MALTODEXTRIN BASED PRONIOSOMES- A PROMISING CARRIER FOR DRUG DELIVERY OF ANTICANCER AGENT

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INTRODUCTION

Decreasing the adverse effects and improving its therapeutic index, is considered as a challenge in the cancer therapy. Capecitabine is having stability problems[1], constant efforts have been pursued in order to design such an ideal drug delivery system, which improves therapeutic index, decreases the adverse effects and also increases the stability of drug. Vesicular drug delivery systems in the form of liposomes or niosomes are investigated. Liposomes have limitation of poor stability where as niosomes exhibit physical instability, aggregation, fusion, leaking of entrapped drug thus limiting shelf life of dispersion.[2,3] Proniosomes are dry formulations of surfactant coated carrier and hydrated before use to obtain a suspension of niosomes. The additional convenience is transportation, distribution, storage and dosing which make it a cost effective industrial product.[4] Capecitabine is an orally administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers.[5] Chemically it is a prodrug of 5’-deoxy-5-fluorouridine (5’-DFUR) in figure 1, which is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue.[6,7] 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 tweens as surfactant, which will have advantages of controlled drug release, increased drug stability and high drug load.

MATERIALS AND METHODS

Materials: Capecitabine gift sample was obtained from Shilpa antibiotic Pvt Ltd, Raichur. Maltodextrin was procured from Himedia, Hosur, Cholesterol, Tween80, Tween20 and DCP (Dicetyl phosphate) were purchased from Loba chem Pvt Ltd, Mumbai. All the other ingredients and reagents used were of analytical grade.

METHODS

Preparation of proniosome[8]: Six maltodextrin based capecitabine proniosome formulations were designed by using surfactants viz., Tween80, Tween20: cholesterol at

ABSTRACT

The aim of this investigation was to prepare and evaluate maltodextrin based proniosomes loaded with capecitabine for improvement in the physical stability and prolong the release time in a controlled manner. Capecitabine proniosomes were prepared by slurry method and further formulations were evaluated for shape, surface morphology, entrapment efficiency and in vitro drug release. The proniosomes were found to be free flowing and uniform coating over maltodextrin powder. The vesicular size of the optimized formulation showed the vesicular size of 3-6µ. The evaluation of entrapment efficiency showed that it played a significant role by varying the concentration of cholesterol and tweens. The highest entrapment efficiency was found in formulation C4 with 62.33 ± 0.34 highest cumulative percent drug release was observed with formulation C3 with 94.58 ± 0.53 in 36h. The results demonstrated that capecitabine loaded proniosomes offers an alternative carrier approach in increasing its physical stability and are capable of releasing the drug for the extended period of time.

KEYWORDS: Capecitabine, Proniosome, Maltodextrin, Tween80, Tween20.
1:1; 1:0.75 and 1:0.50 molar ratio by conventional slurry method keeping drug and DCP concentration constant in table1.

**Slurry method**[9,10]: A 250μmol stock solution of tween 80, cholesterol and dicetyl phosphate was prepared in chloroform: methanol (2:1). The accurately measured volumes of tween 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 1g 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 allow to evaporate at temperature of 45±2°C 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 desicator under vacuum at room temperature. Similarly another batch of proniosome was prepared using tween 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.

### Table 1: Maltodextrin based capecitabine proniosomes formulations.

<table>
<thead>
<tr>
<th>Codes</th>
<th>Surfactant</th>
<th>Drug (mg)</th>
<th>Surfactant: Cholesterol Molar ratio</th>
<th>Surfactant (mg)</th>
<th>Cholesterol (mg)</th>
<th>Maltodextrin (mg)</th>
<th>DCP (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Tween 80</td>
<td>100</td>
<td>1:1</td>
<td>1.25</td>
<td>386</td>
<td>1000</td>
<td>5</td>
</tr>
<tr>
<td>C2</td>
<td>Tween 80</td>
<td>100</td>
<td>1:0.75</td>
<td>1.25</td>
<td>289</td>
<td>1000</td>
<td>5</td>
</tr>
<tr>
<td>C3</td>
<td>Tween 80</td>
<td>100</td>
<td>1:0.50</td>
<td>1.25</td>
<td>193</td>
<td>1000</td>
<td>5</td>
</tr>
<tr>
<td>C4</td>
<td>Tween 20</td>
<td>100</td>
<td>1:1</td>
<td>0.896</td>
<td>386</td>
<td>1000</td>
<td>5</td>
</tr>
<tr>
<td>C5</td>
<td>Tween 20</td>
<td>100</td>
<td>1:0.75</td>
<td>0.896</td>
<td>289</td>
<td>1000</td>
<td>5</td>
</tr>
<tr>
<td>C6</td>
<td>Tween 20</td>
<td>100</td>
<td>1:0.50</td>
<td>0.896</td>
<td>193</td>
<td>1000</td>
<td>5</td>
</tr>
</tbody>
</table>

**Evaluations**

**FTIR studies**: The FTIR spectra for capecitabine, maltodextrin, tween80, tween20 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**[11]: The angle of repose of dry proniosome 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.

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

Where, \( \theta \) - Angle of repose;
\( h \) - Height of the heap;
\( r \) - Radius of the heap

**Preparation of niosomes**: Niosomes were prepared for all the designed 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 90sec 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 h). 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,

\[ \% \text{Entrapment efficiency} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug}} \times 100 \]

**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 for calibration. 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 niosome 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 processes 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 Nikon camera.

**In vitro release study:** The release of capecitabine from niosomes derived from proniosome was determined using membrane diffusion technique. The niosome suspension prepared from proniosomes equivalent to 50 mg of capecitabine was taken in a glass tube having a diameter 2.5 cm with an effective length of 8 cm that was previously covered with soaked osmosis cellulose membrane, which acts as a donor compartment. The glass tube was placed in a beaker containing 200 ml of phosphate buffer pH 7.4, which acts as receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing suspension was just touched (1-2mm deep) the surface of diffusion medium. The temperature of receptor medium maintained at 37±10°C and the medium was agitated at 100 rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analyzed at 303nm for capecitabine using phosphate buffer pH 7.4 as blank.[12] 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 tweens and cholesterol sealed in glass vials and stored in refrigerated temperature (2-8°C) 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 compare initial data.

**RESULTS AND DISCUSSION**

**FTIR study:** The interaction between pure drug with surfactants and cholesterol in the niosome formulations were studied by FTIR. The FTIR spectra of capecitabine, maltodextrin, tween 80, tween 20 and cholesterol and selected niosome formulations were recorded and are given in figures 2. The FTIR characteristic capecitabine bands are -NH stretching at 3516.49cm⁻¹, -CH stretching at 2959.47cm⁻¹ and C=O stretching at 1710.90cm⁻¹. The characteristic capecitabine -NH stretching band was observed in selected niosomes in the range of 3462.2cm⁻¹ to 3426.75 cm⁻¹, -CH stretching ranging from 2998.63 cm⁻¹ to 2927.62 cm⁻¹ and C=O stretching ranging from 1733.05 cm⁻¹ to 1735.04 cm⁻¹. FTIR spectra of selected niosomes showed all the characteristic absorption bands of capecitabine with negligible shifting toward lower/higher wavelength indicating minor interaction or no interaction. The results suggest that no remarkable changes in their position after successful method of preparation.

![Figure 2: FTIR graphs of pure drug capecitabine, cholesterol, maltodextrin, tween80, tween20 and C1, C3, C4 and C6 formulations.](image)

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

![Figure 3: Angle of repose of proniosomes.](image)
Drug content: The percentage drug content was found to be in the range of ±SD 99.43 ± 0.30, 99.22 ± 0.22, 99.03 ± 0.34, 99.60 ± 0.55, 99.49 ± 0.42 and 99.12 ± 0.33 for C1 to C6 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: Niosomes derived from proniosomes are characterized by shape and surface niosome dispersions under optical microscope at 200x magnifications to observe the formation of vesicles. The particles were found to be uniform in size and shape and the size distribution was in the range of 4.58 to 4.97 µm. The particle size of the niosomes dispersion were found to be in the range of 4.95µ, 4.87µ, 4.97µ, 4.58µ, 4.63µ and 4.79µ for C1 to C6 formulations respectively (figure 4). Microphotographs of niosome dispersions showed that the niosomes were spherical in their shape as shown in figure 5.

![Figure 4](image_url)

**Figure 4:** Particle size distribution histogram of C1 to C6 niosome formulations.

![Figure 5](image_url)

**Figure 5:** Microphotographs of C1 to C6 niosome formulations.
Entrapment efficiency study: The percentage entrapment efficiency was found to be in the range of ±SD 32.27 ± 0.32 to 62.33 ± 0.34 for C-1 to C-6. Entrapment efficiency for proniosomes prepared with tween 20 was higher than that with tween 80. This shows that the longer the alkyl chain of the surfactant, the fewer drugs will be entrapped. Tween 80 has a longer saturated alkyl chain than tween 20 and hence lower entrapment efficiency. The length of the alkyl chain influences the hydrophilic-lipophilic balance (HLB) value of the surfactant and the lower the HLB value of the surfactant, the lower will be the entrapment efficiency. A low HLB value was found with tween 80 and a higher HLB value with tween 20. In both the cases the as the concentration of cholesterol increases the entrapment efficiency decreases (figure 6).

In vitro drug release study: The in vitro drug release studies were conducted for all niosome formulations and the profile given in figure 7 and 8, the model fitting data in table 2 the drug release was found to be 20.86%, 18.05% and 18.05% for tween 80 formulations similarly 24.02%, 20.66 and 13.51 % for tween 20 formulations at the end of 1.5 h. 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 upto 6 h the drug release follows first order and at the start of 12h the release was found to be steady because stable niosomes retains and the release was extended upto 36 h with sustained action. Increasing cholesterol concentration markedly reduced the efflux of the drug and fills the pores in vesicular bilayers 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.

**Figure 6: Entrapment efficiency all formulations.**

**Figure 7: Comparative dissolution profile of pure drug with C1 to C3 formulations.**
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Figure 8: Comparative dissolution profile of pure drug with C4 to C6 formulations.

Table 2: Model fitting data for C1 to C6 formulations.

<table>
<thead>
<tr>
<th>Model fitting values</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
</tr>
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<tbody>
<tr>
<td>Zero order</td>
<td>0.7485</td>
<td>0.7708</td>
<td>0.7714</td>
<td>0.7178</td>
<td>0.7550</td>
<td>0.7484</td>
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<tr>
<td>1st order</td>
<td>0.9197</td>
<td>0.9827</td>
<td>0.9908</td>
<td>0.8897</td>
<td>0.9250</td>
<td>0.9512</td>
</tr>
<tr>
<td>Matrix</td>
<td>0.9723</td>
<td>0.9861</td>
<td>0.9887</td>
<td>0.9648</td>
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<td>0.9790</td>
</tr>
<tr>
<td>Peppas</td>
<td>0.9602</td>
<td>0.9623</td>
<td>0.9662</td>
<td>0.9574</td>
<td>0.9611</td>
<td>0.9637</td>
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<tr>
<td>Hix.Crow.</td>
<td>0.8791</td>
<td>0.9437</td>
<td>0.9561</td>
<td>0.8455</td>
<td>0.8845</td>
<td>0.9072</td>
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<tr>
<td>n</td>
<td>0.6664</td>
<td>0.6280</td>
<td>0.5869</td>
<td>0.6593</td>
<td>0.6739</td>
<td>0.6254</td>
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<td>Best fit</td>
<td>Matrix</td>
<td>Matrix</td>
<td>Matrix</td>
<td>Matrix</td>
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</table>

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 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. The in vitro drug release was conducted up to 36h. Hence it is concluded from the obtained data that the optimum storage condition for niosomes was found to be 4°C. The data was given in table 3.

Table 3: Stability study data for C3 to C4 formulations.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>% Drug content±SD*</th>
<th>Entrapment efficiency ±* SD</th>
<th>Cumulative percent drug release ±*SD</th>
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</thead>
<tbody>
<tr>
<td>C3</td>
<td>99.03 ± 0.34</td>
<td>32.27 ± 0.32</td>
<td>94.58 ± 0.53</td>
</tr>
<tr>
<td>C4</td>
<td>99.60 ± 0.55</td>
<td>62.33 ± 0.34</td>
<td>75.75 ± 0.55</td>
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CONCLUSION
Maltodextrin based capecitabine proniosomes can be conveniently prepared by conventional slurry method with nonionic surfactants, negligible loss of drug and further it is convenient to convert into desired niosome by simple hydration process. The evaluation studies concludes 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 anticancer drug targeting.

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