Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Research Article

CURCUMIN LOADED POLYMERIC MICROSPHERES FOR VAGINAL DELIVERY: FORMULATION DESIGN, IN VITRO EVALUATION, KINETICS AND STABILITY STUDIES

J. Adlin Jino Nesalin, Shafiya Khanum *

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar-571422, Maddur Taluk, Mandya District, Karnataka, India

*Corresponding Author Email: shafakbar@gmail.com

DOI: 10.7897/2277-4572.102206

Received on: 18/03/21 Revised on: 10/04/21 Accepted on: 14/04/21

ABSTRACT

The main objective of this research is to evaluate a new approach for the preparation of bio adhesive microparticles and to design an innovative vaginal delivery system for curcumin which is able to enhance the drug anticancer activity. Curcumin encapsulated microspheres were prepared by solvent evaporation method. 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) was incorporated into gels with a bio adhesive polymer. The microencapsulated vaginal gels were evaluated for pH, spreadability, extrudability, viscosity, in vitro drug release, drug release kinetics, bio adhesion test, accelerated stability of selected gel formulation. In vitro drug release rate for selected microencapsulated 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. Thus, in conclusion preparation protocol of microencapsulated vaginal gel study may be adopted for a successful development of newer drug delivery system of other drugs for administration to vagina.

Keywords: Curcumin, Microspheres, Microencapsulated vaginal gel, Characterization.

INTRODUCTION

The prevalence of superficial and invasive fungal infections has risen dramatically in the last two decades[1]. Worldwide annually we observe two to three percent of deaths record arise from different types of cancer and it continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviours, particularly smoking[2,3]. Since long time the vagina has been used as a route for drug delivery, traditionally with the purpose of obtaining a local pharmacological effect, although some systemic drug absorption was observed. The ideal vaginal drug delivery system should be easy to use, discreet, painless to the patient, cost effective, widely available, and safe for continuous administration. It should also allow self-administration, with minimal interference with body functioning and daily life, and obtain high bioavailability with other medications[4]. Multiple-unit bio adhesive carriers such as microparticles combine the abilities of the bio adhesive dosage forms with the advantageous features of the multiparticulate delivery systems. Microparticles include a more uniform dispersion in the targeting site, more reproducible drug adsorption and reduced local irritation. Creams, ointments, and gels are the most commonly used semi-solid formulations for vaginal drug delivery. Vaginal semisolids, particularly gels based on bio adhesive polymers currently receiving a great deal of interest as vaginal delivery systems. 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. Gels are semi-solid structures that contain small quantities of solid dispersed in large amounts of liquid but have a solid-like appearance. Gels have a number of advantages over other vaginal drug delivery systems, including increased bioavailability, efficacy, flexibility, and cost savings[5].

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%). Kept under mechanical stirring with a three-blade propeller (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[6]. And the evaluation parameters is shown in Table 2.

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. 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[7].

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. Further to confirm the homogeneity of drug content in the formulation of the gel, 6 tubes were sampled from the different locations in the mixer and assayed for the drug content as stated above. 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. The measurements of pH of each formulation were replicated three times[8].

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[9].

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[10 ,11].

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[12].

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[13].

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 Korsmeyer-Peppas equations. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test[14, 15].

Accelerated stability studies of microencapsulated vaginal gel

Stability studies were performed according to ICH guidelines. The formulations were stored at 5º± 3ºC 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[16].

RESULTS AND DISCUSSION

Drug content and uniformity

The drug content and homogeneity of microencapsulated gel formulations is given in Table 4 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. 4 and it was found to be within the range of 6.8 to 7.4 which is within the limit of semisolid specifications. The almost neutral pH reflected, the gel will be non-irritant to vagina.

Spreadability and extrudability

Spreadability plays an important role in patient compliance and also helps in uniform application of gel to the skin. 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. 5, among all the formulations, formulation FS3 having good spreadability and extrudability and it was selected.

Viscosity

Viscosity is a parameter used for characterizing the gels as it affects the spreadability, extrudability and release of drug. The Table 5 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

Fig. 1. Shows the diffusion profile of various Microencapsulated Bio adhesive Vaginal Gels. 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 6, Fig 1. To categorize the kinetics of drug release from microencapsulated

gel, release data was verified with different kinetic models. The Table 7 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).

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. 2 the results were found to be stable in varying temperature as shown in Table 8.

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

TABLE 2: EVALUATION PARAMETERS OF PREPARED CURCUMIN MICROSPHERES

Evaluation parameter	F1	F2	F3	F4	F5
%Drug content	43.65	74.16	65.22	53.54	68.92
Encapsulation efficiency (%)	58.75	84.23	70.86	64.29	78.15
Invitro drug release (12hr study) (%)	69.70%	81.58%	73.39%	63.14%	72.23%
Stability studies	5º± 3ºC, Room temperature				

TABLE 3: 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.

TABLE 4: 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)

TABLE 5: 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).

TABLE 6: 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

TABLE 7: 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

TABLE 8: ACCELERATED STABILITY STUDY OF SELECTED MICROENCAPSULATED BIOADHESIVE 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

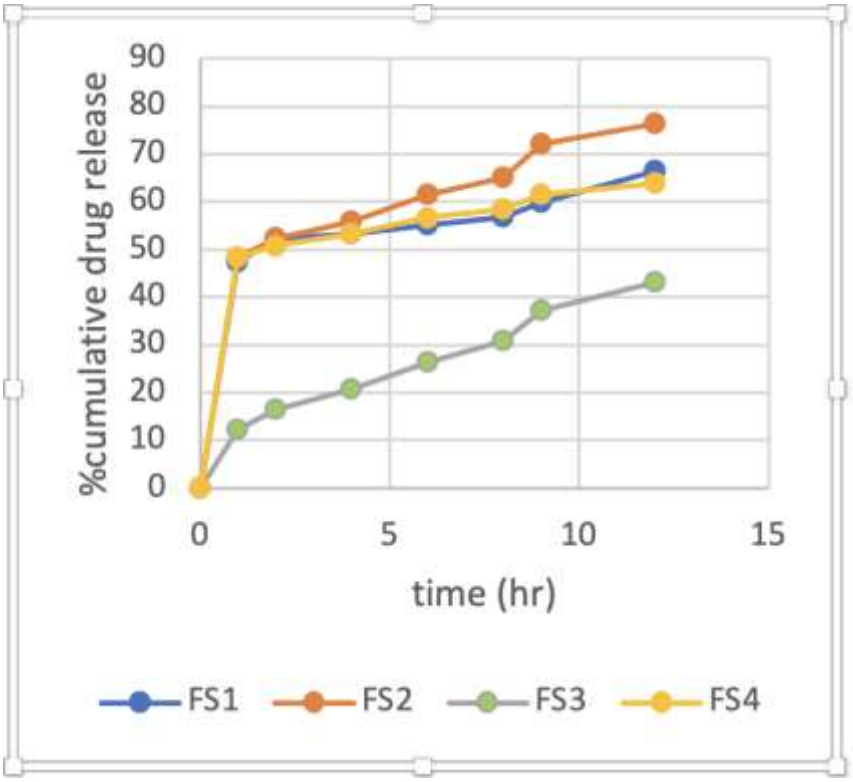

Figure 1: Comparative in vitro release profiles of curcumin bio adhesive vaginal gel

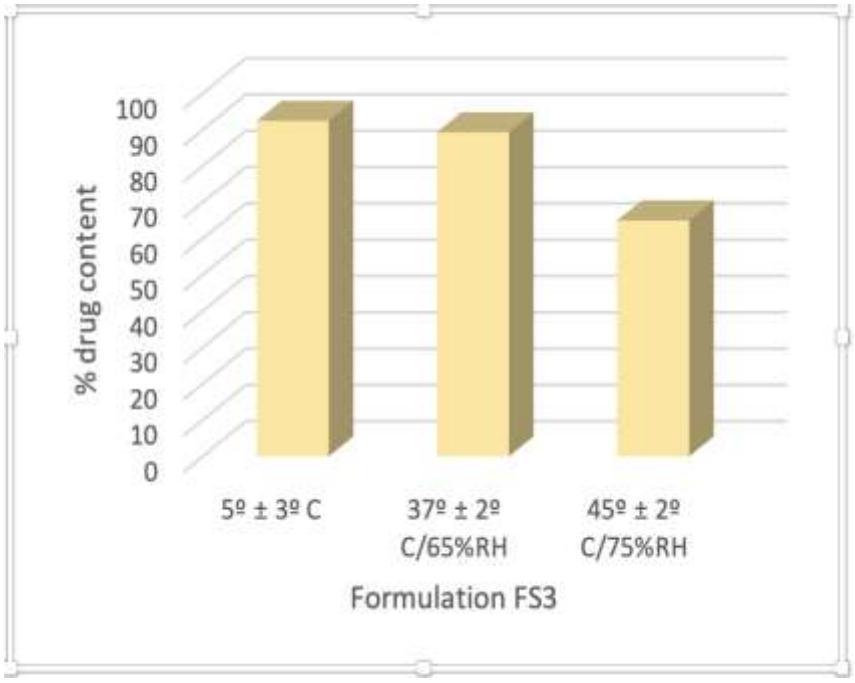

Figure 2: Stability studies of curcumin bio adhesive vaginal gel

CONCLUSION

In conclusion, F2 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 microcapsules in gel by using different concentration 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 successfully. The novel formulation design found to be successful development of Microencapsulated bio adhesive vaginal gel formulation for enhanced vaginal drug delivery by optimum vaginal bio adhesion and longer retention. The data concluded that bio adhesive vaginal gel 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.

ACKNOWLEDGEMENT

The authors are thankful to Natural Remedies for providing the drug as a gift sample for this work.

REFERENCES

1. Kamel R. Study of the influence of selected variables on the preparation of prolonged release bioadhesive vaginal carbohydrate microspheres using experimental design. J Drug Del Sci Tech 2013; 23(3):247-54.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics CA: Cancer J Clin 2005; 55(2):78-108.
3. Jemal A, Bray F, Center MM, J. Ferlay, ward E, Forman D. Global Cancer Statistics CA: Cancer J Clin 2011; 61(2):69-90.
4. Das Neves J, Bahia MF. Gels as vaginal drug delivery systems. Int J Pharma. 2006; 318(1-2):1-4.
5. Albertini B, Passerini N, Di Sabatino M, Vitali B, Brigidi P, Rodriguez L. Polymer–lipid based mucoadhesive microspheres prepared by spray-congealing for the vaginal delivery of econazole nitrate. Eur J Pharm Sci 2009; 36(4-5):591-601.
6. Kalita BA, Saikia KR, Kalita BH. Formulation and evaluation of metronidazole microspheres-loaded bioadhesive vaginal gel Asian J Pharm Clin Res 2017; 10(3):418-24.
7. Pavelić Ž, Škalko-Basnet N, Schubert R. Liposomal gels for vaginal drug delivery. Int J Pharm 2001; 219(1-2):139-49.
8. Bhowmik BB, Nayak BS, Chatterjee A. Formulation development and characterization of metronidazole microencapsulated bioadhesive vaginal gel. Int J Pharm Pharm Sci 2009; 1(1):240-57.
9. Ritger PL, Peppas NA. Modelling of water transport solute release in physiologically sensitive gels. J Cont Rel 1987; 5:37-4.
10. Glibowski P, Zarzycki P, Krzepkowska M. The rheological and instrumental textural properties of selected table fats. J Food Prop 2008; 11:678–86.
11. Garg A, Aggarwal D, Garg S, Singla AK. Spreading of semi-solid formulations: an update. Pharm Tech 2002; 84–105.
12. Carstensen JT. Drug Stability, Principles & Practices. New York: Marcel Dekker; 1989. p. 17-58.
13. Hani U, Bhat RS, Shivakumar HG. Formulation design and evaluation of metronidazole microspheres in a bioadhesive gel for local therapy of vaginal candidiasis. Lat Am J Pharm 2011; 30(1):161-7.
14. Schmolka IS. Formulation and evaluation of ophthalmic gel for sustained release of drug. J Biomed Mater Res 1972; 6:571-75.
15. Chi SC, Jun HW. Release rate of Ketoprofen from Polaxomer Gels in a membrane less diffusion cell. J Pharm Sci 1991; 80(3):281-83.
16. Jones D. Pharmaceutical Statistics. London: Pharmaceutical Press; 2002. p. 315-33.

How to cite this article:
J. Adlin Jino Nesalin and Shafiya Khanum. Curcumin loaded polymeric microspheres for vaginal delivery: Formulation design, In vitro evaluation, kinetics and stability studies. J Pharm Sci Innov. 2021;10(2):56-60.
http://dx.doi.org/10.7897/2277-4572.102206

Source of support: Nil, Conflict of interest: None Declared

Disclaimer: JPSI is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publishing quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. JPSI cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of JPSI editor or editorial board members.