaceutical leaking via suspension microspheres [13]

The leaching of the medication in the surrounding medium is one of the most serious issues in the creation of pharmaceutical sustained release suspensions, upon preservation, a 0.5ml portion of the preparations was taken to test for pharmaceutical leaks via suspension spheres. After straining the portion and washing the microspheres in water to eliminate the suspension vehicle, they were dried in a

37°C oven for 24 hours. Methanol was used to dissolve dried microspheres. A spectrophotometer was used to determine the quantity of dissolved medication.

PH measurements [13]

On 0, 1, 7, and 14 days at 25° C Using a digital pH metre, the pH of the suspensions were monitored, accompanied to reconstituted for any and all formulations.

Rheological studies [13]

The Brookfield viscometer was used to determine the rheological characteristics of each formulation following reconstitution in terms of viscosity. All measurements were carried out with spindle LV 4 at a constant temperature of 25°C. At room temperature, the viscosity was tested on days 0, 1, 7, and 14

In-vitro drug release profile of sustained release suspension

A USP type II dissolving equipment was used to establish the in-vitro release profile of the selected batch of reconstituted suspension. 5ml of reconstituted suspension (corresponding to around 50mg Ofloxacin) was properly measured and placed in 900 ml of pH 1.2 buffers (37°0.5°C) and swirled at 50rpm for the first two hours, with the remaining dissolving test performed in pH 1. % Of medication released cumulatively vs. time (zero-order kinetic model). Phosphate buffers in the range of 7.4 After each sampling, At certain durations, 5ml stock solutions were withdrawn and refilled with a same quantity of fresh fluid. It took up to 10 hours for the disintegration to stop. A UV spectrophotometer was used to determine how much medication was dissolved.

Drug Release Kinetics (Kinetic Modelling)

A. Kinetics of release:

The following four models of data treatment were used to match the outcomes of in-vitro discharge profile analysis for all formulations:

- Proportion of medication released cumulatively vs. time (zero-order kinetic model).
- Chart the log cumulative proportion of medicine left vs. time. (This is a first-order kinetic model.)
- Higuchi's model: cumulative % pharmaceutical delivered vs. square root of time.
- Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation).
- Cubic root of cumulative percentage drug released versus time (Hixson & Crowell‟s cubic root).

Zero Order Kinetics [14]

It means a system where the dosage of a pharmaceutical has no effect on the pace at which it is released. A zero-order release would be predicted by the equation below.

$$\boldsymbol{At = Ao - Ko\,t}$$

Where: A_t = Drug release at time ‘t’

A_0 = Initial drug concentration

K 0 = Zero-order rate constant (hr. 1). The data follows zero-order release kinetics, with a slope equal to K0, when plotted as cumulative percent drug release vs time.

Kinetics of the First Order [15]

It addresses the release of drugs from systems where the rate of release is proportionate to the concentration. A first-order release would be predicted by the equation below.

$$\boldsymbol{logC = \frac{logCo - Kt}{2.303}}$$

Where,

C = Amount of drug remained at time 't'

C_0 = Initial amount of drug

K = First-order rate constant (hr^{-1}).

The data shows a linear model if represented as log cumulative percent pharmaceutical leftover vs. time, indicating that the release follows First-order kinetics. The constant "K" may be obtained by multiplying 2.303 with slope values.

Higuchi's Model [16, 17]

Higuchi's classical diffusion equation was used to describe drug release from matrix devices via diffusion.

$$\mathbf{Q} = \frac{D\varepsilon}{\tau}(2A - \varepsilon Cs)\, Cst$$

Where Q denotes the amount of medication released at a given time, and D = Drug's Diffusion Coefficient in the Matrix, C = Drug solubility in the diffusion medium, A = Total quantity of drug in unit volume of matrix ε = The matrix's porosity t = Time (hours) at which 'Q' amount of medication is released τ = Tortuosity If D, C, and A are assumed to be constants, Equation can be simplified. Equation then becomes:

$$Q = kt^{1/2}$$

When the data is plotted using equation (total drug released against square root of time), the result is a straight line, indicating that the medicine was released through diffusion. The slope corresponds to the letter 'K."

Korsmeyer-Peppas model (Power Law) [18]

When a polymeric system deviates from Fickian diffusion, the power law, as seen in the equation below, characterizes drug release.

$$\frac{Mt}{M\infty} = ktn$$

$$log\frac{Mt}{M\infty} = logk + n\, logt$$

Where Mt and M are cumulative quantities of drug release at time t and infinite time (i.e. fraction of drug release at time t), k = constant combining structural and geometrical properties of CR device, and n = diffusional release exponent indicative of drug dissolving process, and k = constant combining structural and geometrical properties of CR device To characterise the release process, the dissolution data Mt / M 0.6 is studied. The intercept of a plot of log Mt / M against log t will be the value of log k, and the slope will be n. The antilog of log k gives the value of k. Pepas used the n value to characterise various release mechanisms, as seen in the table below.

Table 3 Release mechanisms

'n'	mechanism
0.5	Fickian diffusion
0.5 < n >1	Non- Fickian diffusion
1	Class II transport

The cubic root law of dissolution proposed by Hixson and Crowell [19]

The Noyes-Whitney equation assumes that the surface area of the dissolving solid remains constant during the operation, which is extremely difficult for dissolve molecules. Dissolution techniques including the use of constant surface area discs are used to assess the rate of dissolution. To account for the drop in particle size and change in surface area that happens during dissolution, Hixson and Crowell's cubic root law of dissolution is used:

$$W_0^{1/3} - W^{1/3} = Kt$$

Stability studies [20]

Dosage form stability refers to a formulation's capacity to stay within its physical, chemical, therapeutic, and toxicological requirements when packaged in a certain container.

RESULTS AND DISCUSSION

To increase patient compliance and hide the severe bitter taste of Ofloxacin, microspheres of the drug were generated using the Emulsion solvent diffusion technique and several assessment criteria were tested. The reconstitutable suspensions, which were generated using previously manufactured Ofloxacin microspheres, were evaluated utilising size of the particles, microstructural, drug encapsulation ability, in-vitro release of drug investigations, and stabilization research.

Compatibility Studies on Drug Excipients

To find possible molecular interactions between the pure drug and additional additives in the formulation, Fourier Transform Infrared Spectroscopy (FT-IR) investigations were carried. Table 4 shows the unique maxima of drug and the physical mixture of polymeric material. As demonstrated in Figures 1 and 2, there is no significant difference in the FT-IR spectra of the physical combination when compared to the pure drug, demonstrating that the drug and the additives have no interaction.

Table 4: Major peaks of Ofloxacin in FTIR spectra

Sample code	C-F	C=O	C-N
Pure Drug	1396.73	1715.13	1288.47
Drug + Ethyl cellulose	1305.06	1710.12	1287.94

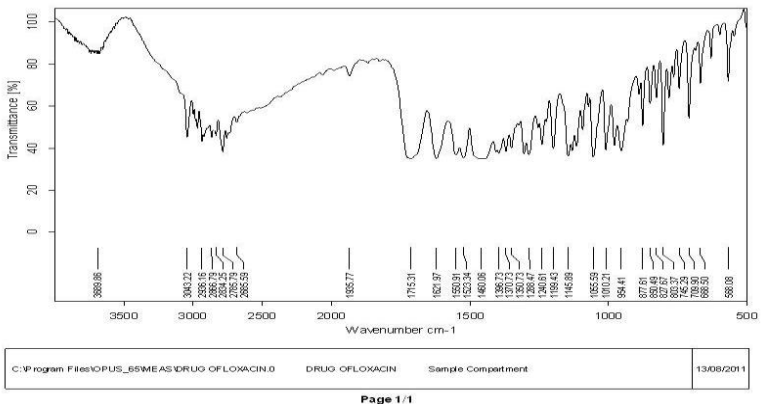


Figure 1: FT-IR Spectra of Pure Ofloxacin

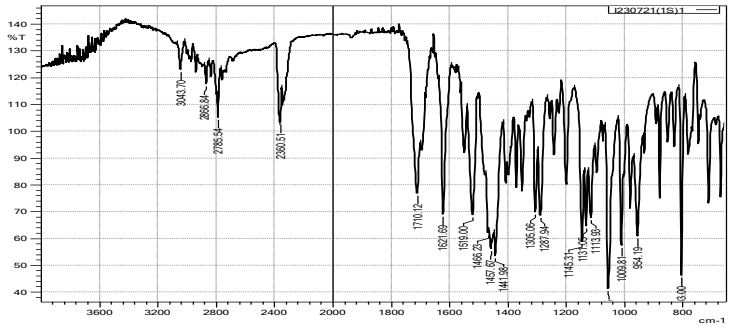


Figure 2: FT-IR Spectra of Ofloxacin + Ethyl cellulose

DSC Analysis (Differential Scanning Calorimetry)

The use of DSC in the study of solid-state interactions is beneficial. Figures 3 and 4 illustrate the DSC patterns of pure Ofloxacin and its physical combination with different excipients. At 278.71oC, pure Ofloxacin displayed a pronounced endothermic peak, matching to its melting point. When compared to pure medication, the melting endotherm of the formulation (275.520C) changed very little.

This observation backs up the IR spectroscopic findings, which showed no interaction between the medication and the additives employed in the formulations.

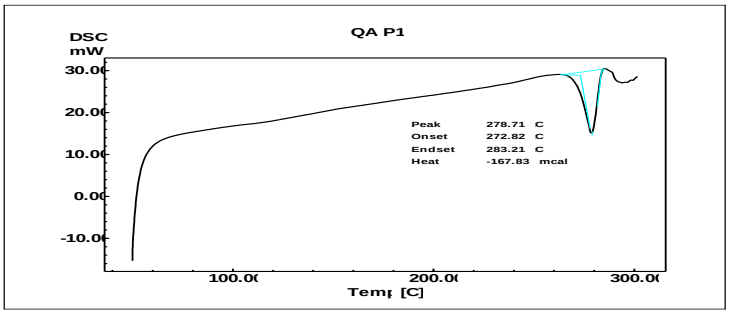


Figure 3: DSC of pure Ofloxacin

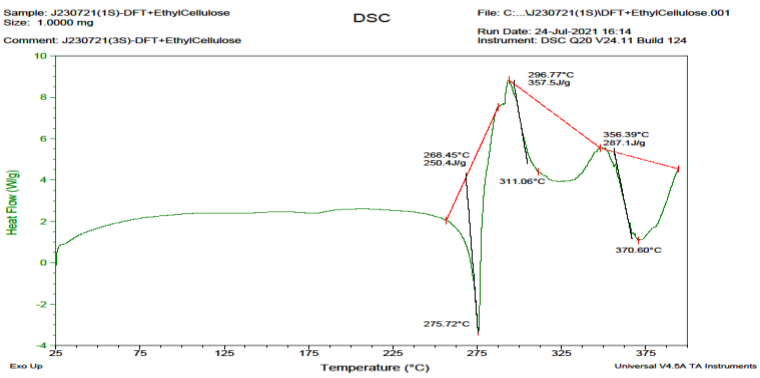


Figure 4: - DSC of reconstitutable suspension containing Ofloxacin loaded microsphere (SHM3)

FORMULATION OF OFLOXACIN MICROSPHERES

Ofloxacin belongs to the class-3 antibiotics (high solubility and low permeability). Ethyl cellulose (synthetic polymer) is a biocompatible hydrophobic polymer that helps water soluble and insoluble drugs stay longer in their matrix.

Dichloromethane was chosen as the organic solvent since it has a lesser toxic potential than other solvents and has no harmful effects on the body because it evaporates throughout the procedure. Emulsion solvent diffusion method and table was the right term for the method utilised. The experimental independent variables, such as polymer ratio, have been changed at various levels, as shown in Figure 5

OF1, OF2, and OF3 are the microspheres containing ethyl cellulose. Various factors were optimised to provide a decent output of discrete micro particles.

EVALUATION OF MICROSPHERES

Percentage yield:

As shown in Table 5 and Figure 1, the percentage yield ranged from 82.48 ±1.44 to 93.03±2.34 percent, and the yield was judged to be adequate in all formulations. 6.8. The formulation OF3 has the highest yield.

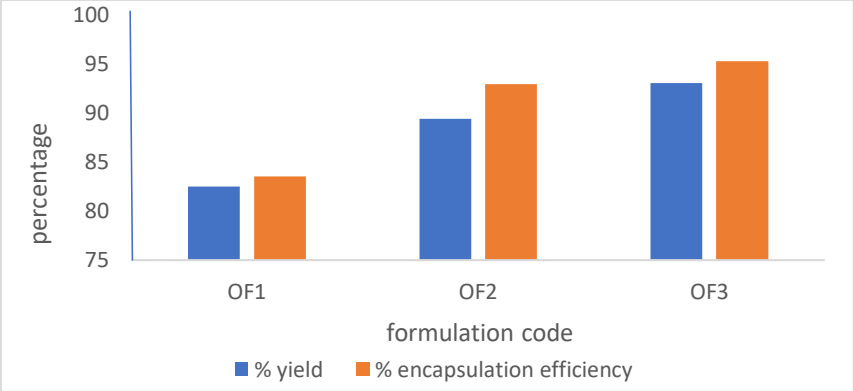
Drug Entrapment Efficiency:

The efficiency of trapping ranged from 83.53± 42 percent to 95.25±2.04%. (See Table 5 and Figure 5) Entrapment efficiency was also revealed to be affected by the nature of the polymer used in the formulation. The drug's solubility in the solvent and continuous phase were used to calculate its entrapment efficiency. Entrapment efficiency increased as the concentration of polymer in a constant volume of organic solvent increased.

Table: 5 Effect of polymer ratio on the % yield and encapsulation efficiency

Formulation code	Theoretical Yield (mg)	Practical Yield (mg)	% Yield	%Encapsulation Efficiency
OF_1	1000±0.000	620.37±31.75	82.48±1.44	83.53±1.42
OF_2	1500±0.000	1238.1±33.8	89.37±2.28	92.91±1.88
OF_3	2000±0.000	1740.8±8.06	93.03±2.34	95.25±2.04

Figure 5: % yield and encapsulation efficiency of microspheres



Mean particle size of microspheres

The created microsphere was determined to be spherical and free-flowing in nature using the emulsion solvent diffusion technique. The particle sizes varied from 52.371.86m to 72.451.28m on average (Table.6 and fig.6). It was discovered that when the polymer content

increased, the mean particle size increased as well. This might be owing to a considerable increase in viscosity in a constant amount of solvent, resulting in larger emulsion droplets and, ultimately, larger microspheres.

Table: - 6 Average particle sizes of microspheres

SI No	Formulation code	Particle size distribution (µm)
1	OF_1	52.37±1.86
2	OF_2	65.43±0.580
3	OF_3	72.46±1.28

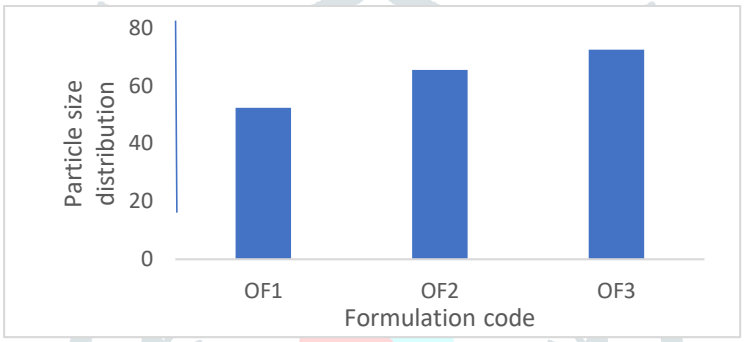


Figure: 6 Average particle size of Ofloxacin microspheres

Morphology of the Surface (SEM)

The surface topography, particle size, morphology, interior cross - sectional area, and microstructure of spheres were studied using scanning electron microscope (SEM). Figure.no.10 shows scanning electron imaging of ethyl cellulose microspheres (OF3). The microspheres were porous, smooth, spherical, and agglomeration-free. Due to the quick escape of volatile solvent during formulation, the surface topography reveals that the microsphere was very porous.

Figure no.11 shows scanning electron photography of a reconstitutable suspension (SHM1). The microspheres were smooth, round, and non-aggregated, with suspended particulate debris visible on the surface. This may prevent the scattered particles from aggregating.

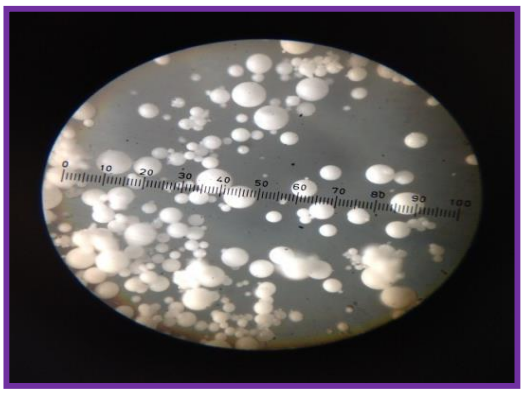


Figure 7: Photographs of Ofloxacin microsphere of OF_1(Microscopy Method)

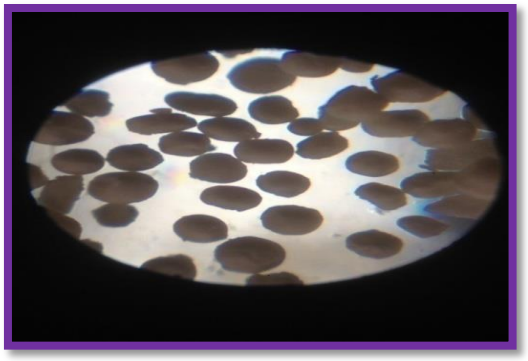


Figure 8: Photographs of Ofloxacin microsphere of OF_2(Microscopy Method)

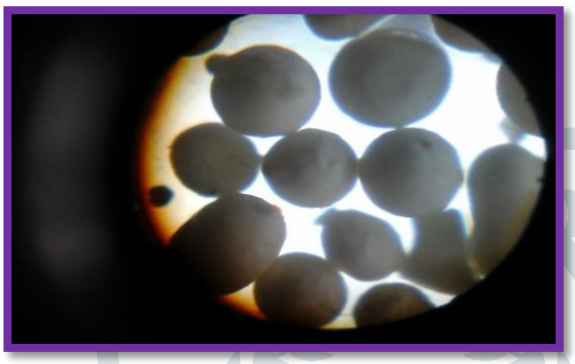


Figure no. 9: Photographs of Ofloxacin microsphere of OF_3 (Microscopy Method)

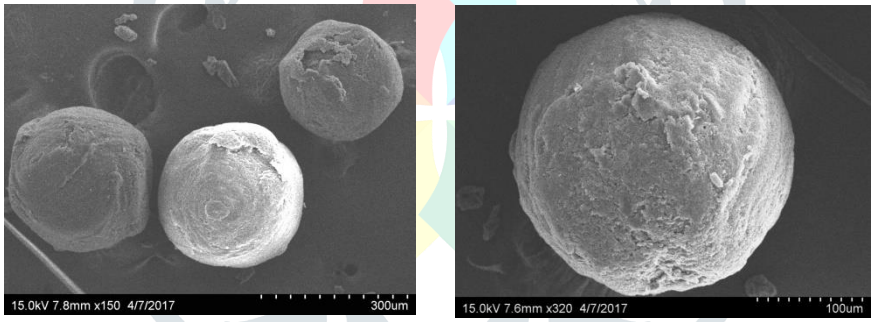


Figure 10: SEM images of microspheras (OF_3)

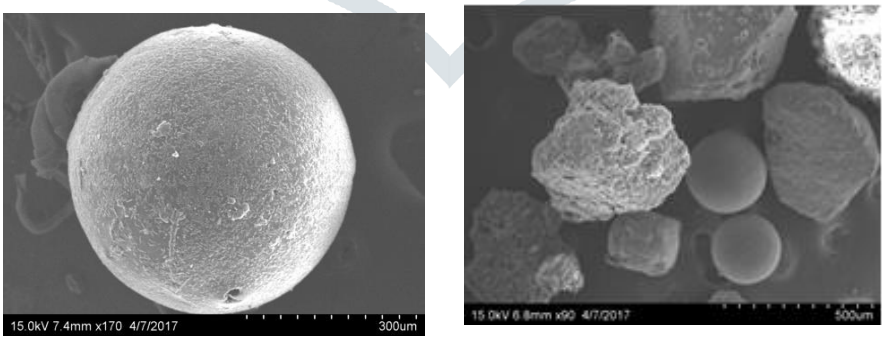


Figure no.11: SEM images of Reconstitutable Suspension (SHM_1)

In-vitro dissolution:

To imitate physiological circumstances, drug release behaviour was studied for up to 12 hours using simulated stomach fluid (pH 1.2) and simulated intestinal fluid (pH 7.4). Using the Type-I dissolving device from the USP. The data on in-vitro dissolution was analysed in terms of cumulative percent drug release vs. time. Table.7 and picture no.12 show the in-vitro dissolving statistics of Ofloxacin microspheres. The amount of Ofloxacin released is mostly determined by the polymer concentration. The rate of drug release from

microspheres was observed to decrease as the polymer content was increased. This might be due to a thickening of the coat enclosing the drug particles, that extends the length the drug penetrates through the coat. The release of ofloxacin from all formulations was found to be gradual and maintained over a 12-hour period.

Table: 7 In vitro release profile of microspheres of OF_1 to OF_3formulation

Sl No	Sampling time in (min)	Cumulative % drug release ± SD		
		OF1	OF2	OF3
1	0	0	0	0
2	30	12.5±2.12	9.07±2.76	8.27±2.23
3	60	20.9±2.34	18.9±1.23	15.37±2.92
4	90	29.77±1.86	23.32±2.64	20.15±1.12
5	120	34.77±1.27	30.54±2.33	27.34±0.88
6	150	46.47±2.52	42.47±2.98	39.34±1.64
7	180	51.44±1.66	49.32±3.02	45.94±1.28
8	240	55.22±2.28	53.67±1.54	51.32±2.42
9	300	66.73±1.88	61.72±2.12	57.32±1.62
10	360	69.23±1.28	63.64±1.64	60.02±2.12
11	420	72.52±2.76	69.53±1.22	65.4±0.88
12	480	76.14±1.94	72.52±1.43	70.9±1.24
13	540	81.12±2.12	76.43±1.76	74.34±1.66
14	600	86.78±2.66	81.63±2.82	80.24±1.28
15	660	90.45±2.42	86.79±2.12	85.33±2.26
16	720	93.67±1.34	90.01±1.38	89.55±1.82

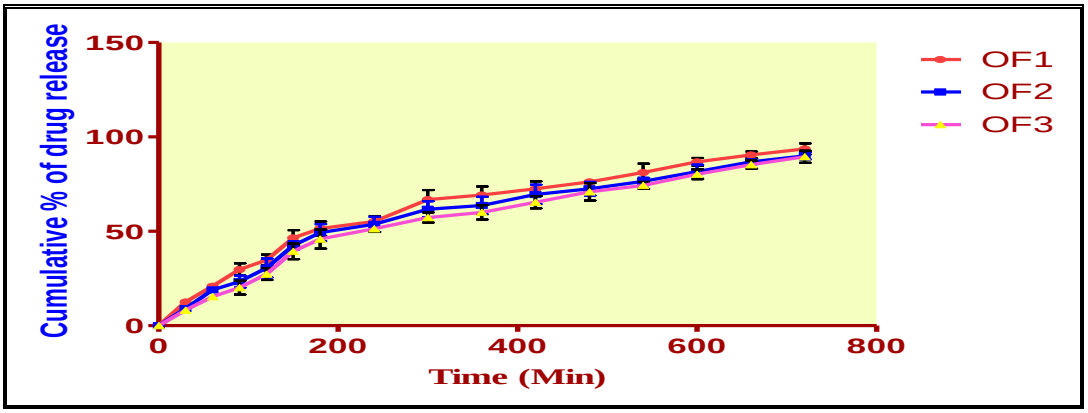


Figure 12: Microspheres of the OF1 through OF3 formulation in vitro release profile

Reconstitutable sustained release suspension containing Ofloxacin loaded microspheres

Ofloxacin-loaded microspheres in a reconstituted sustained-release suspension Optimized microspheres (OF3) were chosen and suspended in palatable carriers individually. Three batches of Ofloxacin microspheres reconstitutable suspensions were made. SHM1, SHM2, SHM3, Due to the risk of pharmaceutical escaping in the suspending medium while storage, the suspension formulation was designed as a dry suspension to be reconstituted before use. Because it imparts high viscosity with thixotropic flow properties, xanthan gum was utilised as a suspending agent at the same concentration, 0.6 percent. A pH adjustment of 3-4 has no effect on the viscosity of xanthan gum solution.

D-sorbitol is a flavouring ingredient used in vehicles where microspheres are suspended for a lengthy period of time. With a 0.6 percent xanthan gum concentration and a 10% D-sorbitol concentration, sedimentation was higher. As a result, the D-sorbitol content was raised from 10% to 20%, Even after 14 days of standing, the suspension was found to be steady. i.e., a sedimentation volume near to one.

The presence of D-sorbitol and xanthan gum in the dispersion medium at the appropriate concentration was clearly necessary for achieving a stable suspension, as evidenced by the sedimentation volume of the suspension. The pH of the generated suspension was adjusted to pH 3-4 using a buffer composition (citric acid and tartaric acid).

EVALUATION

Physical stability and redispersibility of suspension

The suspension with a 20% sorbitol content had a greater sedimentation volume, which might be due to the suspension's optimal viscosity. As a result, a suspension made with 0.6 percent suspending agent and 20% D-sorbitol, as indicated in the table, is appropriate and has good redispersibility. Table no.8

Even after 14 days of settling, all of the prepared suspensions redispersed easily and gave a uniform redispersion upon shaking. While the suspension prepared with 10% D-sorbitol showed a faster rate of sedimentation, it also showed better redispersibility, indicating a good physical stable suspension result, as shown in Table no.8 and Figure no.13.

Table 8: Sedimentation volume and % ease of redispersibility

Days	SHM_1	SHM_2	SHM_3
0	1	1	1
1st	0.881	0.921	0.941
7th	0.722	0.782	0.833
14th	0.643	0.681	0.702

% Ease of redispersibility	90	85	88

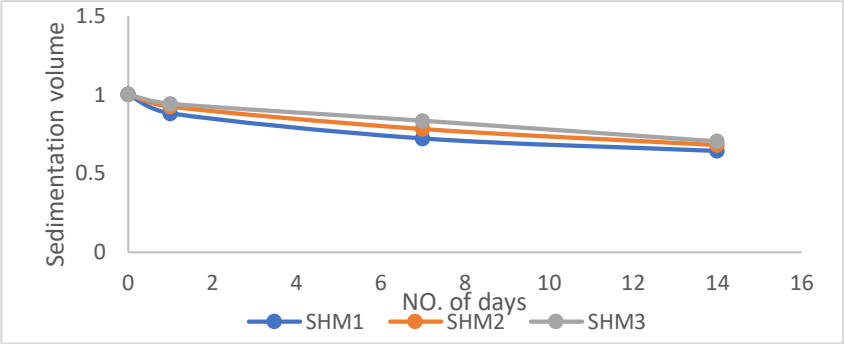


Figure 13: Plot of Sedimentation volume

determination of drug content

Prepared suspensions are evaluated for the drug content. The results of drug content of suspensions given in the Table.9. It was concluding that drug content was within the standard limits.

The measurement of pharmaceutical leaking through suspension spheres

An examination of the amount of ofloxacin leaked from the microspheres in the solution during storage revealed no significant drug leakage. (Table.10). The poor solubility of ethyl cellulose, and thus little drug was diffused out of the microsphere matrix. The acidity of the suspension medium was blamed for preventing considerable medication leakage from the microspheres.

Table: 9 Drug Content of reconstitutable suspension

Days	**Drug content % SHM_1**	**Drug content % SHM_2**	**Drug content % SHM_3**
0	91.07	96.2	98.8
1^{st}	88.13	95.4	97.48
7^{th}	87.89	93.15	96.98
14^{th}	86.05	92.78	95.20

Table 10: Drug leakage of reconstitutable suspension

Days	**Drug leakage % SHM_1**	**Drug leakage % SHM_3**	**Drug leakage % SHM_3**
0	0	0	0
1^{st}	0.73	0.81	0.84

7th	1.03	1.10	1.04
14th	1.98	2.34	2.87

pH measurements

The pH of the suspensions was measured with a digital pH metre on the 0th, 1st, 7th, and 14th days after reconstitution, and the findings are shown in Table 11. All formulations had a pH range of 3 to 4, which could be linked to buffer components (citric acid, sodium citrate).

Rheological studies

The formulas all had a viscosity that made them convenient to drop out from jar and had an apparent viscosity effect. The viscous data for all suspensions is shown in Table 11.

Table 11: pH and viscosity of Reconstitutable suspension

Days	PH after reconstitution SHM1	PH after reconstitution SHM2	Days	Viscosity (cps) SHM_1	Viscosity(cps) SHM_2	Viscosity (cps) SHM_3
0	3.4	3.5	0	654	768	792
1st	3.6	3.7	1st	644	752	772
7th	3.8	3.9	7th	620	734	753
14th	3.92	3.98	14th	612	723	734

Sustained release suspension pharmaceutical release profile in vitro

In-vitro dissolution tests have been widely studied, developed, and utilised as an indirect way of determining drug availability, particularly in the preliminary assessment of formulation factors and manufacturing methods that may impact bioavailability. As indicated in Table.12 and Figure 14, the drug release rate of suspended microspheres was examined in pH 1.2 and pH 7.4 buffers. Suspended microspheres released Ofloxacin at a somewhat quicker rate than dry microspheres. This might be due to the scattered microspheres getting moist in the dispersion liquid. This study suggested that the suspension medium had little impact on the drug release qualities**.**

Table 12: In vitro drug release profile of Ofloxacin reconstitutable suspensions

Sl.no	Sampling time in (min)	Cumulative % drug release ± SD SHM_1	Cumulative % drug release ± SD SHM_2	Cumulative % drug release ± SD SHM_3	Cumulative % drug release ± SD OF_3
1	0	0	0	0	0
2	30	8.34±1.45	7.13±0.45	6.34±0.45	8.27±2.52
3	60	11.94±1.52	10.23±0.68	9.03±0.48	15.37± 1.65
4	90	12.16±0.65	11.14±1.4	10.13±1.25	20.15±2.75
5	120	24.13±2.24	20.15±2.8	18.34±2.4	27.34±0.45
6	150	32.36±0.27	29.16±1.7	25.13±2.6	39.34±3.87
7	180	38.08±2.22	35.65±0.48	33.07±0.58	45.94±3.45
8	240	46.14±3.54	42..27±2.7	40.88±0.65	51.32±0.54
9	300	50.13±0.68	49.73±2.9	46.37±0.87	57.2±2.24
10	360	63.45±2.9	59.34±1.5	55.34±1.56	60.02±1.45
11	420	69.13±1.45	65.27±2.4	62.14±1.85	65.4±1.68
12	480	74.35±1.8	70.67±1.3	69.37±1.25	70.91±1.47
13	540	82.19±2.8	79.37±2.8	72.14±1.65	74.91±1.58
14	600	88.20±2.7	85.03±0.67	80.27±2.54	80.24±2.71
15	660	93.35±1.4	90.13±1.4	88.29±1.25	85.24±2.98
16	720	97.23±1.2	95.17±0.54	92.14±0.25	89.55± 3.45

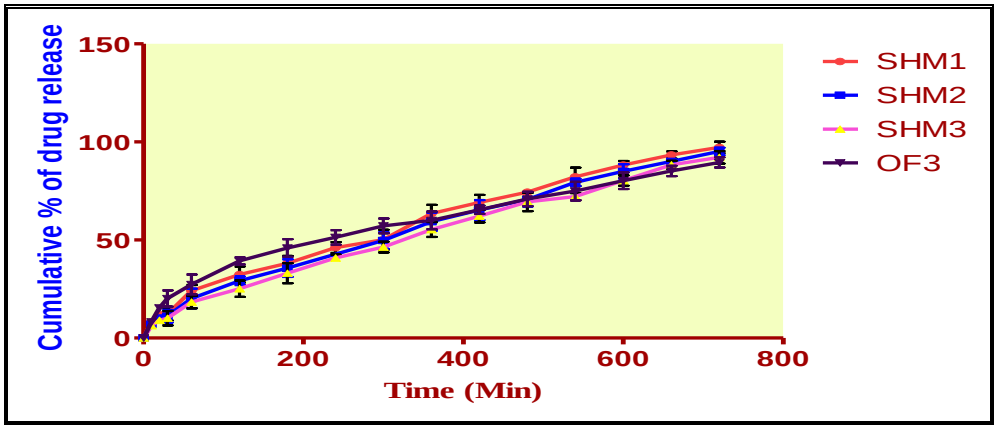


Figure 14: In vitro release profile of SHM1, SHM2, SHM3, and pure microsphere OF3 formulations in reconstitutable suspension.

Drug Release Kinetics (Kinetic Modelling)

To evaluate the drug release mechanism, the in-vitro release data was submitted to many kinetic models, including zero order, first order, Higuchi's, Korsmeyer-peppas, and Hixson Crowell cube root model. According to the results of the kinetics experiment, drug release followed a zero-order kinetics with R2 Figure no:15. Release of the First Order SHM1, SHM2, and SHM3 formulations in a reconstituted solution. All of the formulations had a value of between (0.975 to0.984). Higuchi and Korsenmeyer-Peppas equations, as well as Hixson Crowell equations, were included in the formulation. The plots of all the formulations were found to be fair linear and regression values, as shown in table no.13, with n values ranging between (0.730 to 0.735). This indicated that the medication was dispersed in a non-Fickian way.

Table :13 Data of drug release kinetics all suspension.

Sr. no.	Formulation Code	Zero order model	First-order model	Higuchi model	Korsenmeyer-peppas model		Hixson and Crowell's
		R^2	R^2	R^2	R^2	M	R^2
1	SHM_1	0.975	0.916	0.969	0.977	0.730	0.740
2	SHM_2	0.981	0.935	0.965	0.970	0.734	0.759
3	SHM_3	0.984	0.946	0.960	0.962	0.735	0.774

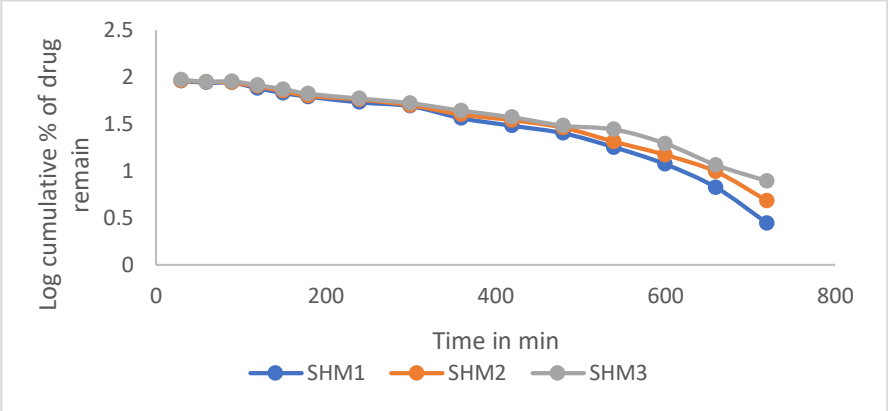


Figure 15: First Order Release Reconstitutable suspension of SHM_1, SHM_2 and SHM_3 formulations.

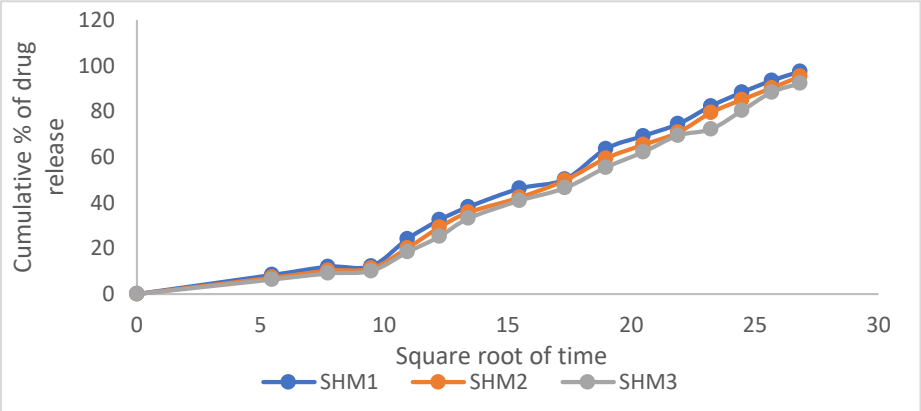


Figure 16: Higuchi Model of reconstitutable suspension of SHM_1, SHM_2 and SHM_3 formulations

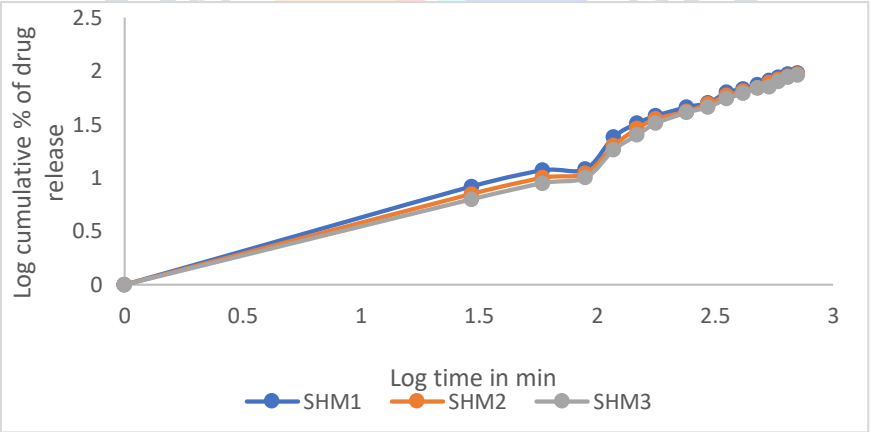


Figure 17: Korsmeyer-Peppas Model of reconstitutable suspension of SHM_1, SHM_2 and SHM_3 formulation

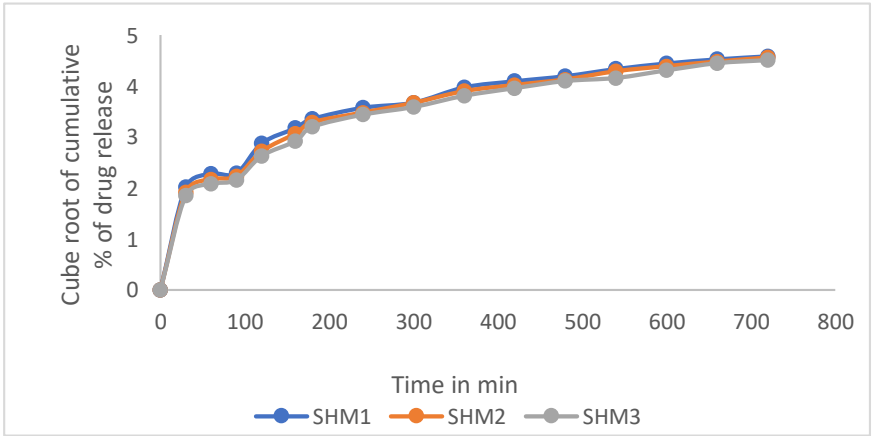


Figure 18: Hixson and Crowell Model of reconstitutable suspension of SHM_1, SHM_2 and SHM_3 formulations

STABILITY STUDIES

The stability of the improved formulation (SHM3) was tested according to ICH recommendations, and it was discovered that the formulation was stable, with no change in drug content and a negligible difference.

CONCLUSION:

With 0.6 percent w/v xanthan gum and 20 percent w/v D-sorbitol as a coexisting polyol, stable solutions of Ofloxacin packed microspheres could be synthesized at pH 3-4 with 0.6 percent w/v xanthan gum. On the 14th day during preservation, there was so little pharmaceutical escape out from microspheres in the reconstituted suspensions. Finally, there were no statistically meaningful abnormalities in the release of pharmaceutical from the suspension formulation compared to the profiles of microspheres alone. We can conclude from this research that stable suspensions of Ofloxacin-loaded microspheres might be established to fulfil a safe and effective dosage form with improved stability and ease of administration for paediatric and geriatric patients, diminishing dosing frequency and steadily rising bioavailability.

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