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FORMULATION AND EVALUATION OF AMPHOTERICIN B LOADED NANOSPONGES FOR TOPICAL DELIVERY

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ABSTRACT

In this work, solvent evaporation was used to create nanosponges, which were then combined with Amphotericin B to create a gel. The Nanosponges formulations were made utilising the solvent evaporation process with PVA acting as a co-polymer and rate-retarders HP-β Cyclodextrin and HPMC K4M. Fourier Transform Infra-Red (FTIR) spectroscopy was used to determine the drug's compatibility with formulation ingredients. We looked at the drug entrapment effectiveness, production yield, and surface shape of nanosponges. Using scanning electron microscopy, the Nanosponges' shape and surface morphology were investigated. Scanning electron microscopy demonstrated that the Nanosponges were spherical and porous. SEM images showed that the Nanosponges were spherical in all of their variations, but at larger ratios, drug crystals were visible on the surface of the nanosponge. An increase in the polymer concentration led to an increase in the drug/polymer ratio (1:1 to 1:3), which is growing in order. However, beyond a certain concentration, it was found that the particle size reduced as the drug-to-polymer ratio developed. All formulations have an average particle size that falls between 331.5 and 463.9 nm. The range of 82.21 to 97.78% was found for the drug content of various formulations. The drug release of the optimised formulation was found to be 94.92 % in 9 hours, while the entrapment efficiency of the other formulations ranged from 92.75 to 94.45%. According to stability experiments, the optimised gel formulation remained stable for a period of 15 days.

KEYWORDS - *Amphotericin B, HP β-Cyclodextrin, Nanosponges, Drug Delivery System.*

INTRODUCTION

Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. These are used for the passive targeting of cosmetic agents to skin, there by achieving major benefits such as reduction of total dose, retention of dosage form on the skin and avoidance of systemic absorption. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving patient compliance by prolonging dosing intervals. Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy. The size of the nanospongs ranges from 250nm-1μm in diameter. Nanosponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Nanosponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles.

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The Nanosponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consist of macro porous beads, typically 10-25 microns in a diameter, loaded with active agent. When applied to the skin, the nanosponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over the counter (OTC) skin care, sunscreens and prescription products.

MATERIALS AND METHODS

MATERIALS

The gift sample Amphotericin B is from Hetero Labs Hyderabad, while the Polyvinyl alcohol (PVA) and HPMC K4M polymers are from Colorcon Goa and other polymers such as HP β cyclodextrin, Xanthan gum, Guar gum and Karaya gum from B.M.R.Chemicals, Hyderabad, Propylene Glycol (ml), Ethanol and Triethanolamine (2%v/v) (ml) are from Narmada Chemicals, Hyderabad.

METHODS

PRE-FORMULATION STUDIES

Prior to the development of nanosponge dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The overall objective of the pre-formulation is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.

Determination of absorption maximum (λ_{max})

The wavelength at which maximum absorption of radiation takes place is called as λ_{max}. This λ_{max} is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (407nm), as they are aromatic or contain double bonds.
Accurately weighed 10mg Amphotericin B separately was dissolved in 10 ml of methanol in a clean 10ml volumetric flask. The volume was made up to 10ml with the same which will give stock solution-I with concentration 1000µg/ml. From the stock solution-I, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using methanol buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using methanol buffer to get a concentration of 10µg/ml.

Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 4000 to 400cm.

Preparation of Nanosponges

Table 1
Formulation table of Amphotericin B loaded nanosponges

S. No	Excipients	F1	F2	F3	F4	F5	F6
1	Amphotericin B (gm)	1.0	1.0	1.0	1.0	1.0	1.0
2	PVA (gm)	1.0	1.0	1.0	1.0	1.0	1.0
3	HPMC K 4M (gm)	1.0	1.5	2.0	--	--	--
4	HP β cyclodextrin	--	--	--	1.0	1.5	2.0
5	Ethanol (ml)	10	10	10	10	10	10
6	Water	100	100	100	100	100	100

Method of Preparation of Nanosponges

Nanosponges using different proportions of β-cyclodextrin, HP β-cyclodextrin, HPMC KM4 as rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by solvent evaporation method. Disperse phase consisting of Amphotericin B (1gm) and

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requisite quantity of PVA dissolved in 10 ml solvent (ethanol) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using magnetic stirrer. The reaction mixture was stirred at 1000 rpm for three hours on a magnetic stirrer for 2hours. The nanosponges formed were collected by filtration through whatman filter paper and dried in oven at 50^{O}C for 2 hours. The dried nanosponges were stored in vaccum desicator to ensure the removal of residual solvent.

Evaluation parameters of Nanosponges

The Nanosponges was evaluated for various parameters
Entrapment efficiency
Scanning electron microscopy
Particles size and shape

Entrapment Efficiency

The 100mg of the Amphotericin B weight equivalent nanosponge was analyzed by dissolving the sample in 10ml of distilled water. After the drug was dissolved 10ml of clear layer of dissolved drug is taken. Thereafter the amount of drug in the water phase was detected by a UV-spectrophotometric method at 407nm (U.V Spectrophotometer, systronics). The test was repeated with another nanoparticulate sample. The amount of the drug in the suspension was analyzed by centrifugation at 500rpm for 5 mins and by measuring the concentration of the drug in the clear supernatant layer by the UV-spectrophotometric method. The concentration of the drug is determined with the help of calibration curve. The amount of drug inside the particles was calculated by subtracting the amount of drug in the aqueous phase of the suspension from the total amount of the drug in the nanoparticle suspension. The entrapment efficiency (%) of drug was calculated by the following equation.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of drug in nanosponge}}{\text{Mass of drug used in formulation}} \times 100$$

Scanning Electron Microscopy

The morphological features of prepared nanospongess are observed by scanning electron microscopy at different magnifications.

Particle size and shape

Average particle size and shape of the formulated nanospongess was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned for determination of particle size.

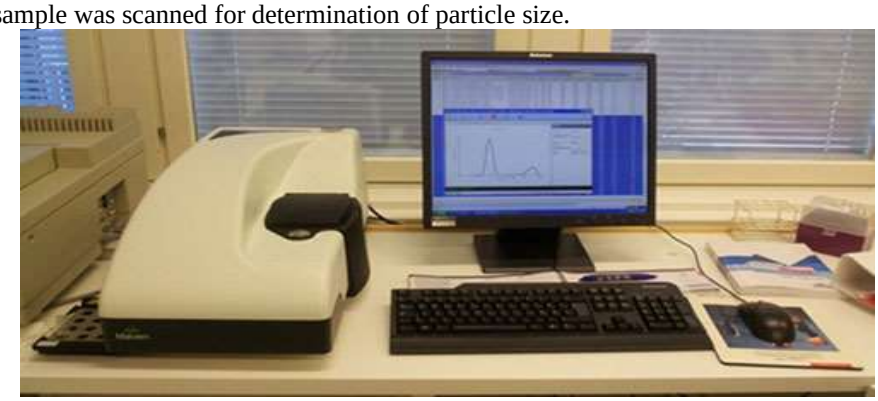

Figure 1

Photography representation of Malvern zeta sizer used for finding particle size & zeta analysis

Formulation of Nanosponge loaded gel:

The polymer was initially soaked in water for the gel for 2 hrs and dispersed by agitation at 600rpm by using magnetic stirrer to get smooth dispersion. Triethanolamine (2% v/v) was added to neutralise the pH. The previously prepared optimized nanosponge was thereby added and permeation enhancer's Propylene glycol were added as ethanolic solution to the aqueous dispersion. The composition of nanosponge gels is shown in table 4:

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Table 2
Formulation of Nanosponge loaded gel

Ingredients	F7	F8	F9
Optimize Nanosponge(mg)	400	400	400
Xanthan gum	100		
Guar gum		100	
Karaya gum			100
Propylene Glycol(ml)	1	1	1
Distilled Water(ml)	5	5	5
Triethanolamine(2%v/v)(ml)	1	1	1

Visual Appearance and Clarity
Visual appearance and Clarity was done under fluorescent light against a white and black back ground for presence of any particulate matter.

pH
The pH of the prepared in-situ gelling system after addition of all the ingredients was measured using pH meter.

Drug Content uniformity
Drug content uniformity of prepared in-situ gelling systems was carried out using Spectrophotometric method. The assay of these formulations was carried out by pipetting 1 ml of all optimized formulations, and it was diluted up to 100 ml of Simulated Tear Fluid (pH 6.8). The formulations were shaken for 2-3 min, until it gives a clear gel solution. The solution was filtered through Millipore membrane filtrate (0.45um) and the absorbance was measured at 407 nm using UV-Visible spectrophotometer.

***In-Vitro* Gelation**
The Gelling capacity of the formulations containing different ratio of poloxamer and HPMC was evaluated. It was performed by placing a drop of polymeric solution in vials containing 1 ml of Simulated Tear Fluid, freshly prepared and equilibrated at 37^0C, and visually assessed the time for gelation as well as time taken for the gel to dissolve.

Rheological Studies
It is the important factor to determine the residence time of drug in the eye by considering the viscosity of the instilled formulation. The prepared solutions were allowed to gel at physiological temperature and then the viscosity determination was carried out by using Brookfield viscometer (Brookfield DV+Pro, Brookfield Engineering Laboratories, Middleboro, MA, USA).

In vitro Drug Release studies of nanosponge gel formulations
In vitro evaluation studies of topical gel were performed using dialysis membrane method. The membrane was soaked for 12hr in 0.1NHCl and the receptor compartment was filled with 6.8pH phosphate buffer. Test vehicle equivalent to 100mg was applied evenly on the surface of the membrane. The prepared membrane was mounted on the cell carefully to avoid entrapment of air bubbles under the membrane. The whole assembly was maintained at 37°C, and the speed of stirring was kept constant (600 rpm) for 12 hrs. Aliquots of drug sample (4mL) was taken at 1hr time intervals and replaced with equal amount of freshly prepared buffer. Each experiment was performed in triplicate. The drug analysis was done using UV spectrophotometerically at 247nm.

Modelling of Dissolution Profile
In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of Amphotericin B from the matrix tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

RELEASE ORDER KINETICS

Mathematical models
Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r2) was calculated.

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Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation

$$Qt = Q0 + K0t$$

First Order Model

Release behavior generally follows the following first order equation:

$$Log\ C = Log\ C_o - kt/2.303$$

Higuchi model

In a general way the Higuchi model is simply expressed by following equation

$$Q = K_H - t^{1/2}$$

Korsmeyer-Peppas model

Korsmeyer et al.(1983) derived a simple relationshipwhich described drug release from a polymeric system equation. To find out the mechanism of drug release, first60% drug release data were fitted in Korsmeyer-Peppas model,

$$Mt / M\infty = Kt^n$$

In this model, the value of n characterizes the release mechanism of drug as described in the following table.

Table 3

Drug transport mechanisms suggested based on 'n' value.

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

To find out the exponent of n the portion of the release curve, where Mt / M∞ < 0.6 should only be used. To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Stability studies

The optimized formulation were kept for stability studies for 3 months at room temperature (30 ± 2°C), at refrigerator temperature (4 ±2°C) and at accelerated condition (40±2°C, 75%RH) in programmable environmental test chamber (Remi) to determine physical and chemical stabilities. The formulation was evaluated visually and for entrapment efficiency and drug release after 5, 10 and 15 days.

RESULTS AND DISCUSSION

PREFORMULATION STUDY

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of Pure drug with that of various excipients used in the formulation.

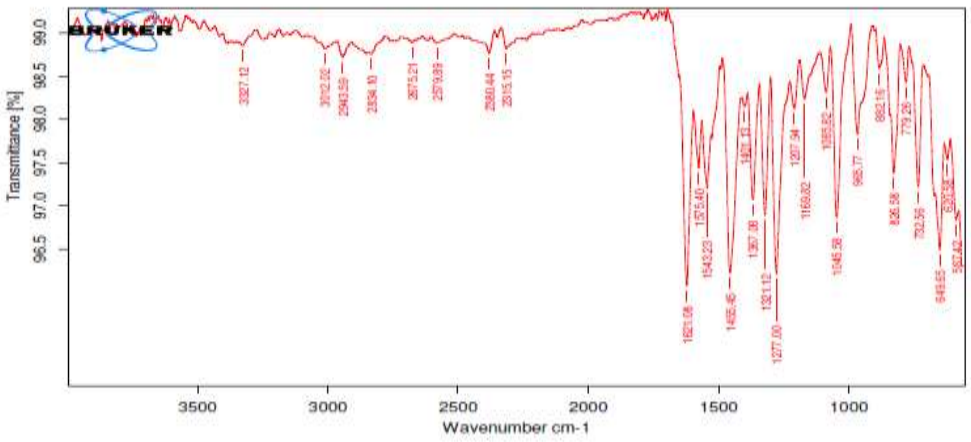

Figure 2 FTIR Spectra of Pure Drug

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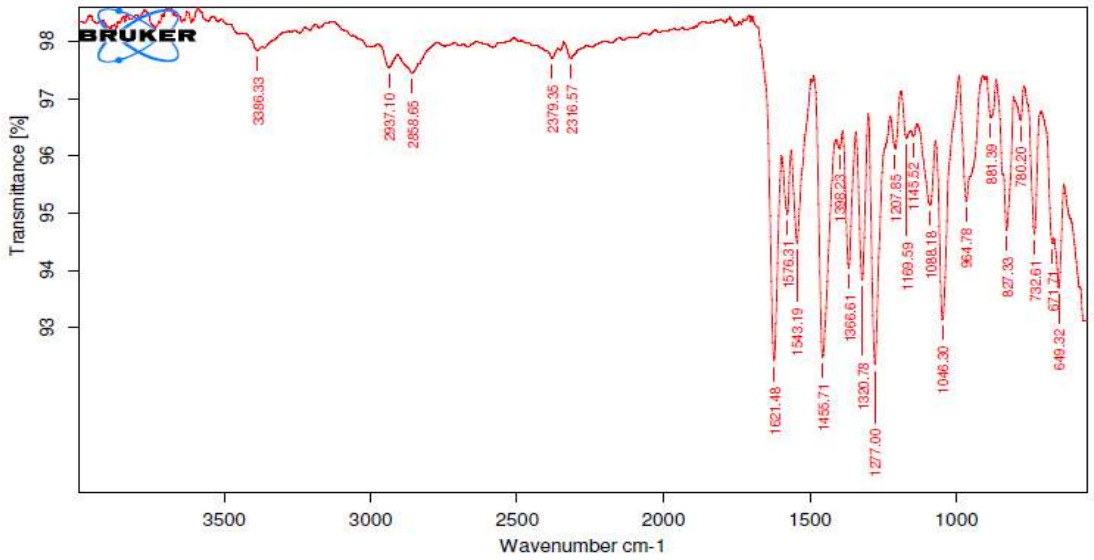

Figure 3
FTIR Spectra of drug and excipients

Spectral data
The major functional groups are primary amine, nitro, and carbonyl group
Obtained peak in IR spectra are as follows.

IR (KBr) cm-1
732.50-732.61(CH- bending), 1169 (C=C stretching), 1277 (C-O stretch in aromatic compound), 1456 (C-C "oop" in aromatic compound) 1543 (N-N stretching).The spectral data confirm the structure of the compound.

It indicates that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric network in the free form.

EVALUATION STUDIES

A) Particle size analysis of Nanosponges
The particle size of the nanosponge was determined by optical microscopy and the nanosponges were found to be uniform in size. The average particle size of all formulations ranges from 331.5 nm to 463.9 nm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratio, the amount of polymer available per nanosponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the drug and reducing the thickness of polymer wall and nanosponges with smaller size were obtained. By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio.

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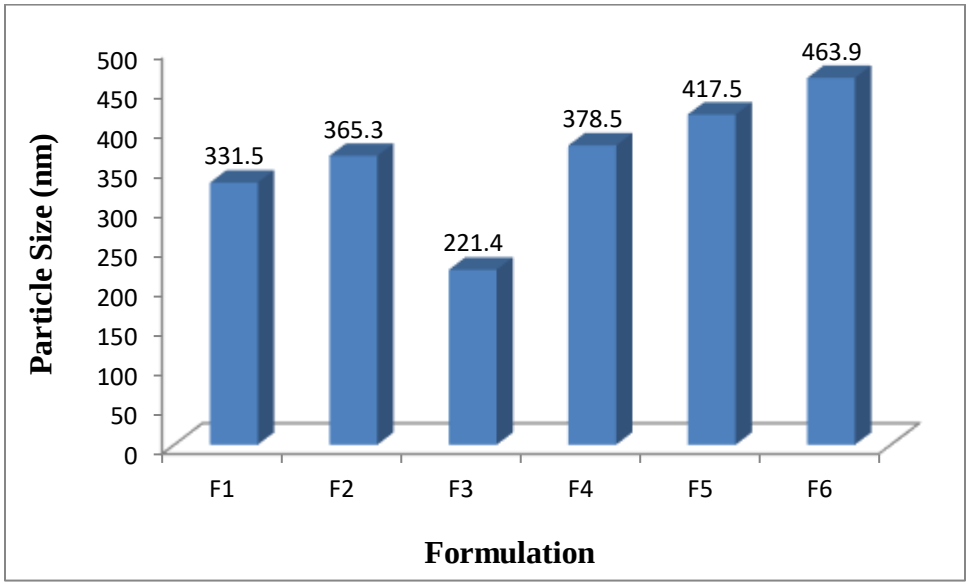

Figure 4
Particle size of Nanosponges

B) Morphology determination by scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared nanosponges. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10 -10 to 10 -12 grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens.

It was observed that the nanosponges were spherical, and uniform with no drug crystals on the surface. The shape of the nanosponges affects the surface area and surface area per unit weight of spherical nanosponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.

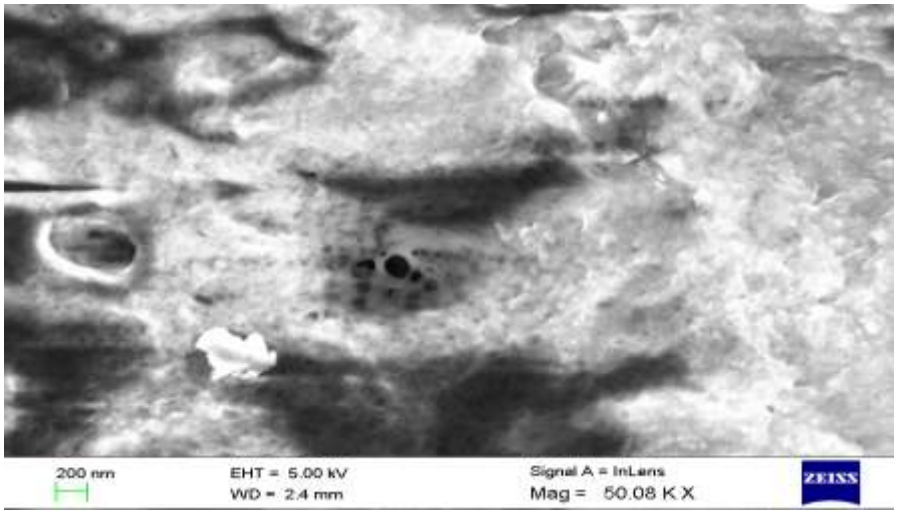

Figure 5
Nanosponges structure optimized formulation (F3)

Drug content: The drug content of the formulated Nanosponges (F1-F6) was found in the range of 82.21 to 97.78% respectively.

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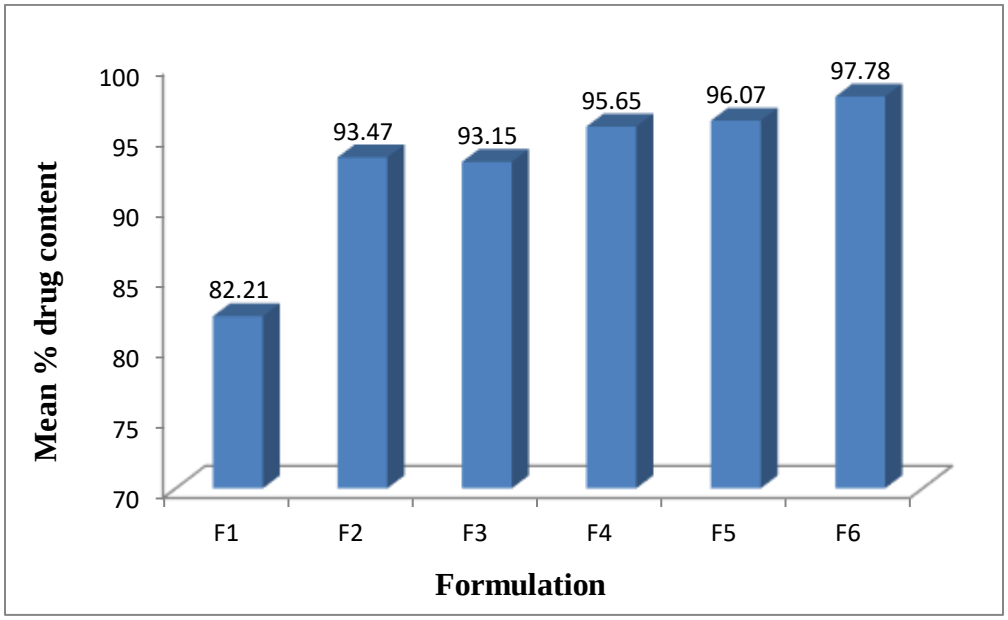

Figure 6
Drug content of Formulated Nanosponges

The percentage of drug content of formulation F1 was found to be 82.21%, formulation F2 was found to be 93.47%, formulation F3 was found to be 93.15%, formulation F4 was found to be 95.65%, formulation F5 was found to be 96.07%, and formulation F6 was found to be 97.78%.

Entrapment efficiency

It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the Practical yield was calculated as Nanosponges recovered from each preparation in relation to the sum of starting material (Theoretical yield).

It can be calculated using following formula.

Entrapment efficiency = $\frac{\text{Practical yield}}{\text{Theoretical yield}}$ X 100

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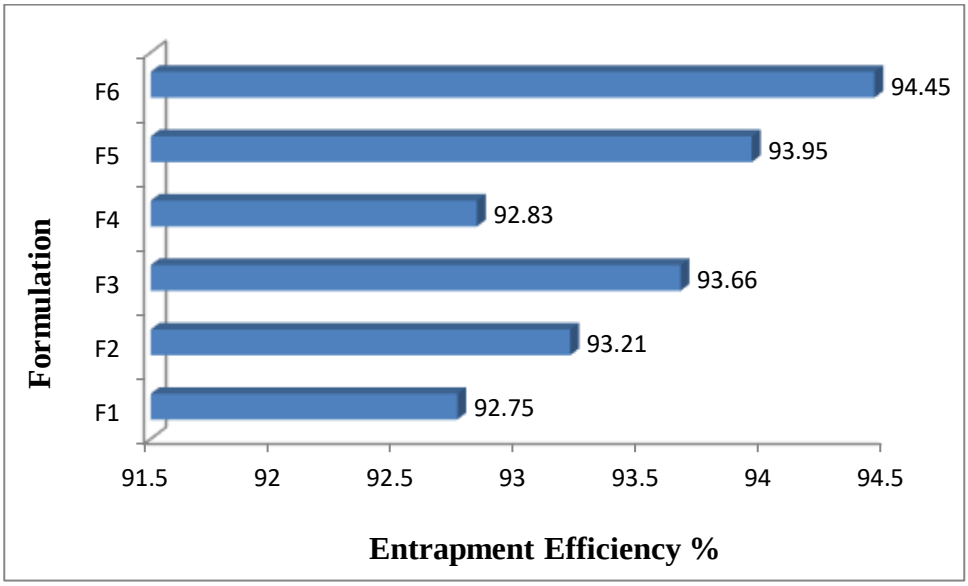

Figure 7
Entrapment efficiency of Nanosponges

The entrapment efficiency of formulation F1 was found to be 92.75%, formulation F2 was found to be 93.21%, formulation F3 was found to be 94.66%, formulation F4 was found to be 92.83%, formulation F5 was found to be 93.95% and formulation F6 was found to be 93.42%,. Among all the formulations F3 shows high entrapment efficiency of 94.66%.

Table 4
Evaluation Parameters of Nanosponges

S. No	Formulation code	Particle size (nm)	Mean % drug content	Entrapment efficiency %
1	F1	331.5	82.21	92.75
2	F2	365.3	93.47	93.21
3	F3	221.4	93.15	93.66
4	F4	378.5	95.65	92.83
5	F5	417.5	96.07	93.95
6	F6	463.9	97.78	94.45

Visual Appearance and Clarity

Table 5
Visual appearance and clarity of all (F7-F9) formulations

Formula	Appearance	Clarity
F7	Transparent	Clear
F8	Transparent	Clear
F9	Transparent	Clear

The clarity and appearance of the all formulations (F7-F9) were observed clear and transparent and the formulations were liquid at both room temperature and refrigerated conditions.

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pH Measurement

All the formulations have satisfactory pH ranging from 6.7 to 6.9, which is acceptable for ocular delivery.

Drug Content Uniformity

The drug content of the formulated gels was found in the satisfactory ranging from 94.37 to 97.21 %.

Table 6
pH measurements and Drug content of formulated gels (F7-F9)

Formulation	pH	Drug content
F7	6.6	94.37 ± 0.48
F8	6.7	96.43 ± 0.62
F9	6.8	97.21± 0.73

Gelling Capacity

Table 7
Gelling capacity of all formulations (F7-F9)

Formulation	Gelling capacity at 25 °C	Gelling capacity at 37°C
F7	---	+
F8	-----	++
F9	---	+++

+ Gelation within 50-60 seconds dissolves rapidly

++ Gelation within 60 seconds and remains stable for 3 hours

+++ Gelation within 60 seconds and remains stable for 6 hour

All the formulations showed instantaneous gelation when contact with buffer. However the nature of the gel formed depended on the concentration of the polymer used.

Rheological Studies

Table 8
viscosity studies of formulations:

Angular Velocity (rpm)	F7	F8	F9
10	103.0	107.1	113.3
100	96.0	97.2	98.4

The viscosity of the formulations was evaluated by a Brookfield DV 3 programmable rheometer, using varying the angular velocities or shear rate. The viscosity of formulations F7-F9 ranged from 96.0 to 113.3cps.at 100 rpm. As the angular velocity increased viscosity decreased indicating no thixotropic property.

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Table 9
***In vitro* diffusion studies of Amphotericin B Nanosponge incorporated gel**

S. No	Time (Hrs)	% of Drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1 Hrs	5.54	3.06	5.96	8.12	6.58	13.14	14.64	7.68	11.23
2	2 Hrs	19.62	16.96	16.24	11.71	15.42	16.98	29.32	12.36	17.06
3	3 Hrs	27.96	24.46	23.59	25.63	19.32	23.16	33.16	24.64	24.80
4	4 Hrs	38.68	31.58	32.64	37.12	23.16	33.94	37.72	39.32	38.64
5	5 Hrs	41.58	45.42	49.32	43.68	37.06	46.31	47.86	43.16	46.38
6	6 Hrs	55.42	57.06	50.91	49.54	47.08	58.64	52.48	55.32	50.22
7	7 Hrs	67.06	64.8	74.81	61.24	59.42	60.98	65.60	68.64	74.12
8	8 Hrs	70.19	72.48	81.10	72.26	62.64	71.11	78.62	74.19	81.86
9	9 Hrs	88.64	80.22	89.12	77.12	70.26	76.56	87.28	89.86	94.92

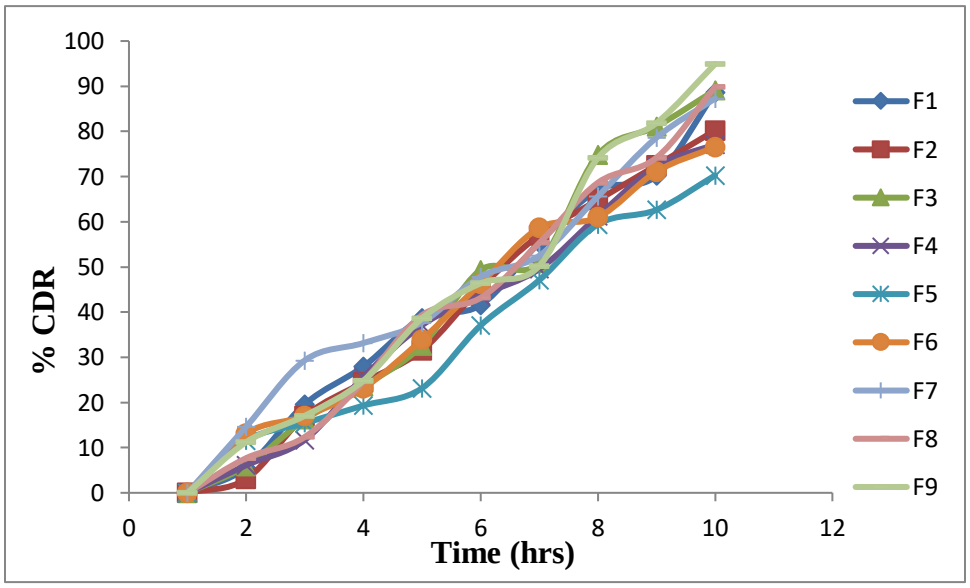

Figure 8
Percentage of drug release graph F1-F9

From the above invitro studies it was observed that the formulations containing xanthan gum, guar gum and karaya gum as polymers shows that the maximum drug release was found in the nanosponge formulation containing Karaya gum, whereas xanthan gum and guar gum didn't show sustained drug release. So formulation F9 containing karaya gum was considered as the optimized formulation. Drug release kinetics was performed for F9 formulation.

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Kinetics Analysis for F9

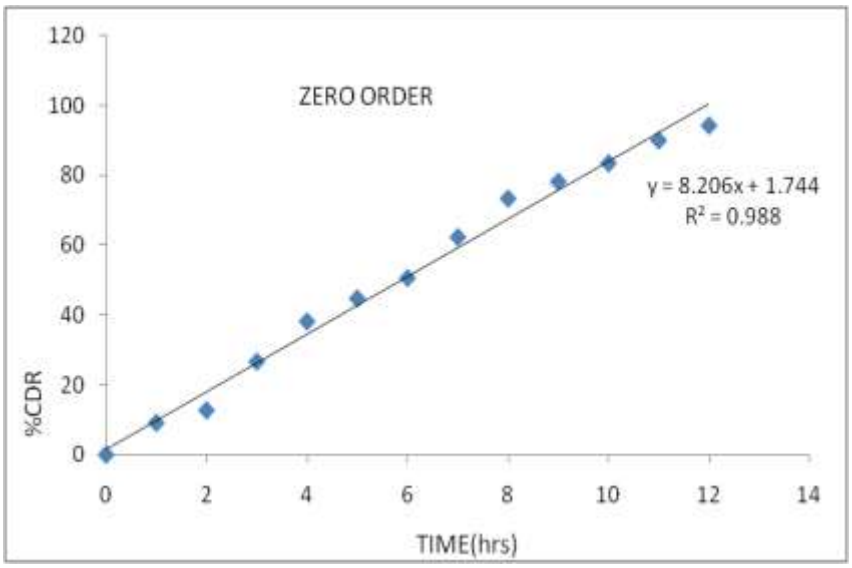

Figure 9
Zero Order Plot for F9

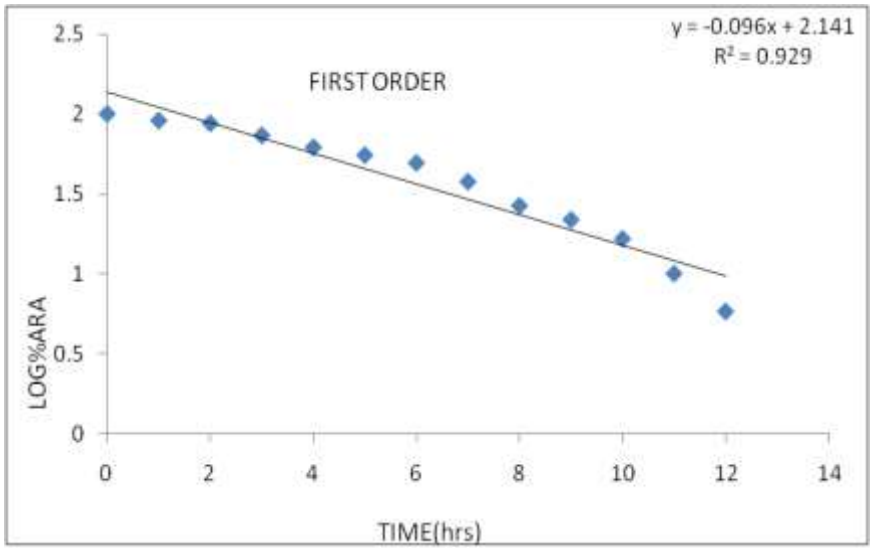

Figure 10
First Order Plot for F9

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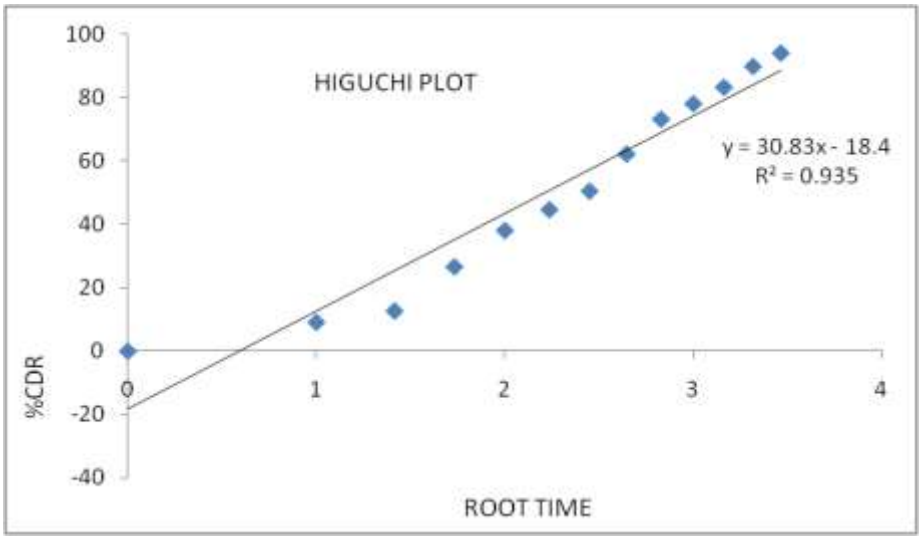

Figure
Higuchi Plot for F9

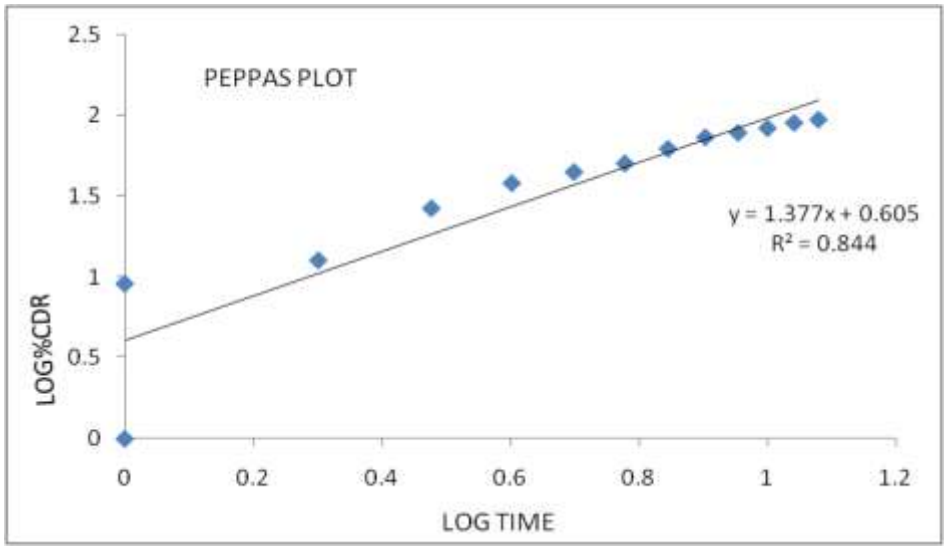

Figure 12
Korsmeyer Peppas Plot for F9

Regression values of F9

Table 10
Regression values

S. No	Zero order	First order	Higuchi	Peppas
Code	R^2	R^2	R^2	R^2
F9	0.988	0.929	0.935	0.844

The optimized formulation F9 has coefficient of determination (R^2) values of 0.988, 0.929, 0.935 and 0.844 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.382 for optimized formulation. Thus n value

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indicates the Super case transport mechanism. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed zero order drug release with super case transport mechanism.

Stability studies

Table 11
Gelling capacity of all formulations (F9)

Formulation	Gelling capacity at 25 °C	Gelling capacity at 37°C
5th day	+++	+++
10th day	+++	+++
15th day	+++	+++

Drug Content Uniformity:

Table 12
Drug content of Formulated gels:

Formulation Code	Drug content
5th day	99.04 ± 0.61
10th day	98.82 ± 0.15
15th day	98.86 ± 0.58

From the stability studies of Nanosponges loaded gel using karaya gum, it was observed that the drug content and gelling capacities were found to be satisfactory as there was not much decrease in the gelling capacity and drug content at the time of formulation and after the 15days.

CONCLUSION

The optimized formulation F9 has good gelling property with pH of 6.8, and drug content of 97.21% and coefficient of determination (R^2) values of 0.988, 0.929, 0.935 and 0.844 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.382 for optimized formulation. Thus n value indicates the super case transport mechanism. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed zero order drug release with super case II transport mechanism. The stability studies revealed that the formulated Nanosponge gel was found to be stable for the period of 15days.

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