IJRDPL

International Journal of Research and Development in Pharmacy & Life Science

An International open access peer reviewed journal

ISSN (P): 2393-932X, ISSN (E): 2278-0238

Journal homepage:http://ijrdpl.com

Original Article

Preparation and evaluation of Maltodextrin based Proniosomes containing Capecitabine

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Keywords: Capecitabine, Proniosome, Maltodextrin, Span 80, Span 20

Article Information:

Received: September 11,2017;
Revised: October20, 2017;
Accepted: November08, 2017

Available online on:
15.12.2017@http://ijrdpl.com

http://dx.doi.org/10.21276/IJRDPL.2278-0238.2017.6(7).2856-2861

ABSTRACT: Maltodextrin based capecitabine proniosomes were fabricated by conventional slurry method with different surfactant: cholesterol molar ratio keeping constant capecitabine and dicetyl phosphate concentration. The fabricated proniosomes were evaluated for FTIR and flow properties. Further proniosomes were hydrated to get desired niosomes and the obtained niosomes were subjected for various evaluation parameters such as entrapment efficiency, *in vitro* drug release and stability studies as per ICH guidelines. The entrapment efficiency followed the trend, span 80 (C_{18})> span 20 (C_{12}) as increasing the alkyl chain lengths are leading to higher entrapment efficiency. The *in vitro* data suggest biphasic drug release, initial burst followed steady state. In all the case, best-fit model was found to be matrix with Peppas exponential value was greater than 0.5 indicating drug released by non Fickian (anomalous) mechanism. The result of investigation demonstrated that proniosomes offers an alternate drug carrier with targeted specificity.

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INTRODUCTION

Research in the field of novel drug delivery system, which continues to progress rapidly, aims at the development of drug delivery systems (DDS) with optimum therapeutic benefits including safe and effective management of disease [1]. The concept of drug delivery to a specific site for the treatment of localized disease in the body, thereby decreasing drug adverse effects and improving its therapeutic index, is often considered a challenge [2]. The idea of a drug carrier with targeted specificity has always fascinated scientists for decades and in the last decade, limited success have been achieved in this regard. One such approach involves the use of vesicular drug carrier that can provide site specificity combined with optimal drug release profile [3]. Amongst various carriers utilized for target-oriented drug delivery, vesicular drug delivery systems in the form of liposome and niosomes have been most extensively investigated.

Liposomal formulations have thelimitation of poor stability andlow drug entrapment efficiency while niosomes exhibit physical instability, aggregation, fusion, and leakage of entrapped drug, thus limiting the shelf-life of the dispersion [4,5]. Proniosomes are free flowing dry product which could be hydrated immediately before use, avoid many of the problems associated with aqueous niosome dispersions and problems of physical stability viz., aggregation, fusion, leaking [6]. Proniosomes are dry formulations of surfactant coated water-soluble carrier particles and can be hydrated easily by simple agitation in hot aqueous media to form multilamellar niosome dispersions suitable for administration by oral or other routes [7, 8]. Capecitabine is an orally administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers [9]. Chemically it is a prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) figure 1, which is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue [10,11].

The objective of the present research work is to develop a vesicular drug delivery system for capecitabine in the form of proniosomes using maltodextrin as carrier and different grades of spans as surfactant, which will have advantages of controlled drug release, increased drug stability and high drug load.

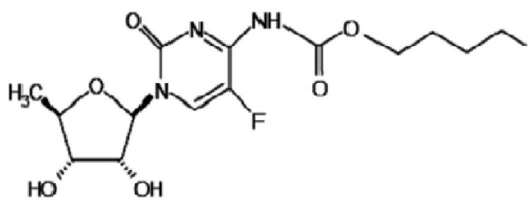

Figure 1: Chemical structure of capecitabine.

MATERIALS AND METHODS

Materials:Capecitabine gift sample was obtained from Shilpa antibiotic Pvt Ltd, Raichur. Maltodextrin was procured from Himedia, Hosur, Cholesterol, Span 80, Span 20 and DCP (Dicetyl phosphate) were purchased from LobaChemPvt Ltd, Mumbai. All the other ingredients and reagents used were of analytical grade.

METHODS

Preparation of proniosomes:Six maltodextrin based capecitabine proniosome formulations were fabricated using surfactants viz., span 80 and span 20: cholesterol at 1:1; 1:0.75 and 1:0.50 molar ratio by conventional slurry method. The different formulae were given in table1.

Slurry method [12, 13]: A 250µmol stock solution of Span 80, Span 20, cholesterol and dicetyl phosphate was prepared in chloroform: methanol (2:1). The accurately measured volumes of span 80, cholesterol, dicetyl phosphate stock solutions and capecitabine (50mg) dissolved in chloroform: methanol (2:1) solutions were added into a 250ml round bottom flask containing previously 2g of maltodextrin powder as carrier. Additional chloroform: methanol (2:1) solution added to form slurry. Further the flask was attached to a rotary flash evaporator rotated at 60 to 70 rpm. The solvent is allowed to evaporate at temperature of 45±2ºC in a reduced pressure of 600mm/Hg until the mass in the flask had become a dry, free flowing product. The obtained proniosome powder was further dried overnight in a desiccator under vacuum at room temperature. Similarly, another batch of proniosome was prepared using Span 20 by adapting the same procedure as described above. The obtained dry proniosome powders were stored in air tight amber colored vials kept in a refrigerator for further evaluation.

Table 1: Different formulae of maltodextrin based capecitabine proniosomes.

Batches	Surfactant	Drug (mg)	Surfactant : CholesterolMolar ratio	Surfactant (mg)	Cholesterol (mg)	Maltodextrin (2 G)	DCP (mg)
B1	Span 80	50	1:1	430.62	386	2	7.5
B2		50	1:0.75	430.62	289	2	7.5
B3		50	1:0.50	430.62	193	2	7.5
B4	Span 20	50	1:1	346.45	386	2	7.5
B5		50	1:0.75	346.45	289	2	7.5
B6		50	1:0.50	346.45	193	2	7.5

EVALUATION

FTIR studies:The FTIR spectra for capecitabine, maltodextrin, span80, span20 and selected proniosome formulations were recorded. The samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2Tcm-2 for 3min. The scanning range was 450- 4000cm-1 and the resolution was 1cm-1.

Angle of repose [14]**:**The angle of repose of dry proniosomes powder and maltodextrin powder was measured by a cut funnel method. The maltodextrin powder and proniosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a heap on the surface and the angle of repose was then calculated by measuring the height of the heap and the diameter of its base. Angle of repose was calculated by using following formula.

$$\theta = \tan^{-1}(h/r)$$

Where, Θ - Angle of repose;h - Height of the heap; r - Radius of the heap

Preparation of niosomes: Niosomes were prepared for all the fabricated proniosomes by simple hydration method. In this method accurately weighed proniosome formulations were filled in series of vials to this add measured volume of phosphate buffer pH 7.4, the components are mixed for 2min on vortex mixer followed by sonication for 30sec to get desired niosomes. The prepared niosomes were stored in air tight container for further evaluation.

Drug content: Niosomes equivalent to 50 mg of capecitabine were extracted with 25ml of distilled water in a 100ml volumetric flask further, it was made up to 100ml and keep undisturbed for 30 minutes to achieve complete extraction. The extract was filtered and diluted serially with phosphate buffer pH 7.4 and the absorbance was measured at 303 nm thus drug content was calculated from the calibration curve and Average of three readings were taken and computed.

Entrapment efficiency:Niosome entrapped capecitabine was estimated by dialysis method. The calculated amount of prepared niosomes was placed in the dialysis bag (presoaked for 24 hrs). Free capecitabine was dialyzed for 30 minutes each time in 100 ml of phosphate buffer pH 7.4.

The dialysis of free capecitabine always completed after12-15 changes, when no capecitabine was detectable in the recipient solution. The dialyzed capecitabine was determined by finding out the concentration of bulk of solution by UV spectrophotometer at 303 nm. The samples from the bulk of solution diluted appropriately before going for absorbance measurement. The free capecitabine in the bulk of solution gives us the total amount of unentrapped drug. The percentage entrapment efficiency is calculated by using following formula,

$$\%\ \textbf{Entrapment effeciency} = \frac{\textbf{Amount of drug entrapped}}{\textbf{Total amount of drug}} \times \mathbf{100}$$

Particle size distribution and average particle size determination: Particle size analysis was carried out using an optical microscope (compound microscope) with a calibrated eyepiece micrometer.

Calibration of eye piece micrometer:A standard stage micrometer was used forcalibration. Each division value on stage is 10μ. The eye piece micrometer consists of 100 divisions. Calibration was undertaken to find out the measure of each division using the standard stage micrometer. After calibration, the eye piece micrometer was used for particle size determination. A drop of niosomal preparation was mounted on a slide and observed under the microscope. About 200 niosomes were measured individually with the help of eye piece micrometer, average was used to plot size distribution curve and calculate average mean diameter.

Microphotography:The vesicle formation by the hydration process was confirmed by mounting niosome preparation on a slide and observed under the optical microscopy at 200x resolution. The micro photomicrographs of the niosomes were recorded by using a digital SLR camera.

In vitro release study:All the niosome formulations were subjected for in vitro drug release study by using dialysis bag method. 10 mg equivalent of capecitabine niosome preparation was taken in dialysis bag and the bag was placed in a beaker containing 75 ml of phosphate buffer pH 7.4. The beaker was placed over magnetic stirrer having stirring speed of 100 rpm and the temperature was maintained at 37 ± 1^0C. At a predetermined interval of time 5ml samples were withdrawn and same were replaced with phosphate buffer pH 7.4 to maintain the sink condition throughout the release period. The withdrawn samples were appropriately diluted with phosphate buffer pH 7.4 and analyzed for drug content using UV spectrophotometer at 303nm keeping phosphate buffer pH 7.4 as blank. The diffusion studies were carried out in triplicate and the data were interpreted, model fitted by using dissolution software PCP-DISSO V.3.

Stability Study:Physical stability study was carried out to investigate the degradation of drug from proniosome during storage as per ICH guideline. Best two of the optimized capecitabine proniosome formulations composed of spans and cholesterol sealed in glass vials and stored in refrigerated temperature (2-8^0C) and room temperature for a period of 3 months. Samples from each batch were withdrawn after the definite time intervals and converted into niosome formulations and determine the entrapment efficiency, drug content and in vitro drug release and interpret the data.

RESULTS AND DISCUSSION

FTIR study: The drug excipient compatibility studies were done by FTIR and comparative spectra were shown in figure 2. The FTIR of capecitabine shows a characteristic band of -NH stretching at 3516.49cm^{-1}; -CH stretching at 2959.47cm^{-1}and C=O stretching at1710.90cm^{-1}.

The characteristic capecitabine -NH stretching band was observed in selected proniosomes in the range of 3426.75cm^{-1} to 3423.33 cm^{-1}; -CH stretching 2999.38cm^{-1} to 2957.72 cm^{-1}and C=O stretching 1742.23 cm^{-1} to 1737.63 cm^{-1}.

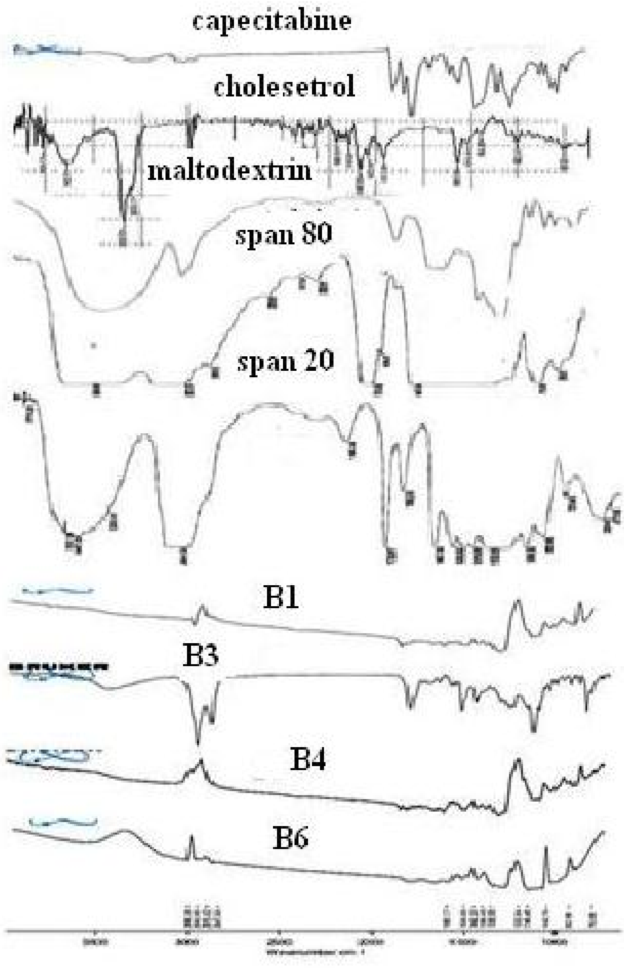

Figure 2: Comparative FTIR spectra of capecitabine, cholesterol, maltodextrin, span80, span20 and selected proniosomes.

Angle of repose: Angle of repose of maltodextrin powder compared with fabricated maltodextrin based proniosomes the results were shown in figure 3.

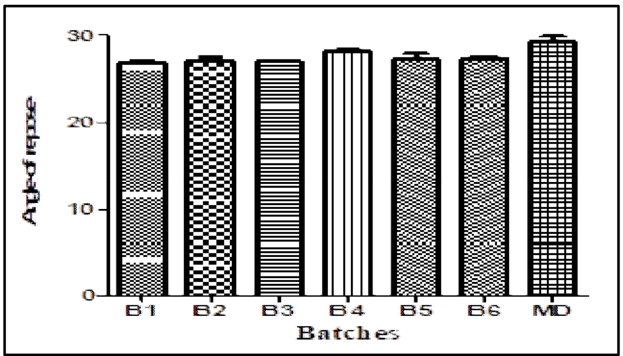

Figure 3: Angle repose profile of dry proniosomes

Drug content: The percentage drug content was found to be in the range of 99.10± 0.32, 99.70± 0.11, 99.20 ± 0.42, 99.00 ± 0.61, 99.60 ± 0.41and 99.30 ± 0.11 for B1 to B6 formulations. The low standard deviation (SD) and low coefficient of variation (CV) i.e.<2 indicates drug distribution was uniform in all the niosome formulations.

Morphology Study: Shape and surface characteristic of maltodextrin based proniosome formulations were converted into niosomal suspensions were studied under optical microscope at 200x magnifications to observe the formation of vesicles and are shown in figure 4 and figure 5.

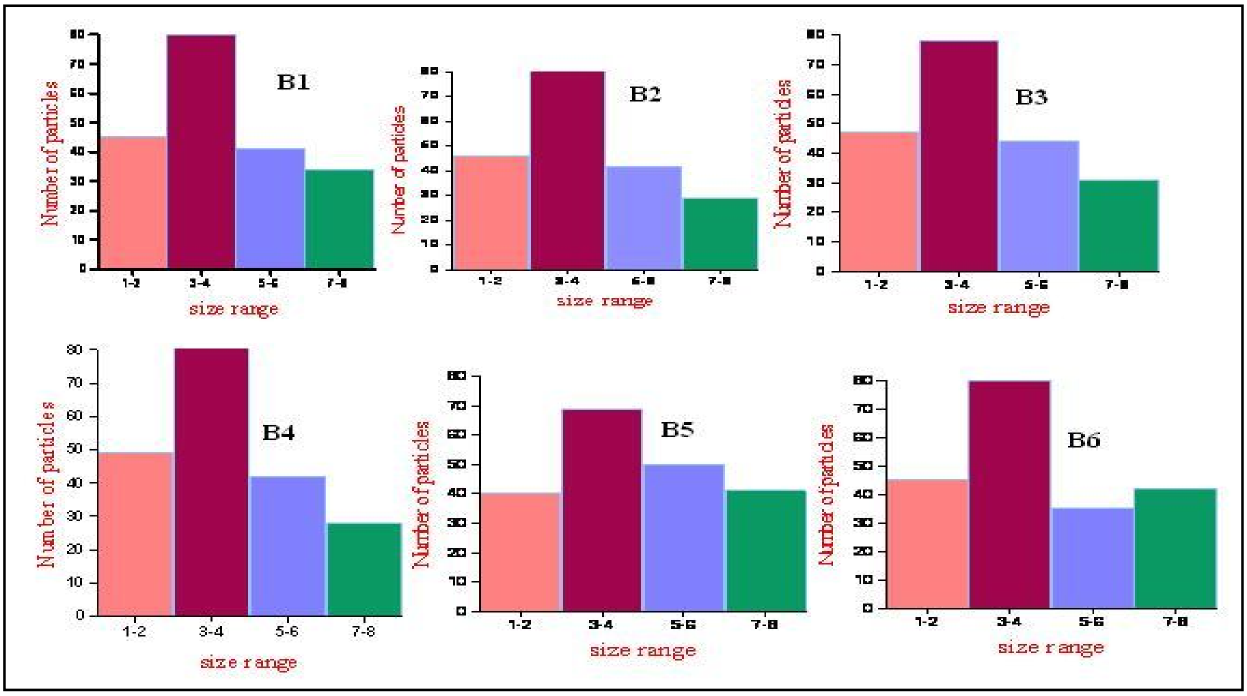

Figure 4: Particle size distribution curve of B1 to B6 niosome formulations

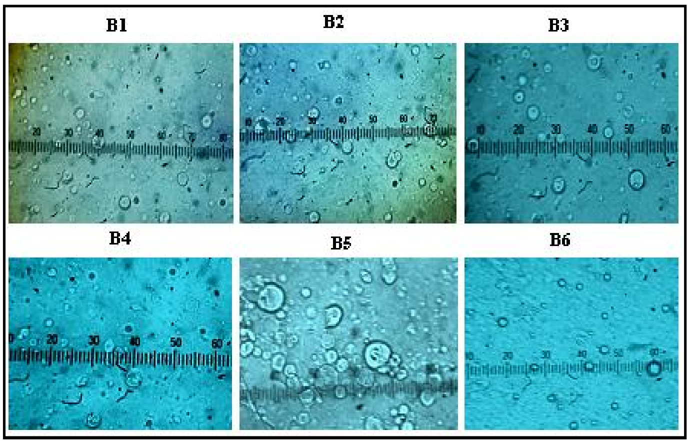

Figure 5: Microphotographs of B1 to B6 niosome formulations.

Entrapment efficiency study: The percentage entrapment efficiency was found to be in the range of 76.91 ± 0.54 to 92.06 ± 0.18 for S-1 to S-6. The data was given in table 2 and profile in figure 6.

Table 2: Entrapment efficiency data of B1 to B6 niosome formulations.

Batches	% Entrapment efficiency±* SD
B1	76.91 ± 0.54
B2	81.75 ± 0.33
B3	84.89 ± 0.19
B4	86.62 ± 0.53
B5	88.86 ± 0.14
B6	92.06 ± 0.18

*Average of three determinations

***In vitro* drug release study:** The *in vitro* drug release studies were conducted for all niosome formulations and the data were shown in table 3 and profile in figure 7.

Stability study: Stability studies of all prepared niosomes were performed by storing 4°C, 25°C and 37°C for a period of 3 months. The data was given in table 4.

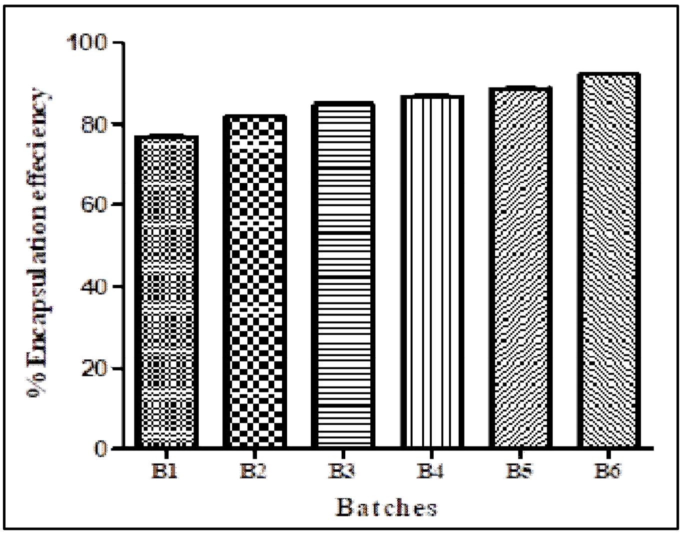

Figure 6: Entrapment efficiency profile

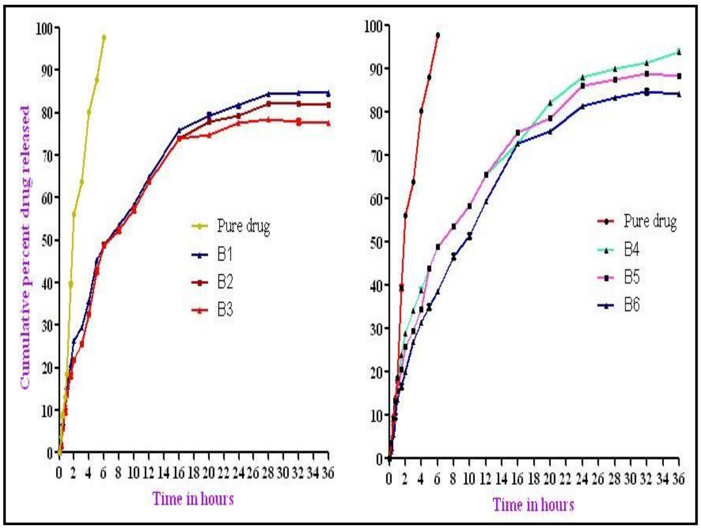

Figure 7: Comparative dissolution profile of pure drug with B1 to B3 and B4 to B6 formulations

Table 3: Model fitting data for B1to B6 formulations

Model fitting values	B1	B2	B3	B4	B5	B6
Zero order	0.7380	0.7641	0.7252	0.7690	0.7785	0.8400
1st order	0.9449	0.9362	0.8997	0.9897	0.9218	0.9728
Matrix	0.9772	0.9757	0.9672	0.9883	0.9845	0.9887
Peppas	0.9627	0.9618	0.9581	0.9660	0.9668	0.9706
Hix.Crow.	0.8986	0.8953	0.8565	0.9535	0.9330	0.9448
n	0.6237	0.6754	0.6662	0.6861	0.6320	0.6766
k	12.8524	10.8179	10.8561	14.8033	12.7367	10.335
Best fit	**Matrix**	**Matrix**	**Matrix**	**Matrix**	**Matrix**	**Matrix**

Table 4: Stability study data for B1to B6 formulations

Batches	% Drug content±SD*	% Entrapment efficiency ±* SD	Cumulative percent drug release ± *SD (after 36hrs)
B3	99.10 ± 0.32	82.69 ± 0.21	77.57± 0.39
B6	99.20 ± 0.21	91.00 ± 0.32	84.28± 0.22

DISCUSSION

The FTIR results suggest the characteristic absorption bands of capecitabine were shifting little toward lower/higher wavelength indicating minor or no interaction. The angle of repose of dry proniosome powder is smaller than that of pure maltodextrin and the values obtained were within the standard limit of flowability. The particles were found to be uniform in size and shape and the size distribution was in the range of 3 to 8 μm and the particle size of the niosomes were found to be in the range of 4.45μ, 4.81μ, 4.36μ, 4.79μ, 4.93μ and 4.69μ for B1 to B 6 formulations respectively, microphotographs of niosome formulations reveals that the niosomes were spherical in their shape. All span types have the same head group and different alkyl chain. Increasing the alkyl chain length is leading to higher entrapment efficiency. The entrapment efficiency followed the trend span 80 (C_{18})> span 20 (C_{12}). In addition, span 80 has the lowest transition temperature (Tc- −12°C) when compared to span 20 i.e. 16°C. In both the cases the as the concentration of cholesterol increases the entrapment efficiency decreases.

In niosome formulations, the drug release was found to be 20.96%, 18.15% and 18.15% for span 80 formulations similarly 24.03%, 20.76 and 13.61 % for span 20 formulations at the end of 1.5 hrs. This initial burst release was mainly due to improper formation or any adherence of drug particles around the niosomes and release of adsorbed drug from the lipophilic region of niosomes.

Fast drug release in the initial hours may help to achieve the optimal loading dose. Further, the drug release follows a biphasic drug release, up to 6 hrs the drug release follows first order and at the start of 12hrs the release was found to be steady because stable niosomes retains and the release was extended up to 36hrs with sustained action. Increasing cholesterol concentration markedly reduced the efflux of the drug and fills the pores in vesicular bilayer and abolishes the gel-liquid phase transition of niosome systems resulting in less leakage of drug from niosomes. This confirms that cholesterol in the formulation acts as a membrane stabilizing agent that helps to sustain drug release.

The *in vitro* drug release data was model fitted with various models and the result suggest best fit model was found to be matrix with Peppas exponential 'n' value was greater than 0.5 suggesting the drug was released by non Fickian (anomalous) mechanism i.e., the drug released by erosion followed by diffusion controlled. The residual drug content was determined at the end of third month. It was observed that the drug leakage from the vesicles was least at 4°C followed by 25°C and 37°C. This may be attributed to phase transition of surfactant and lipid causing vesicles leakage at higher temperature during storage. Hence it is concluded from the obtained data that the optimum storage condition for niosomes was found to be 4°C.

CONCLUSION

Maltodextrin based capecitabine proniosomes can be conveniently prepared by conventional slurry method with negligible loss of drug and further it is convenient to convert into desired niosome by simple hydration process. The evaluation studies conclude that niosomes are superior in their convenience of storage, transport and dosing as compare to niosomes prepared by conventional method. The result of investigation demonstrated that proniosome offer an alternate colloidal carrier approach in achieving drug targeting.

ACKNOWLEDGEMENT

The authors are thankful to Shilpa Antibiotic Pvt. Ltd., Raichur-Karnataka for providing gift sample of capecitabine. The authors are also grateful to the Principal, staff and Management of V.L.College of Pharmacy, Raichur for providing all necessary facilities to carry out the research work.

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How to cite this article:
Srikanth, Anand Kumar Y and MallikarjunaSettyC. Preparation and evaluation of Maltodextrin based Proniosomes containing Capecitabine. *Int. J. Res. Dev. Pharm. L. Sci.* 2017; 6(7):2856-2861.doi: 10.13040/IJRDPL.2278-0238.6(7).2856-2861

