Ind. J. Pharm. Edu. Res., 2024; 58(1):91-98.
https://www.ijper.org

Original Article

Fabrication and Evaluation of Poloxamer Facilitated, Glyceryl Monooleate based 5-Fluorouracil Cubosomes

Jawaher Abdullah Alamoudi[1], Yosif Almoshari[2], Hadil Faris Alotaibi[1,*]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, SAUDI ARABIA.
[2]Department of Pharmaceutics, College of Pharmacy, Jazan University, Jazan, SAUDI ARABIA.

ABSTRACT

Objectives: This study aims to prepare a topical cubosomal formulation that contains 5-Fluorouracil (5-FU), a hydrophilic anti-cancer drug, that belongs to the Biopharmaceutics Classification System (BCS-III) i.e., high solubility and low permeability. **Materials and Methods:** The 5-FU loaded cubosomes were prepared using Glyceryl Monooleate (GMO) as a lipid polymer, in the presence of Poloxamer 407 (Polox-407) and Tween 80 (T80) as stabilizers. Four formulations of cubosomes were formulated by varying concentrations of Polox-407 and GMO while keeping the concentration of T80 constant. A melting, followed by homogenization technique has been used for the preparation of 5-FU cubosomes. Several *In vitro* characterization experiments, chemical compatibility studies, pH, viscosity, Scanning Electron Microscopy (SEM), particle size analysis, zeta potential, *in vitro* drug release studies, *in vitro* permeation study, and stability studies were performed. **Results:** The compatibility studies have confirmed the chemical compatibility of the drug and ingredients, while stability analysis has assured that the prepared formulations were stable. Particle size analysis and surface morphology showed that particles were nano-sized with suitable cubical shapes, well segregated from each other. The zeta potential was -0.6 mV and viscosity has been recorded as 18 cP. The drug release and permeation studies revealed that the cumulative amount of the drug was 95% and 94% respectively. **Conclusion:** Altogether, these findings suggested that upon further optimization, this formulation may have the potential to be translated as an effective therapy for the clinical management of superficial cancers.

Keywords: Cubosomes, Permeation, Drug release, Thermal analysis.

Correspondence:
Dr. Hadil Faris Alotaibi
Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, SAUDI ARABIA.
Email: HFAlotaibi@pnu.edu.sa

Received: 21-04-2023;
Revised: 30-08-2023;
Accepted: 24-10-2023.

INTRODUCTION

5-Fluorouracil (5-FU), has been considered as a fluorinated pyrimidine analogue. It is an anti-neoplastic molecule that has been extensively used alone as well as in combination with chemotherapy regimens for treating the cancer of GIT.[1] However, 5-FU is restricted due to its GIT toxicity, severe bone marrow disturbances, and hematologic side effects.[2] Furthermore, due to the low plasma half-life (10-20 min) as well as the elevated metabolism rate of this drug in the body, the care of a therapeutic concentration of serum levels needs some constant high-dose administration.[3,4] Raised 5-FU levels in plasma could affect hazardous side effects as well as antitumor properties of this drug contingent on the exposure time rather than the concentration of plasma.[5] Prior reports have specified that the 5-FU sustained release formulations[6-8] as well as selective transport towards the site of tumor[9,10] not only recover antitumor activity nonetheless it correspondingly decrease the side effects of 5-FU when associated with the clinically available 5-Fluorouracil formulation.

In the presence of too much water, Glycerol Monooleate (GMO) has been shown to spontaneously transform into fluid crystalline cubic phases made up of bi-continuous bilayers of lipids that extend in 3 dimensions as well as divided into 2 sets of water channels.[11] Cubic phases can include and regulate the release of medicines with different molecular weights and polarity because of the special structure of GMOs.[12] There are 3 common macroscopic types of cubic phase: precursor, bulk, and particle (also known as cubosomes). Typically liquid, precursor materials only enter the cubic phase in reaction to external stimuli like dilution.[13] Bulk forms of the cubic phases are fluid-like crystalline substances that are often composed of hydrated monoolein and frequently contain a medication.[14] The bulk cubic gel is a superb option for use as a drug delivery matrix due to its biodegradability, high viscosity, capacity to integrate and distribute pharmaceuticals of various sizes, and solubility in water as well as capacity to improve the biochemical and physical properties of included drugs. However, cubic gel's substantial viscosity and stiffness restrict its ability to be used as a delivery system on its own.[15] Cubosomes are produced as a result of the cubic lipid phases being

DOI: 10.5530/ijper.58.1.9

emulsified in water. These nanoparticulate dispersal systems have great bioadhesion and biocompatibility.[16] It has been established that the internal structure and properties of the bulk phase are retained by the dispersed particles. These adaptable systems of delivering drugs can be used for a variety of administration methods, including parenteral, intravenous, and percutaneous.[17] Cubosomal dispersions have some advantages over bulk gel, for example, a higher surface area and great fluidity (less viscosity).[18] However, cubosomes are not anticipated to provide the same chances to control the release of drugs as compared to the bulk cubic phase because of their extremely small dimensions (and consequently short diffusion paths).[19] Additionally, the integration of water-soluble medicines is challenging due to the substantial quantity of liquid present during cubosome formation.[20]

This study describes the formulation of cubosomes of hydrophilic drug 5-Fluorouracil (5-FU). The prepared four formulations of 5-Fluorouracil cubosomes have been extensively characterized and evaluated *in vitro* as a potential topical drug delivery approach that can deliver a high concentration of 5-Fluorouracil.

MATERIALS AND METHODS

Materials

5-Fluorouracil, Glycerol Monooleate (GMO), poloxamer 407, and tween-80 were purchased from Sigma-Aldrich (Milwaukee, USA). All the chemicals used were of analytical grade.

Preparation of 5-FU cubosomes

Different combination of the ingredients was tried to formulate the cubosome. Stearic acid, glyceryl monostearate, poloxamer 188, and beta-cyclodextrin have been used in various ratios, but the trials were unsuccessful. However, the use of poloxamer-407 in combination with glyceryl monooleate was found useful in preparing the cubosomes. Cubosomes were prepared as discussed in a recent study.[21] Poloxamer 407 and GMO have been melted at 70°C in a water bath for blank cubic gel. Dropwise, the formulated molten solution was then added to distilled water (70°C) then vortexed at a very high speed at room temperature to attain a homogenous state. The drug was added in this phase and was mixed until a homogenous solution was formed. The prepared formulations were stored at room temperature for about 48 hr to obtain the cubosomes (Figure 1). The composition of all the ingredients is mentioned in Table 1.

CHARACTERIZATION

Chemical compatibility studies

The FTIR analysis was performed as one of the important and common techniques for conducting compatibility studies.[22,23] All the ingredients, individually as well as the formulation were subjected to FTIR scan in the range of 600 to 3800 cm^{-1}.[24]

pH

Compatibility of pH with physiological pH is very critical for stability and patient compliance. 1 mL of the formulation was taken and the probe of bench top digital pH meter was dipped in the formulation until a constant value was achieved.[25] The measurements were taken at 25±0.5°C.

Viscosity

The viscosity of all formulations was measured using Brookfield Viscometer (Brookfield Laboratories, Inc., Middleboro, MA). A Low Viscosity (LV) spindle was utilized and operated at 60 rpm. All the measurements were done at 25±0.5°C.

Determination of linearity curve

The linearity curve of 5-FU was plotted by screening 5-Fluorouracil in distilled water using a double-beam UV-visible spectrophotometer (Shimadzu, 2401/PC, Japan) at 266 nm. A stock solution of 1 mg/mL was prepared, followed by preparation of serial dilution in the range of 1-12 µg/mL, which was evaluated spectrophotometrically. A linearity curve taking absorbance at the Y-axis and concentration at the X-axis has been drawn.

Zeta potential and Particle size analysis

Zeta analysis and particle size distribution have been performed through dynamic light scattering by the use of Zeta Sizer (Nano ZS, Malvern, Worcestershire, UK). All the samples have been diluted (100-fold) by distilled water and then were measured at 2570.5 1C in triplicate.[21]

Scanning electron microscopy (SEM)

The morphology and structure of cubosomes were observed by using scanning electron microscopy (ZEISS EVO LS10 Germany) with a point-to-point resolution. On the grid of the holey film, a single drop of prepared formulation was instantly applied for the SEM interpretations, as well as then the images were obtained after drying.

X-ray Diffraction (XRD)

By the use of an X-ray diffractometer (JDX-3523, Tokyo, Japan), an X-ray Diffraction investigation of 5-FU loaded cubosomes and pure drug was performed. The pure drug and cubosome formulation were stored securely by using an aluminum cell and then were exposed to Cuka monochromatic radiations of the wavelength 1.54056 A°. Samples have been observed between 5° and 60° using 2θ° at a rate of 3/min.[26]

Entrapment Efficiency (EE) %

The Entrapment Efficiency (EE) is an essential parameter to assure that a suitable amount of drug has been entrapped and the particles would be able to provide a suitable amount of drug for therapeutic effect. For the determination of EE, 1 mL of the

formulation was taken in an Eppendorf and centrifuged at 10,000 rpm in a centrifuge machine, followed by separation of supernatant to check unbound drug in the sample. The spectrophotometric analysis was performed for the quantification of the drug, using a double-beam UV-visible spectrophotometer at the wavelength of 266 nm. Finally, the following mathematical equation has been used to calculate the %EE.[27]

$$\%EE = \text{Total drug added} - \text{Free drug} \div \text{Total drug added}) \times 100$$

In vitro drug release studies

In vitro release of the drug was performed in 500 mL distilled water, which had been performed via the USP XXIV method (Dissolution apparatus II, at 50 rpm and 37±0.5°C).[28] In a dialysis bag, 1 mL of the prepared formulation was placed. Then, samples of about 1 mL were taken out at very even time intervals and an aliquot quantity of distilled water was substituted. The samples were then investigated by the use of a UV-spectrophotometer at 266 nm.

Stability studies

Centrifugation

The prepared formulations were subjected to stability studies. The formulation was centrifuged at high speed to check the stability by observing any separation or formation of distinct layers. One mL sample of cubosomes was taken in Eppendorf and placed in a centrifuge machine (Refrigerated microcentrifuge, INNO MC 16 R) and spun at 5000 rpm for 30 min and then the formulations were observed.[29]

Freeze-thaw method

The formulations after passing through the centrifugation were subjected to the Freeze-thaw technique, in that, the formulations were shifted to the NMR tubes for the freeze-thaw cycle. After that, on a daily basis, the samples were frozen in a -20°C freezer for about 17±2 hr, and at last, they were thawed at about 40°C for 1 hr, and then the analysis was performed.[29]

Thermal stability analysis (DSC)

DSC was performed for the thermal analysis of the optimized formulation via TG and DSC analyzer (PerkinElmer STA 6000, USA). A sample of the formulation was retained in a closed aluminum pan and then was scanned from 25 to 400°C at 10°C/min flow rate heat. From the DSC thermograms of the samples, the peak transition temperature was observed.[30]

RESULTS AND DISCUSSION

Chemical compatibility of the ingredients

PF-127 exhibited a stretching region of C-H in the range of 2810-2889 cm^{-1}. Prominent peaks of alcohols, carboxylic acids, and ethers have also been observed at 1075cm^{-1}, 1100 $cm^{-1,}$ and 1120cm^{-1} respectively.[31] Similarly, the FTIR scan of GMO showed a sharp and intense peak corresponding to C=O at about 1700 cm^{-1} and a broad band appeared at 3320-3400 cm^{-1}, showing the presence of the -OH group. The Tween 80 FTIR spectra revealed the presence of both asymmetric as well as symmetric stretching bands of -CH_2 between 2850-2900 cm^{-1}, respectively. The strong band at 1730 cm^{-1} has exhibited the presence of the ester of C=O. The spectra of 5-FU confirm the presence of CH bend, CF and CN stretch, NH bend, and NH stretch at 775, 1280, 1416, 1555, 1655, and 3183 cm^{-1}, respectively.[32] The FTIR spectra of GMO

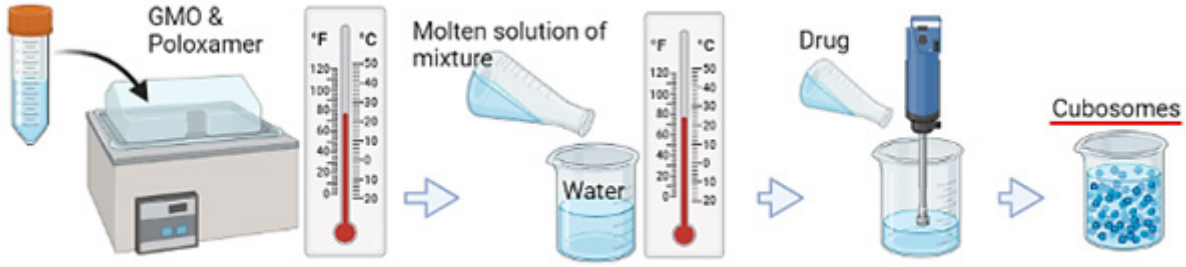

Figure 1: Pictorial illustration of cubosomes preparation.

Table 1: Composition of Formulations used for cubosomes preparation.

Formulations	Poloxamer 407 (g)	GMO (mL)
F1	0.1	1
F2	0.2	1.5
F3	0.3	2
F4	0.4	2.5

All the formulations contained equal volume (1 mL) of Tween 80.

revealed a sharp and characteristic band, that corresponds to C=O at about 1700 cm^{-1}, whereas in the region of 3320-3400 cm^{-1}, the existence of a broad band has confirmed the presence of the -OH group. After scanning for the FTIR spectrum, it was observed that all the characteristic peaks of the drug were preserved in the formulation, confirming the chemical compatibility of the excipients with the drug (Figure 2).

pH

The prepared formulations exhibited a pH range from 6.5-6.9 shown in Table 2, supporting the non-irritant nature of the formulation. The typical pH of the poloxamer ranges between 5 and 7.4, while that of GMO is between 4.5 and 4.8. Hence; the pH of the formulation due to both of these along with drug and tween 80, ranged from 6.5 to 6.9.

Viscosity

The manufactured formulation's viscosity ranges from 12.67 to 33.32 cP. Reduced viscosity guarantees quicker drug release from the formulation, which promotes rapid absorption and, as a result, rapid beginning of action. The formulation with greater concentration of GMO and lesser concentration of Tween 80, has shown greater viscosity and vice versa.

Determination of linearity curve

The linearity curve of 5-Fluorouracil was constructed at wavelength 266 nm having concentration at the horizontal x-axis and absorbance at the vertical y-axis. The linearity curve was further used for the quantification of drugs in various analyses, including drug release and drug permeation studies.

Zeta potential and Particle size analysis

The mean zeta potential of 5-FU-loaded cubosomes was -0.6 mV (Figure 3). The mean size of particles of 5-Fluorouracil cubosomes has been measured as 291.3 nm. For the formation of relatively smaller particles, relatively greater poloxamer 407 concentrations have been useful in that they also enhance the development of vesicular particles over the formation of the cubic structure of particles.[33]

Scanning Electron Microscopy (SEM)

To examine the surface morphology of the cubosomes, scanning electron microscopy was performed. The outcomes have revealed that nanosized, a bit cubic-shaped particles have been observed. Moreover, well-segregated and dispersed particles were detected which indicates the stability of the formulation (Figure 4).

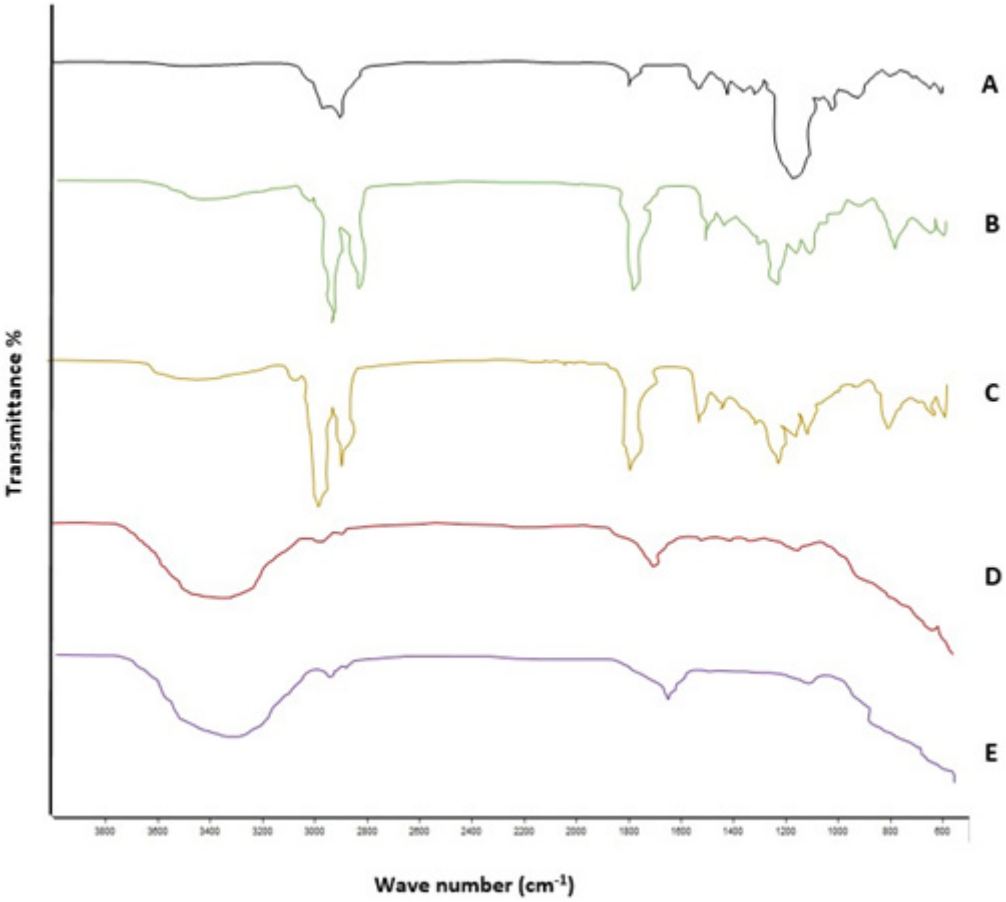

Figure 2: FTIR Spectrum of (A) tween 80, (B) poloxamer 407, (C) GMO, (D) 5-FU, (E) Formulation.

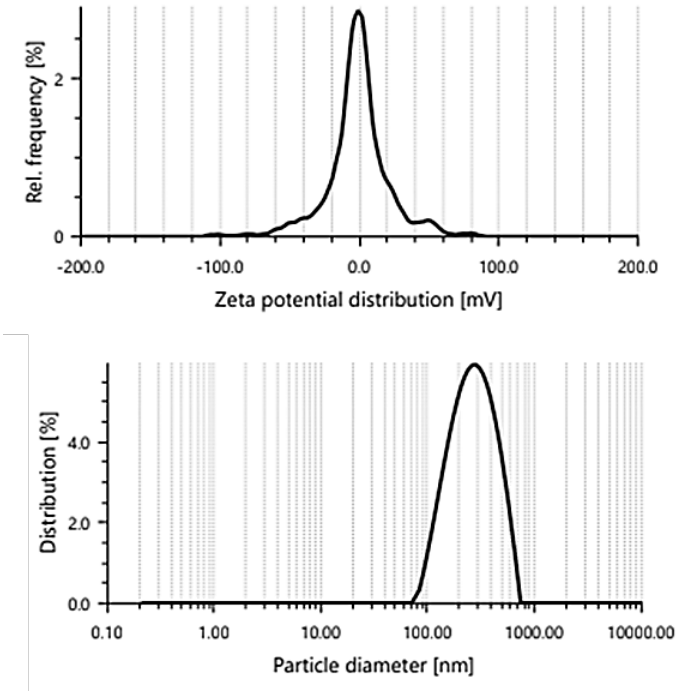

Figure 3: Representation of surface charge and particle size of the cubosomes.

X-ray Diffraction (XRD)

XRD analysis was employed to analyze the pure form of 5-FU drug and 5-FU loaded cubosomes. As shown in Figure 5, peaks were found to be at 16.5, 19.28, 20.7, 28.28 and 31° (θ). Thus, confirming the crystalline nature of the drug.[34] The intense peaks were greatly diffused and their intensity has been reduced to a great extent, hence indicating the encapsulation of the drug in cubosomes. Few less intense peaks could be due to the presence of some un-entrapped drug molecules that might be present on the surface (Figure 6).

Drug entrapment efficiency

The entrapped drug ranged from 89-96% in the prepared formulations. 5-FU belongs to BCS-III, having hydrophilic nature. Both poloxamer-407 and tween 80 can improve drug entrapment efficiency. The poloxamer is a block co-polymer, having both hydrophilic and hydrophobic characteristics, which can increase the entrapment of hydrophilic drugs into a hydrophobic carrier like GMO. This might be the reason that formulation with increased concentration of poloxamer has shown better entrapment efficiency and vice versa (Figure 6).

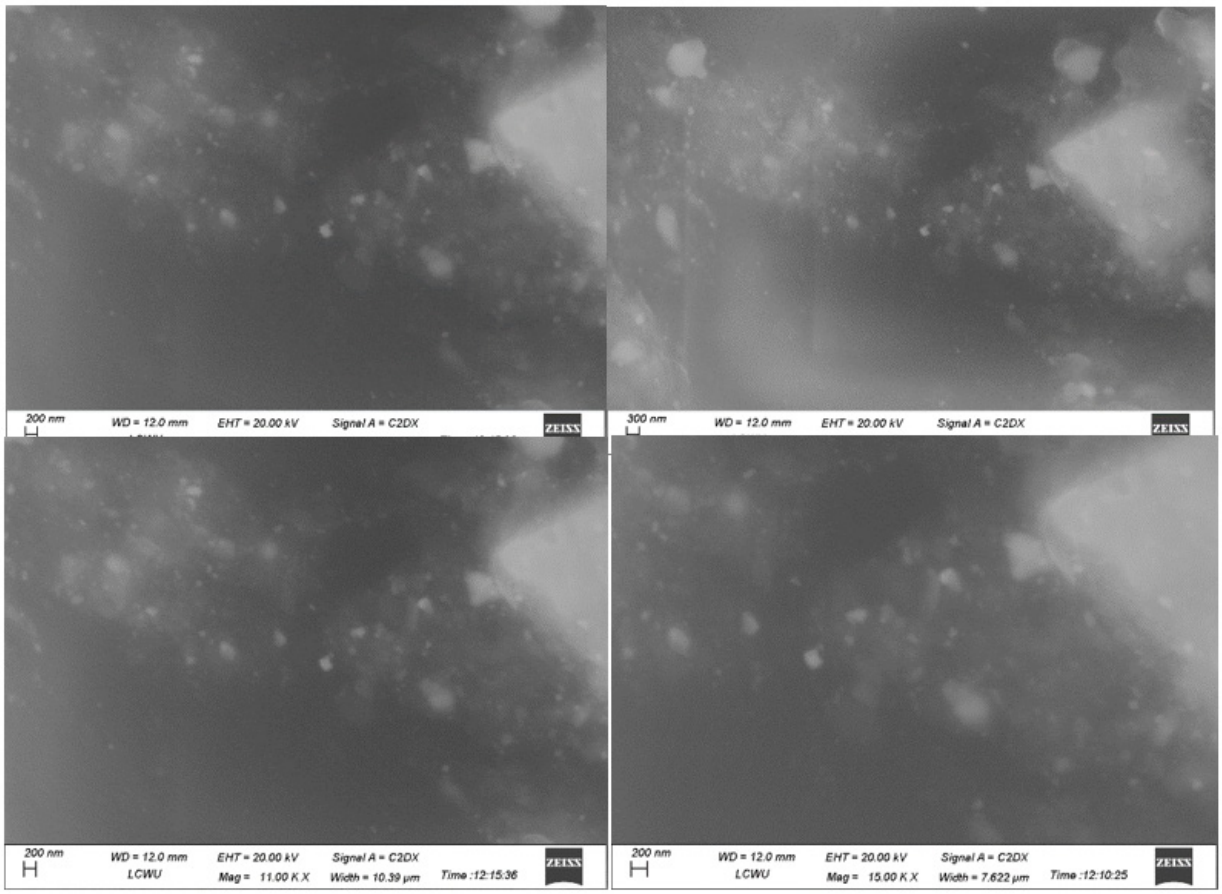

Figure 4: Scanning Electron Microscopy, indicating nano-sized particles with suitably cubic-shaped structures.

Table 2: pH and Viscosity of prepared formulations.

Formulations	pH	Viscosity (cP)
F1	6.5	12.67
F2	6.8	18.43
F3	6.7	25.52
F4	6.9	33.32

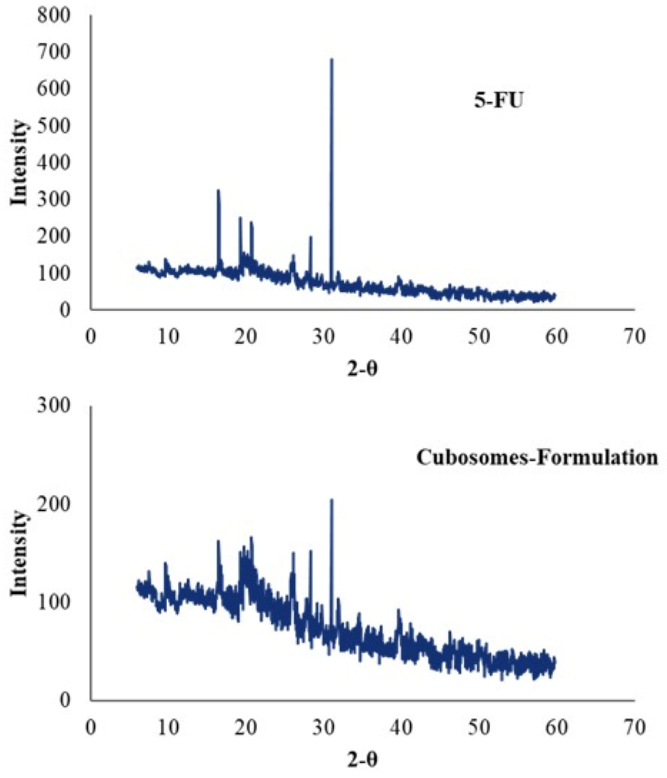

Figure 5: XRD patterns of 5-FU and cubosomes formulation.

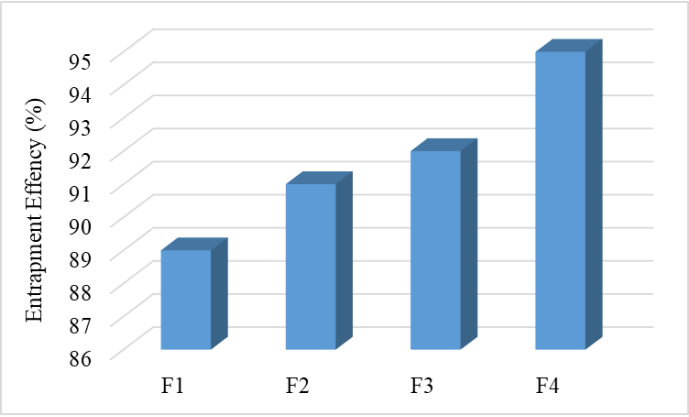

Figure 6: Illustrating the %EE of the drug in cubosomes.

In vitro drug release studies

In vitro release of drug was performed at 266 nm and the results are shown in Figure 7. F4 had shown a higher drug release as compared to the other formulations. There was a significant

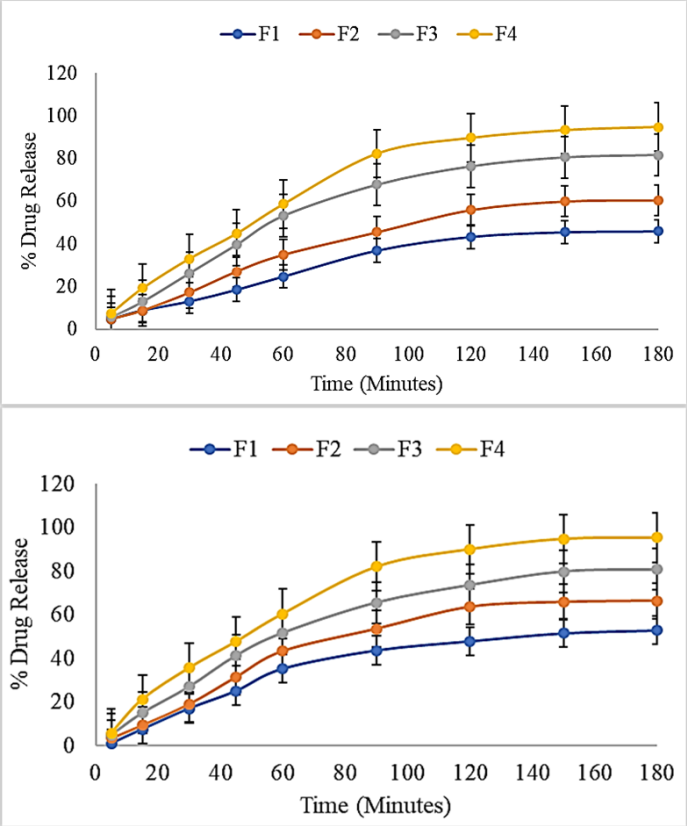

Figure 7: Illustration of *in vitro* drug release and *in vitro* permeation studies.

enhancement in the release of the drug that was observed as the ratios of poloxamer 407 as well as GMO were increased. The dissolution studies have suggested that the addition of poloxamer 407 has a considerable impact on the release of the drug.[35] Being a member of the block copolymers and release modifiers, the poloxamer has the ability to improve the dissolution as well as release profile of the drugs. The same effect has been observed in current studies, as the formulation with its greater concentration has released more drugs and vice versa.[36]

In vitro permeation studies

Samples were taken out at different time intervals and the absorbance was recorded at 266nm wavelengths. The graph between the concentration and the absorbance was plotted (Figure 7), showing the graphical representation of the percentage drug permeation of the formulations through the membrane. F4 was shown to have the highest drug permeation among all other formulations majorly due to the highest quantities of Polox-407

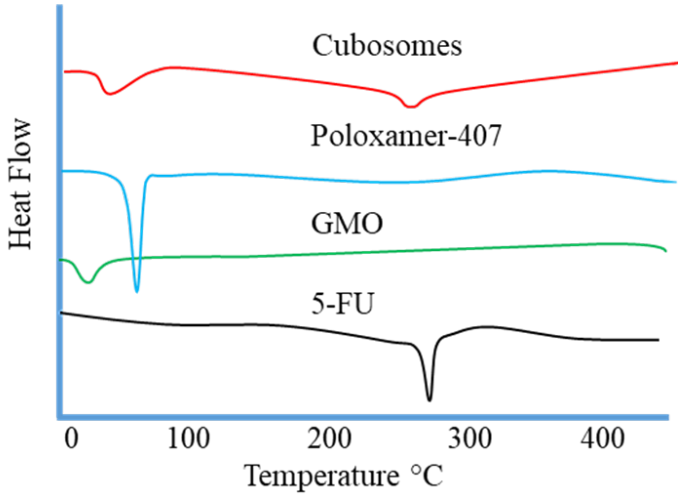

Figure 8: DSC analysis of individual ingredients and prepared of 5-FU cubosomes.

and GMO. The increase in permeation might be due to the fact that the ratio between the Polox-407 and GMO was the highest. The greater concentration of Polox-407 assisted the drug to dissolve and permeate across the membrane.

Stability Studies

Centrifugation

After the centrifugation the formulations were observed, there were no signs of phase separation nor any kind of instability, thus they were subjected to study under the freeze-thaw method. Recent investigations have advised that from scientific and industrial perspectives, the method of centrifugation involves the centrifugal force for the separation of heterogeneous mixtures. Nevertheless, after this test, no layers or particle sedimentation was detected indicating a stable formulation.

Freeze-Thaw Method

No particle sedimentation or separation of layers was observed in the formulations indicating the high stability of the formulations. The better the dewatering results, the gentler will be the thawing process. The finest thawing conditions are either in a water bath or in ambient air at a temperature below 20°C.[37,38]

Thermal stability analysis (DSC)

Figure 8 shows the DSC thermogram of 5-Fluorouracil formulation cubosomes. It is clear that the DSC thermogram of 5-Fluorouracil shows a single sharp endothermic peak at 280-285°C, which is related to a study reported previously.[34,39-41] GMO and poloxamer have shown endotherms at around 30-35 and 55-60°C. Furthermore, the thermogram of 5-Fluorouracil loaded cubosomes has shown a border peak between 30-60°C, that night has shown the presence of both GMO and poloxamer, however, the sharp characteristic endotherm 5-FU has been converted into a broader peak, confirming that drug now, has been captured by the cubosomes of GMO, assisted by poloxamer 407.

CONCLUSION

In the present study, we have developed and evaluated cubosomal formulations for potential topical anti-cancer therapy. The characterization studies have shown the cubic-shaped structures and a good stability behavior. Also, drug release and permeation studies have indicated a suitable release and permeation profile of the drug. As evidenced in these results, we envision that upon further optimization, this drug carrier system may have the potential to be translated as an effective therapy for the clinical management of superficial tumors.

ACKNOWLEDGEMENT

This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University, through the Research Funding Program, Grant No. (FRP-1443-27).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

5-FU: 5-Fluorouracil; **EE:** Entrapment efficiency; **FTIR:** Fourier-transform infrared spectroscopy; **GIT:** Gastro intestinal tract; **GMO:** Glycerol monooleate.

SUMMARY

This study aimed to prepare cubosomes containing 5-Fluorouracil (5-FU), a hydrophilic anti-cancer drug, using a Glyceryl Monooleate (GMO)-based lipophilic structure. Four formulations were formulated with varying concentrations of Polox-407 and GMO, while maintaining T80 concentration. *In vitro* characterization, chemical compatibility studies, pH, viscosity, SEM, particle size analysis, zeta potential, drug release, and permeation studies were performed. Results confirmed the drug and ingredients' chemical compatibility and stability.

REFERENCES

1. Midgley RS, Kerr DJ, Flaherty KT, Stevenson JP, Pratap SE, Koch KM, *et al.* A phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. Ann Oncol. 2007;18(12):2025-9. doi: 10.1093/annonc/mdm366, PMID 17846021.
2. He YC, Chen JW, Cao J, Pan DY, Qiao JG. Toxicities and therapeutic effect of 5-fluorouracil controlled release implant on tumor-bearing rats. World J Gastroenterol. 2003;9(8):1795-8. doi: 10.3748/wjg.v9.i8.1795, PMID 12918123.
3. Zhang N, Yin Y, Xu SJ, Chen WS. 5-fluorouracil: mechanisms of resistance and reversal strategies. Molecules. 2008;13(8):1551-69. doi: 10.3390/molecules13081551, PMID 18794772.
4. Arias JL, Ruiz MA, López-Viota M, Delgado AV. Poly(alkylcyanoacrylate) colloidal particles as vehicles for antitumour drug delivery: a comparative study. Colloids Surf B Biointerfaces. 2008;62(1):64-70. doi: 10.1016/j.colsurfb.2007.09.018, PMID 17961994.

5. Tanaka F, Fukuse T, Wada H, Fukushima M. The history, mechanism and clinical use of oral 5-fluorouracil derivative chemotherapeutic agents. Curr Pharm Biotechnol. 2000;1(2):137-64. doi: 10.2174/1389201003378979, PMID 11467334.
6. Rokhade AP, Shelke NB, Patil SA, Aminabhavi TM. Novel hydrogel microspheres of chitosan and pluronic F-127 for controlled release of 5-fluorouracil. J Microencapsul. 2007;24(3):274-88. doi: 10.1080/02652040701281365, PMID 17454438.
7. Yan S, Zhu J, Wang Z, Yin J, Zheng Y, Chen X. Layer-by-layer assembly of poly (L-glutamic acid)/chitosan microcapsules for high loading and sustained release of 5-fluorouracil. Eur J Pharm Biopharm. 2011;78(3):336-45. doi: 10.1016/j.ejpb.2010.12.031, PMID 21195174.
8. Lai LF, Guo HX. Preparation of new 5-fluorouracil-loaded zein nanoparticles for liver targeting. Int J Pharm. 2011;404(1-2):317-23. doi: 10.1016/j.ijpharm.2010.11.025, PMID 21094232.
9. Soni V, Kohli DV, Jain SK. Transferrin-conjugated liposomal system for improved delivery of 5-fluorouracil to brain. J Drug Target. 2008;16(1):73-8. doi: 10.1080/10611860701725381, PMID 18172823.
10. Cheng MR, Li Q, Wan T, He B, Han J, Chen HX, *et al.* Galactosylated chitosan/5-fluorouracil nanoparticles inhibit mouse hepatic cancer growth and its side effects. World J Gastroenterol. 2012;18(42):6076-87. doi: 10.3748/wjg.v18.i42.6076, PMID 23155336.
11. Pal N, Kumar S, Bera A, Mandal A. Phase behaviour and characterization of microemulsion stabilized by a novel synthesized surfactant: implications for enhanced oil recovery. Fuel. 2019;235:995-1009. doi: 10.1016/j.fuel.2018.08.100.
12. Moshikur RM, Ali MK, Moniruzzaman M, Goto MJC. IRecent advances in surface-active ionic liquid-assisted self-assembly systems for drug delivery. Curr Opin Colloid Interface Sci. 2021;56:101515. doi: 10.1016/j.cocis.2021.101515.
13. Davis DA, Martins PP, Zamloot MS, Kucera SA, Williams RO, Smyth HDC, *et al.* Complex drug delivery systems: controlling transdermal permeation rates with multiple active pharmaceutical ingredients. AAPS PharmSciTech. 2020;21(5):165. doi: 10.1208/s12249-020-01682-4, PMID 32500420.
14. Said S, Mikhail S, Riad M. Recent processes for the production of alumina nano-particles. Mater Sci Energy Technol. 2020;3:344-63. doi: 10.1016/j.mset.2020.02.001.
15. Dhadwal A, Sharma DR, Pandit V, Ashawat MS, Kumar P. Cubosomes: A novel carrier for transdermal drug delivery. J Drug Deliv Ther. 2020;10(1):123-30. doi: 10.22270/jddt.v10i1.3814.
16. Naidjonoka P, Fornasier M, Pålsson D, Rudolph G, Al-Rudainy B, Murgia S, *et al.* Bicontinuous cubic liquid crystalline phase nanoparticles stabilized by softwood hemicellulose. Colloids Surf B Biointerfaces. 2021;203:111753. doi: 10.1016/j.colsurfb.2021.111753, PMID 33845421.
17. Fornasier M, Pireddu R, Del Giudice A, Sinico C, Nylander T, Schillén K, *et al.* Tuning lipid structure by bile salts: hexosomes for topical administration of catechin. Colloids Surf B Biointerfaces. 2021;199:111564. doi: 10.1016/j.colsurfb.2021.111564, PMID 33445076.
18. Anand B, Thomas I, Abraham E. Formulation and evaluation of Cubosomal gel of an anti-inflammatory agent. Res J Pharm Technol. 2021;14(2).
19. Singhal K, Kaushik N, Kumar A. Cubosomes: Versatile nanosized formulation for efficient delivery of therapeutics. Curr Drug Deliv. 2022;19(6):644-57. doi: 10.2174/1567201818666210708123855, PMID 34238187.
20. Zakaria F, Ashari SE, Mat Azmi ID, Abdul Rahman MB. Recent advances in encapsulation of drug delivery (active substance) in cubosomes for skin diseases. J Drug Deliv Sci Technol. 2022;68:103097. doi: 10.1016/j.jddst.2022.103097.
21. Nasr M, Ghorab MK, Abdelazem A. *In vitro* and *in vivo* evaluation of cubosomes containing 5-fluorouracil for liver targeting. Acta Pharm Sin B. 2015;5(1):79-88. doi: 10.1016/j.apsb.2014.12.001, PMID 26579429.
22. Hanif M, Zaman M. Thiolation of arabinoxylan and its application in the fabrication of controlled release mucoadhesive oral films. DARU J Pharm Sci. 2017;25:1-13.
23. Zaman M, Hassan R, Razzaq S, Mahmood A, Amjad MW, Raja MAG, *et al.* Fabrication of polyvinyl alcohol based fast dissolving oral strips of sumatriptan succinate and metoclopramide HCl. Sci Prog. 2020; 103(4): 0036850420964302: 36850420964302. doi: 10.1177/0036850420964302, PMID 33151131.
24. Zaman M, Qureshi S, Sultana K, Hanif M, Mahmood A, Shaheryar ZA, *et al.* Application of quasi-emulsification and modified double emulsification techniques for formulation of tacrolimus microsponges. Int J Nanomedicine. 2018;13:4537-48. doi: 10.2147/IJN.S166413, PMID 30127605.
25. Zaman M, Hanif M, Shaheryar ZA. Development of tizanidine HCl-meloxicam loaded mucoadhesive buccal films: *in vitro* and *in vivo* evaluation. PLOS ONE. 2018;13(3):e0194410. doi: 10.1371/journal.pone.0194410, PMID 29566073.
26. Farooq M, Usman F, Naseem M, Aati HY, Ahmad H, Manee S, *et al.* Voriconazole cyclodextrin based polymeric nanobeads for enhanced solubility and activity: *in vitro*/*in vivo* and molecular simulation approach. Pharmaceutics. 2023;15(2):389. doi: 10.3390/pharmaceutics15020389, PMID 36839711.
27. zur Mühlen A, Schwarz C, Mehnert W. Solid lipid nanoparticles (SLN) for controlled drug delivery-drug release and release mechanism. Eur J Pharm Biopharm. 1998;45(2):149-55. doi: 10.1016/s0939-6411(97)00150-1, PMID 9704911.
28. Nandgude TD, Jadhavrao JN, Jawlekar AR, Poddar SS. Development of self-microemulsifying drug delivery system based solid dosage form containing simvastatin. Int J Pharm. 2004;274(1):65-73.
29. Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm. 2007;66(2):227-43. doi: 10.1016/j.ejpb.2006.10.014, PMID 17127045.
30. Khan S, Madni A, Rahim MA, Shah H, Jabar A, Khan MM, *et al.* Enhanced *in vitro* release and permeability of glibenclamide by proliposomes: development, characterization and histopathological evaluation. J Drug Deliv Sci Technol. 2021;63:102450. doi: 10.1016/j.jddst.2021.102450.
31. Zaman M, Iqbal A, Sarwar HS, Butt MH, Iqbal MO, Nissar N, *et al.* Application of nanoprecipitation technique to develop Poloxamer-407 facilitated solid lipid nanoparticles for the controlled delivery of tacrolimus. Int J Polym Sci. 2023; 2023:1-8. doi: 10.1155/2023/7356899.
32. Rahmani H, Fattahi A, Sadrjavadi K, Khaledian S, Shokoohinia Y. Preparation and characterization of silk fibroin nanoparticles as a potential drug delivery system for 5-fluorouracil. Adv Pharm Bull. 2019;9(4):601-8. doi: 10.15171/apb.2019.069, PMID 31857964.
33. Wörle G, Drechsler M, Koch MH, Siekmann B, Westesen K, Bunjes H. Influence of composition and preparation parameters on the properties of aqueous mono olein dispersions. Int J Pharm. 2007;329(1-2):150-7. doi: 10.1016/j.ijpharm.2006.08.023, PMID 16987623.
34. Samy M, Abdallah HM, Awad HM, Ayoub MMH. Preparation, Characterization and *in vitro* Biological activity of 5-fluorouracil Loaded onto poly (D, L-lactic-co-glycolic acid) Nanoparticles. Polym Bull. 2023;80(6):6197-219. doi: 10.1007/s00289-022-04308-w.
35. Abdeltawab H, Svirskis D, Sharma M. Formulation strategies to modulate drug release from poloxamer based in situ gelling systems. Expert Opin Drug Deliv. 2020;17(4):495-509. doi: 10.1080/17425247.2020.1731469, PMID 32067500.
36. El-Badry M, Hassan MA, Ibrahim MA, Elsaghir H. Performance of poloxamer 407 as hydrophilic carrier on the binary mixtures with nimesulide. Farmacia. 2013;61(6):1137-50.
37. Cekic ND, Savic SM, Savic SD. Dynamic-mechanical thermoanalysis test: a rapid alternative for accelerated freeze-thaw stability evaluation of W/O emulsions. Drug Dev Ind Pharm. 2019;45(12):1896-906. doi: 10.1080/03639045.2019.1672718, PMID 31589077.
38. Al Haj Sleiman S, Izoret L, Alam SY, Grondin F, Loukili A. Freeze-thaw field exposure and testing the reliability of performance test temperature cycle for concrete scaling in presence of de-icing salts. Mater Struct. 2022;55(1):2. doi: 10.1617/s11527-021-01831-6.
39. Lee JS, Chae GS, An TK, Khang G, Cho SH, Lee HB. Preparation of 5-fluorouracil-loaded poly (L-lactide-co-glycolide) wafer and evaluation of *in vitro* release behavior. Macromol Res. 2003;11(3):183-8. doi: 10.1007/BF03218350.
40. Tummala S, Satish Kumar MN, Prakash A. Formulation and characterization of 5-fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer. Saudi Pharm J. 2015;23(3):308-14. doi: 10.1016/j.jsps.2014.11.010, PMID 26106279.
41. Ashwanikumar N, Kumar NA, Nair SA, Kumar GSV. Dual drug delivery of 5-Fluorouracil (5-FU) and methotrexate (MTX) through random copolymeric nanomicelles of PLGA and polyethylenimine demonstrating enhanced cell uptake and cytotoxicity. Colloids Surf B Biointerfaces. 2014;122:520-8. doi: 10.1016/j.colsurfb.2014.07.024, PMID 25108479.

Cite this article: Alamoudi JA, Almoshari Y, Alotaibi HF. Fabrication and Evaluation of Poloxamer Facilitated, Glyceryl Monooleate based 5-Fluorouracil Cubosomes. Indian J of Pharmaceutical Education and Research. 2024;58(1):91-8.