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PREPARATION AND EVALUATION OF MICROENCAPSULATED CURCUMIN VAGINAL GEL

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ABSTRACT

The main objective of this research is to evaluate a new approach for the preparation of bio adhesive microspheres and to design an innovative vaginal delivery system for curcumin which is able to enhance the drug anticancer activity. Five different formulations of curcumin encapsulated microspheres were prepared by solvent evaporation method with different drug/polymer ratio by using the mucoadhesive polymer such as Eudragit S 100. The microspheres were found to be discrete, spherical with free-flowing properties and evaluated for particle size analysis, shape (scanning electron microscopy), drug encapsulation efficiency, FTIR, DSC studies and in vitro release performance. The best selected microsphere formulation (F2, containing drug: polymer ratio 1:2) and FS3 were incorporated into vaginal gel preparation using a stirring method in order to obtain a sustained release microencapsulated curcumin containing bio adhesive gel. The pH, spreadability, extrudability, viscosity, in vitro drug release, drug release kinetics, bio adhesion test, and accelerated stability studies of selected microencapsulated gel formulations were evaluated. In vitro drug release rate for selected bio adhesive vaginal gel (FS3 gel, containing 1 % w/w of drug loaded microspheres and 0.6 % w/w of Carbopol 934) was found to sustain curcumin over 12h. The results were then compared statistically and obtained a satisfactory correlation. Hence in conclusion, the microencapsulated bio adhesive gel of curcumin would be an alternative candidate for treatment of vaginal cancer since it has suitable gel properties with good vaginal retention.

INTRODUCTION

Microspheres are widely used constituents of multiparticulate drug delivery systems, offering both therapeutic and technological advantages. A well-designed controlled drug delivery system can overcome the problems of conventional therapy and increases the therapeutic efficacy of the given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One of the approaches is using microspheres as carriers for drugs.[1] Up to now, only few studies reported the use of microspheres for the treatment of vaginal diseases. For instance, bio adhesive microparticles, PLGA microspheres and polymer lipid based mucoadhesive microspheres were assessed as vaginal delivery systems. Vaginal semisolids, particularly gels based on bio adhesive polymers currently receiving a great deal of interest as vaginal delivery systems.[2] Apart from their durability, the ability of these preparations to stick to surfaces for a fair period of time before being dissolved by washing or natural factors is a common feature. The vagina has been studied as a favourable site for the local and systemic delivery of drugs, specifically for female related conditions. Microbes colonise the human vagina, and infections occur when the equilibrium is disrupted. Disruptions of vaginal pH or lactobacilli may allow potentially pathogenic microorganisms to grow and dominate.[3]

Vaginal cancer is an unusually rare tumour, as it constitutes less than 1% of all gynaecological malignancies. Early-stage vaginal cancer, usually asymptomatic and thus difficult to detect, Squamous cell carcinoma (SCC) accounts for approximately 85% of new cases of vaginal cancer, 5% to 10% will be adenocarcinoma. SCC, the most frequently observed histological type of vaginal cancer, usually occurs in elderly females; the human papillomavirus (HPV) can be detected in around 80% of these elderly SCC cases.[4] Conventional vaginal formulations are associated with disadvantage of low retention to the vaginal epithelium, messiness and leakage causing inconvenience to the patient. To circumvent this problem novel bio adhesive drug delivery systems are being propagated. Bio adhesive Gels can present several advantages over other vaginal drug delivery systems such as prolong residence time, safety, versatility, and economical savings.[5] Curcumin is a natural compound contained in turmeric that is a highly potent, nontoxic, bioactive agent that has been used for centuries as a home remedy for a variety of

ailments. The development of a sustained release delivery system for curcumin would provide long term therapeutic concentrations at the site of infection.[6]

MATERIALS AND METHODS

Curcumin was provided as gift sample from Natural remedies, Bangalore.

Preparation of microspheres

Microspheres were prepared by solvent evaporation technique using the quantity of drug and other excipients as given in the Table 1. The polymer (0.1-0.5gm) and the drug (0.1gm) were co-dissolved in a water immiscible organic solvent (10 mL) was poured into 100 mL of water containing PVA (0.25%). A three-blade propeller was used to keep the mixture mechanically stirred (REMI- RQ 122). Then, stirring was maintained for 2 hr at 1200 rpm, leading to a total evaporation of the solvent (chloroform). The microspheres were then recovered by filtration, washed with deionized water and dried in a desiccator for the next 48 hrs.[7]

Table 1: Formulation details of Eudragit S 100 microspheres of curcumin.

Formulation code	Drug-polymer ratio	PVA (%)	Time (hr)	RPM
F1	1:1	0.25	2	1200
F2	1:2	0.25	2	1200
F3	1:3	0.25	2	1200
F4	1:4	0.25	2	1200
F5	1:5	0.25	2	1200

Characterization of prepared microspheres

Particle size studies

By using an optical microscopy method, the particle size of microspheres was determined. A calibrated microscope was used to count approximately 100 microspheres.

Drug polymer interaction (FTIR) study

FTIR spectroscopy was performed on Shimadzu IR spectrophotometer, model 840, Japan, to check drug polymer interaction and stability of drug. FT-IR study was carried on pure curcumin, eudragit and physical mixture of curcumin.[8]

Drug entrapment efficiency

Microspheres equivalent to 5 mg curcumin were crushed using a glass mortar and pestle. Then, they were suspended in 25 ml of phosphate buffer pH 7.4. After 24 hrs, the solution was filtered and 1 ml of the filtrate was diluted 10 times and analysed for the drug content by UV-visible spectrophotometer at 426 nm. The drug entrapment efficiency was calculated using the following formula:

Entrapment efficiency = (actual drug content/theoretical drug content) ×100.

Surface morphology study (SEM)

The SEM analysis was carried out using a scanning electron microscope. Prior to analysis, samples were placed on an aluminium stub with double-sided adhesive tape and rendered electrically conductive in vacuum coating with a thin layer of gold (approximately 20 nm). The scanning electron microscope was operated at an acceleration voltage of 5 kV and resolution of 3400.[9]

DSC study

The DSC analysis was conducted after the excipients were combined individually with the pure drug in a 1:1 ratio. DSC of the bulk drug curcumin was performed using DSC instrument (Perkin Almer, U.S.A.) for measurement of the heat loss or gain resulting from the physical or chemical changes within a sample as a function of temperature. About 6-7 mg of the individual component or drug excipient combinations were weighted in aluminium DSC pans, and hermetically sealed capsules were prepared with aluminium lids. An initial ramp was used to jump the temperature to 40°C and then a constant heating rate of 10°C/minutes was used up to 300°C under nitrogen atmosphere.[10]

In vitro drug release study

The in vitro release of curcumin microspheres was done in phosphate buffer pH 7.4 for 12 hrs in USP-I Basket-type dissolution apparatus at a temperature of 37°0±0.5°C. The volume of the dissolution medium was 900 ml and agitated at 100 rpm throughout the study. Microspheres equivalent to 100 mg of drug were taken and they were transferred to the basket. The sample was taken in every 1 hour for 12 hrs. The removed samples were replaced with an equivalent amount of dissolution medium to preserve the sink condition. After suitable dilution, samples were analysed by UV-visible spectrophotometer at 426 nm.[11]

Accelerated stability studies of microspheres

Stability studies were performed according to ICH guidelines. The stability study was carried out using the batch F2. Formulation F2 was divided into 3 sets of samples and stored at $5^0 \pm 3^0$C in refrigerator and stored in hot air oven at room temperature for (37 ± 2°C, 65% ± 5% RH) and their % drug content and in vitro releases were determined for every 1 month. Similarly, an accelerated stability study was carried out by storing the selected formulation at (45 ± 2°C, 75% ± 5% RH) for a period of 3 months. Drug content of all samples were determined by the method as in drug content at 0 month,

3 months and 6 months. In vitro release study of formulation F2 was also carried at 0 month, 3 months and 6 months of storage.[12]

Preparation of microencapsulated vaginal bio adhesive gels

Selected batches of curcumin microspheres were incorporated in gels by mechanical stirring method using bio adhesive polymer, such as Carbopol 934 given in Table 2. Carbopol 934 (1 g) was dispersed in distilled water (100 g) by continuous stirring for 15-20 min with other formulation additives. For all batches, the microspheres were mixed with prepared bio adhesive gels. Mixture was stirred until thickening occurred and neutralized by drop wise addition of triethanolamine. Then the prepared gels were packed in wide mouth plastic jars covered with screw capped plastic lid after covering the mouth with an aluminium foil and were kept in cool place for further study.[13]

Table 2: Experimental design of microencapsulated bio adhesive vaginal gels.

Microencapsulated Bio adhesive Vaginal Gels Compositions Amount taken in percentage (w/w)						
Formulation	**Microcapsules**	**Carbopol 934**	**Triethanolamine**	**Alcohol**	**Propylene glycol**	**Distilled water**
FS1	1	0.2	0.5	20	10	q. s.
FS2	1	0.4	0.5	20	10	q. s.
FS3	1	0.6	0.5	20	10	q. s.
FS4	1	0.8	0.5	20	10	q. s.

Characterization of prepared vaginal gels

Estimation of curcumin in vaginal gels

0.5 gm gel was weighed accurately and suspended in 25 ml of simulated vaginal fluid (SVF). Then after constant stirring it was filtered and analysed by using UV-Visible spectrophotometer after suitable dilution at 427 nm.

Drug content uniformity

In the beginning the formulations were tested for homogeneity by visual inspection. 6 tubes were sampled from different locations in the mixer and assayed for drug content as mentioned above to confirm the homogeneity of drug content in the gel formulation. For all the formulations studies were performed in triplicate.

Determination of pH

By using digital pH meter (Model MK–VI, Kolkata, India), the pH of the microencapsulated Carbopol gels were determined. 1 g of gel was dissolved in 25 ml of distilled water, and the electrode was dipped in the gel for 30 minutes before a constant reading was obtained. And then the constant reading was noted. Every formulations pH measurement was repeated three times.[14]

Viscosity measurement

The Brookfield digital viscometer (Brookfield Engineering Laboratories, Model DV-II, Mumbai) with a suitable sample adaptor was used to measure the viscosities of microencapsulated gel prepared in cps.

Determination of spreadability

Spreadability was measured by using a TA-XT2 Texture Analyzer with a TTC Spreadability Rig (HDP/SR) attachment (Texture Technologies Corp.) at 25 °C and 37 ° C. Samples were filled into a beaker with special attention to avoid bubbles formation. Force expressed in Newtons was measured for the duration of the test and spreadability was equated to the AUC24, 25. Each treatment was completed in triplicate.[15][16]

Extrudability study

A closed collapsible tube containing more than 20 g of gel was tightly pressed at the crimped while conducting the test, and a clamp was applied to prevent any rollback. The cap was removed and the microencapsulated gel was extruding until the pressure was dissipated.[17]

In vitro drug diffusion studies of microencapsulated vaginal gels

A modified open diffusion cell was used for drug release from the curcumin microsphere gel. Commercial semi permeable egg membrane was used as the permeation barrier. Before the study the membrane was soaked overnight in SVF. Then 1gm of gel was kept carefully between the donor and receptor compartment. The donor compartment is empty and it is open to the atmosphere but the receptor compartment holds 100 ml SVF. The contents of the receptor compartment were maintained at a temperature 37° ± 5 °C and stirred on a magnetic stirrer with a stirring speed of 25 rpm. Samples of 1 ml were withdrawn from receptor compartment for every hour and replaced with equal volumes of fresh receptor medium. Samples were analysed for curcumin by UV-Spectrophotometer at 427 nm.[2]

Release Kinetic studies of microencapsulated vaginal gels

In order to study the exact mechanism of drug release from the microencapsulated gels, drug release data was analysed according to zero order, first order, Higuchi square root and Korsemeyer-Peppas equations. The goodness of fit test was used as the criterion for selecting the most suitable model.[18]

Accelerated stability studies of microencapsulated vaginal gel

Stability studies were performed according to ICH guidelines. The formulations were stored at $5^0 \pm 3^0$C in refrigerator and in hot air oven at 37°±2°C and 45°± 2°C for a period of 3 months. The samples were analysed for

drug content after 3 months by UV-Visible spectrophotometer at 427 nm. Stability study was also carried out by measuring the change in pH of gel at regular interval of time.[19]

RESULTS AND DISCUSSION

Drug excipient compatibility study using FT-IR

FT-IR spectrum of drug, polymer and drug-polymer mixture is shown in Fig. 1-3 respectively. From the FT-IR spectra of drug and drug polymer mixture, it was found that drug and polymer are compatible with each other.

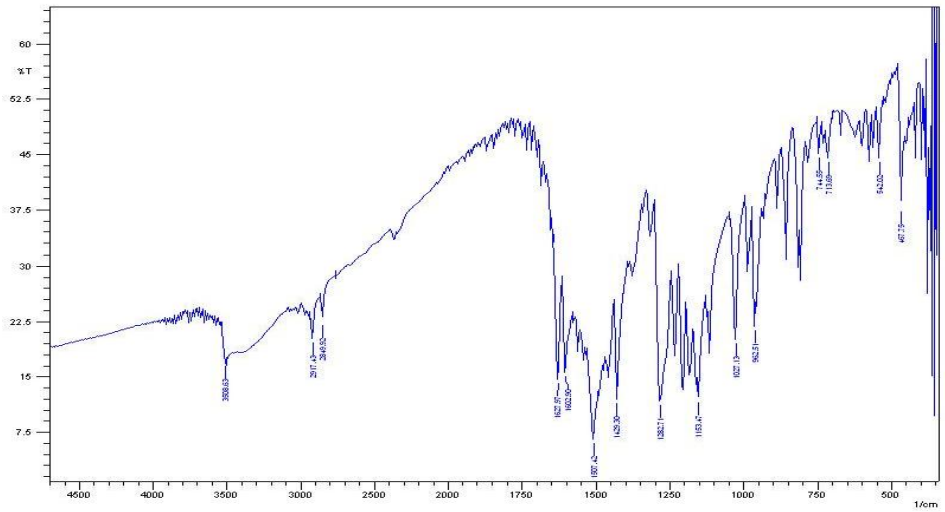

Fig. 1: Fourier transform infrared spectra of curcumin.

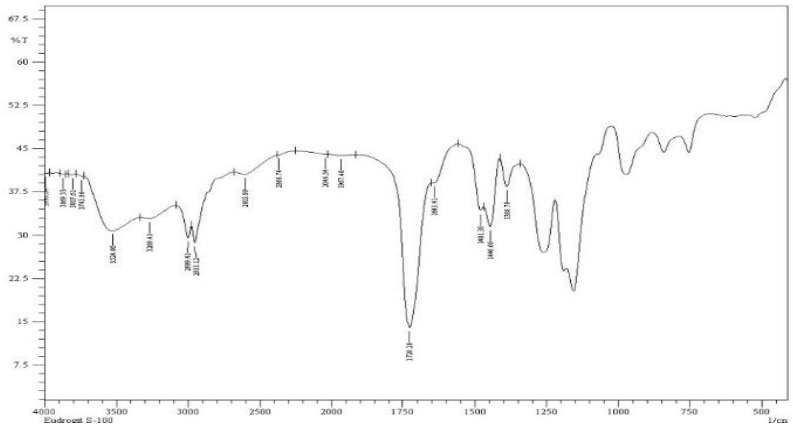

Fig. 2: Fourier transform infrared spectra of polymer (Eudragit S 100).

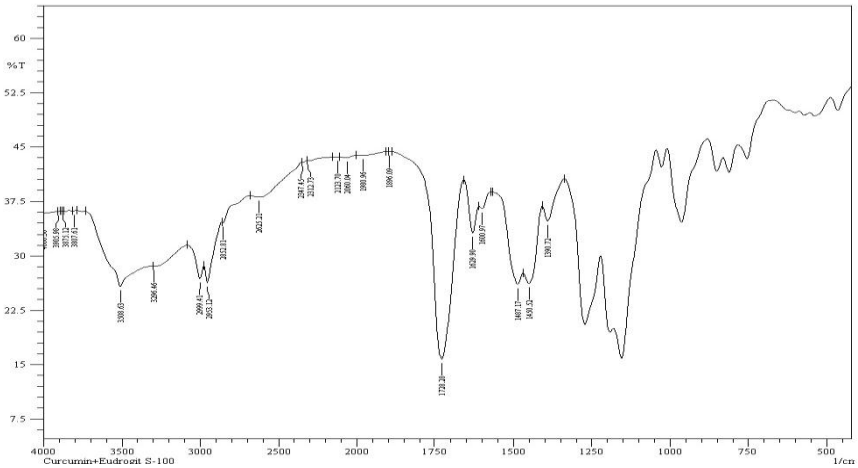

Fig. 3: Fourier transform infrared spectra of physical mixture of drug and polymer (Eudragit S 100).

Drug excipient compatibility study using DSC

When comes to preparation of a drug formulation, it becomes necessary to evaluate the interactions between the drug and the polymer. The DSC thermogram of pure curcumin shows a sharp endothermic peak at 182°C which corresponds to its melting point. The thermogram of curcumin with Eudragit S 100 shows sharp endothermic peak at 184.63°C. Thus, the thermal data shown in Fig. 4, 5 thus, does not show any interaction between the drug and polymer.

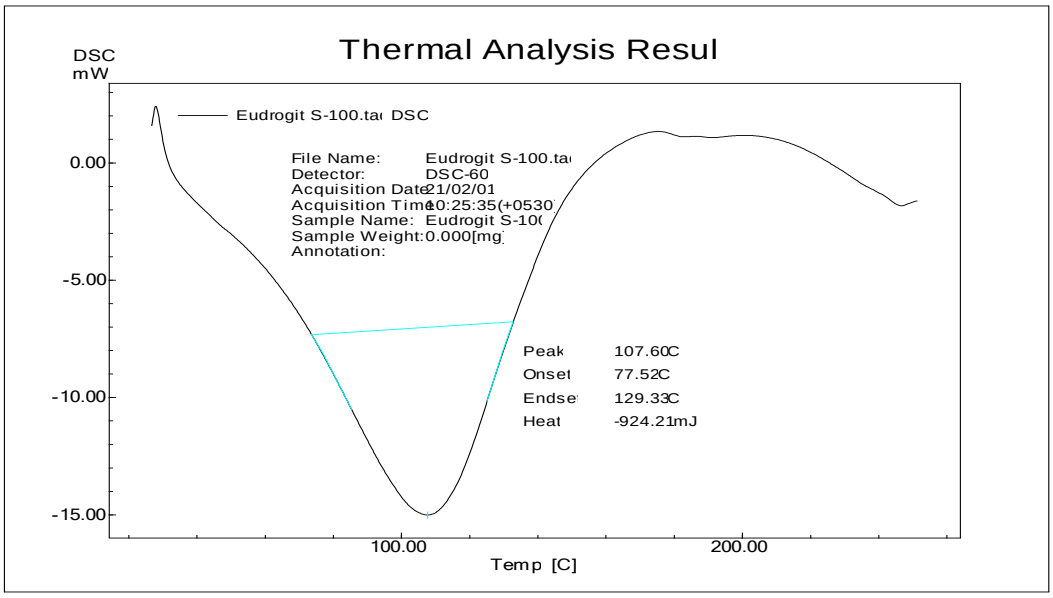

Fig. 4: Differential scanning calorimetry study of polymer (Eudragit S 100).

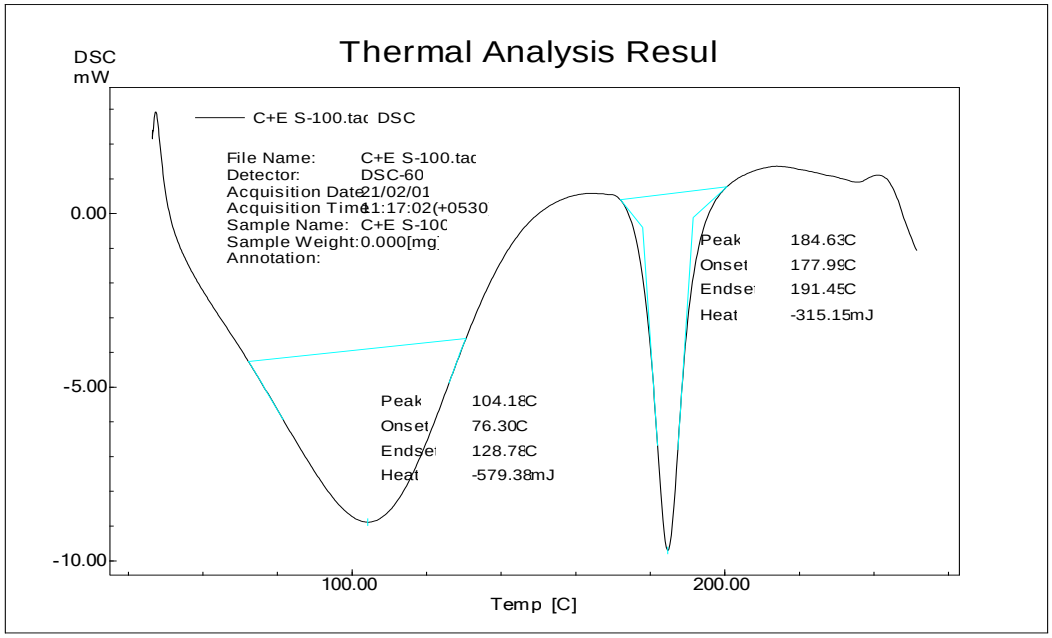

Fig. 5: Differential scanning calorimetry study of physical mixture of drug and polymer.

Physico-chemical characteristics

The average entrapment efficiency (%) of curcumin microsphere formulations is shown in Table 3 and was found to be 58.75%, 84.23%, 70.86%, 64.29% and 78.15% in the formulations F1, F2, F3, F4 and F5. The average entrapment efficiency of the formulations increased with increasing polymer concentration. The maximum entrapment efficiency (84.23%) was observed in formulation F2 which is shown in Fig. 6. Weak aqueous solubility and high drug binding potential on polymer surfaces may explain the shift in drug entrapment.

Table 3: Percentage yield, drug content and entrapment efficiency of formulations F1-F5.

Formulation code	%Yield	%Drug content	%Entrapment efficiency
F1	56.23	43.65	58.75
F2	83.05	74.16	84.23
F3	71.47	65.22	70.86
F4	62.19	53.54	64.29
F5	72.86	68.92	78.15

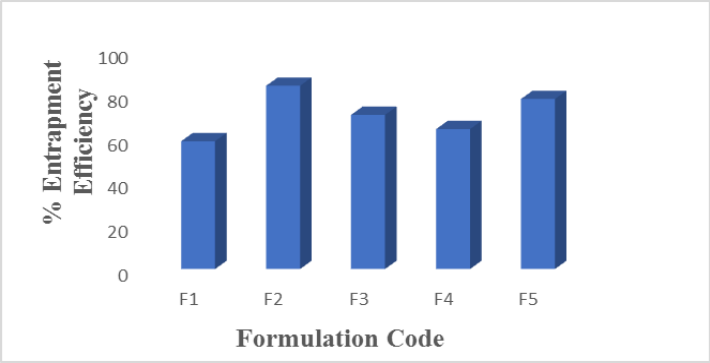

Fig. 6: Percentage Entrapment Efficiency of Formulations F1-F5.

Surface morphology study (SEM)

The microspheres prepared by solvent evaporation method have good spherical shape with smooth surface in its morphology, and the particles were distributed uniformly without forming any clump and it is shown in the Fig. 7. The particle sizes seen in SEM photomicrographs correspond to those calculated by optical microscopic methods.

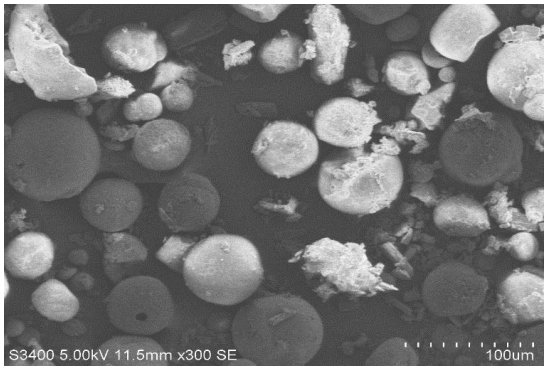

Fig. 7: Scanning electron microscopy of curcumin microsphere.

In vitro release of microspheres

Cumulative percentage drug released for F-1, F-2, F-3, F-4 and F-5 after 12 h were found to be 69.70%, 81.58%, 73.39%, 63.14%, 72.23% respectively. F2 formulation which showed maximum drug release. Hence F2 formulation was considered as an ideal formulation. Fig. 8.

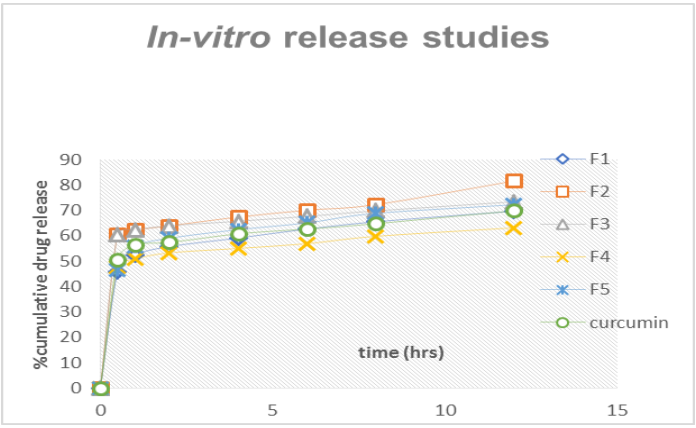

Fig. 8: Comparative in vitro release profiles of Curcumin microspheres.

Stability studies

The results of drug content of ideal formulation F2 after 6 months of stability testing at different storage conditions were shown in Fig.9. Table 4. In vitro release profiles for the same formulation stored at different storage conditions were also showed in Fig. 9. On comparing this data with the previous data of F2, it was observed that there was a slight decrease in drug content when the formulation was stored at $5^0\pm 3^0$C, Room temperature and at $45^0 \pm 2^{\circ}$C/75% RH.

Table 4: Stability study - % drug content of formulation F2 after three months of storage at 5º± 3ºc, room temperature 37º± 2ºc/65%rh and 45º± 2ºc/75% rh.

Temperature in ºC	% Drug content
5º ± 3º C	87.45
37º ± 2º C/65%RH	86.32
45º ± 2º C/75%RH	79.02

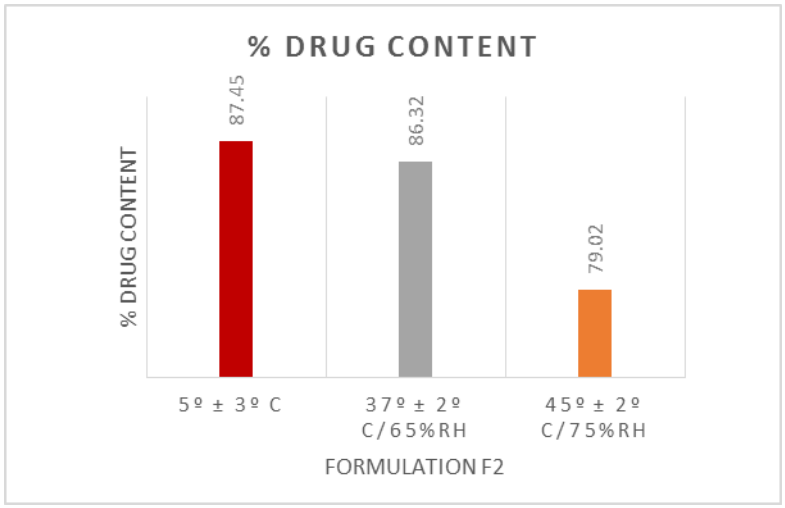

Fig. 9: Stability study - % drug content of formulation F2 after three months of storage at 5º± 3ºC, room temperature 37º± 2ºC/65%RH and 45º± 2ºC/75% RH.

Drug content and uniformity

The drug content and homogeneity of microencapsulated gel formulations is given in Table 5. The drug contents of the prepared microencapsulated gels were found to be in the range of 71.93- 94.52% indicating that the bio adhesive vaginal gel system with high drug content uniformity.

pH measurement

The pH of gels is given in Table 5 and it was found to be within the range of 6.8 to 7.4 which is within the limit of semisolid specifications. Because of the nearly neutral pH, the gel will be non-irritant to vagina.

Table 5: Physical properties of microencapsulated bio adhesive vaginal gels.

Formulation code	Drug content (%)	Drug content uniformity	pH
FS1	71.93	*	7.2
FS2	85.67	**	7.4
FS3	94.52	***	6.8
FS4	90.23	**	7.4

** (good), ** (very good), ***(excellent).*

Spreadability and extrudability

Spreadability is essential for patient compliance and aids in the application of gel to the skin in a uniform manner. A good gel spreads quickly and has a wide spreadability range. The spreadability of formulated gels decreases as the concentration of polymer increases. Extrudability of gel formulations with low polymer content was found to be adequate, whereas extrudability of gel formulations with high polymer content was found to be excellent. By taking the data of spreadability and extrudability as given in Table 6, among all the formulations, formulation FS3 having good spreadability and extrudability and it was selected.

Table 6: Rheological properties of microencapsulated bio adhesive vaginal gels.

Formulation code	Spreadability (g.cm/sec)	Extrudability	Viscosity (cps) (X ×10 ^{4})
FS1	057.69	**	2.325
FS2	150.01	**	1.819
FS3	166.67	***	1.654
FS4	187.51	**	1.544

** (good), ** (very good), ***(excellent).*

Viscosity

Viscosity is a parameter used for characterizing the gels as it affects the spreadability, extrudability and release of drug. The Table 6 showed the data of viscosity. The viscosity of gels was increased with the increasing Carbopol content that may be due to the increase in formation of three-dimensional cross-linking structure of gel, as expected.

In vitro drug diffusion studies and release kinetics

The diffusion profile of various Microencapsulated Bio adhesive Vaginal Gels is shown in Fig. 10. Each point represents as mean ± S.D. The in vitro drug release of all the formulations (FS1-FS4) was found sustained and influenced by the polymer added. The in vitro drug release profile was presented Table 7, Fig. 10. To categorize the kinetics of drug release from microencapsulated gel, release data was verified with different kinetic models. The Table 8 indicated that drug release from the ideal formulation obeyed Higuchi kinetic equation which obeyed Korsemeyer and Peppas kinetics and showed that the ideal formulation released the drug by diffusion following Non Fickian transport mechanism (n>0.5).

Table 7: Vaginal bio adhesive strength, invitro drug release data of microencapsulated bio adhesive vaginal gels.

Formulation code	Vaginal bio adhesive strength (Kg)	Cumulative % drug release (X ± S.D.) (12 h study)
FS1	0.02	66.431 ± 1.31
FS2	0.19	76.312 ± 0.98
FS3	0.23	42.181 ± 1.09
FS4	0.17	63.984 ± 1.14

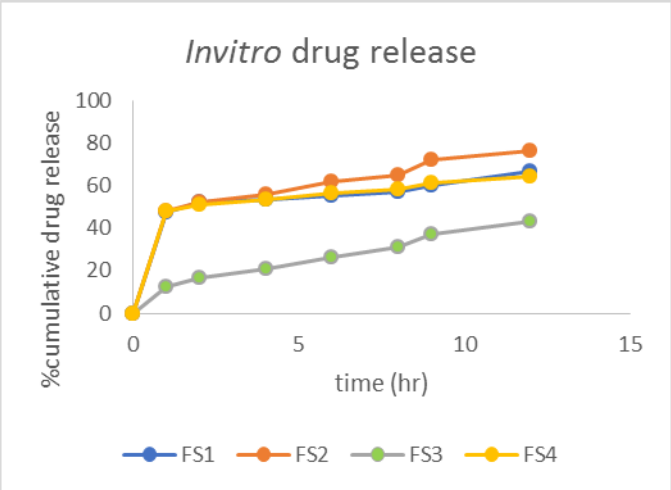

Fig. 10: Comparative in vitro release profiles of curcumin bio adhesive vaginal gel.

Table 8: Drug release kinetics data of optimized microencapsulated bio adhesive vaginal gel.

Model name	r^2
Zero order (r)	0.947
First order (r)	0.969
Higuchi square root (r)	0.979
Korsmeyer peppas (r)	0.634
n	0.94

Accelerated stability studies of microencapsulated gel

The accelerated stability studies were performed according to ICH guidelines for 3 months and the results of drug content of ideal formulation FS3 after 3 months of stability testing at different storage conditions were shown in Fig. 11. the results were found to be stable in varying temperature as shown in Table 9 and Fig.12.

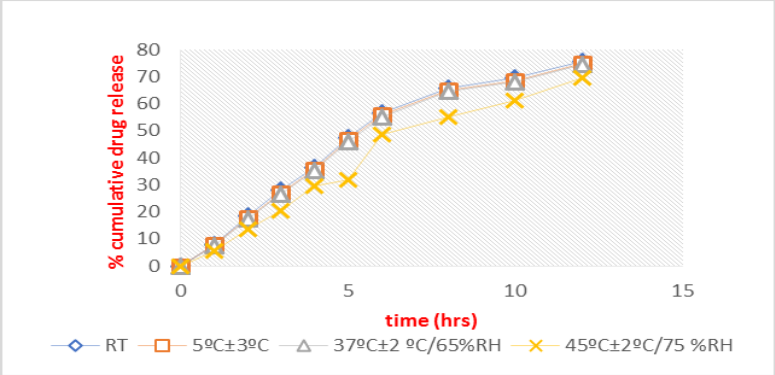

Fig. 11: Stability study - In vitro drug release of formulation F2 after three months of storage at 5º± 3ºC, room temperature 37º± 2ºC/65%RH and 45º± 2ºC/75% RH.

Table 9: Accelerated stability study of selected microencapsulated bio adhesive vaginal gel.

Temperature in ºC	% Drug content
5º ± 3º C	92.45
37º ± 2º C/65%RH	89.32
45º ± 2º C/75%RH	65.02

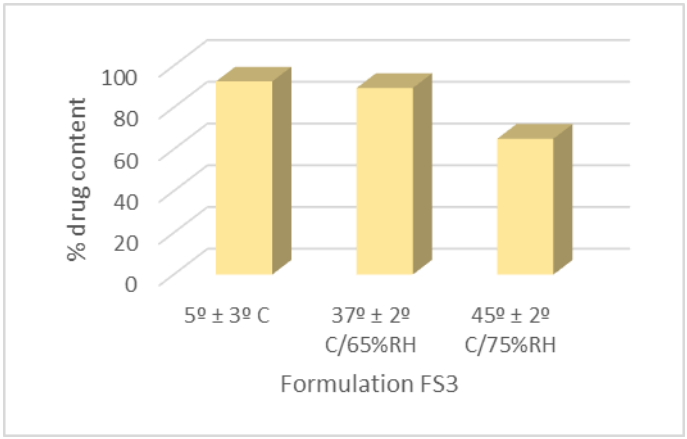

Fig. 12: Stability studies of curcumin bio adhesive vaginal gel.

CONCLUSION

In conclusion, although most of the times regarded as an alternative to more conventional routes of drug delivery, vaginal drug administration has proven to be useful and even advantageous in some particular cases. Gels have been used for quite a long time as drug carriers and recent advances in gel and polymer technology attracted researchers' interest to these polymeric systems. F2 formulation containing drug: polymer ratio 1:2 was found to be the best microsphere formulation, including all the properties evaluated in order to achieve one objective of this study. Formulation F2 was selected on basis of its slower release rate, higher entrapment efficiency and excellent flow property for its use in next objective. Another objective was to further incorporation of selected microspheres in gel by using different concentration of Carbopol 934 polymer for prolonging the bio adhesion and drug release. The evaluation reports of microencapsulated gel explained FS3 gel (containing 1 % w/w of drug loaded microspheres and 0.6 % w/w of Carbopol 934) was found to be the best, releasing about 84% of curcumin over a period of 24 hours in SVF (simulated vaginal fluid) successfully. The novel formulation design facilitated the optimization and successful development of microencapsulated bio adhesive vaginal gel formulations for enhanced vaginal drug delivery by optimum vaginal bio adhesion and longer retention. Thus, the data concluded that the microencapsulated vaginal gel protocol may be an effective strategy for the development of easy, reproducible and cost-effective method to prove its potential for safe and effective vaginal delivery therapy. This technique can be further tested for the development of different vaginal carrier therapeutics.

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