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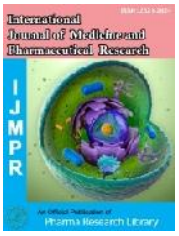

Research Article Open Access

Formulation and Evaluation of Proniosomal Gel of Capecitabine

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A B S T R A C T

The aim of the study is to develop a proniosomal gel for Capecitabine used for the treatment of metastatic breast cancer that is capable of efficiently delivering entrapped drug over an extended period of time. The results showed that the type of lipid incorporated altered the entrapment efficiency of proniosomal gel and higher entrapment efficiency of 61.2 ±2.1%was obtained with the proniosomal gel prepared from Span 40. Different formulations of Proniosomal gel using Span 40 as surfactant were prepared by changing the ratios of surfactant: lecithin and the optimized formulations A1, A2, A3, A4, A5, A6 and A7 were further characterized. SEM studies revealed uniform size and spherical shape of proniosomal gel, FTIR studies revealed that there was no interaction between the drug and excepients, in vitro experiments of the A1, A2, A3, A4, A5, A6 and A7 formulations showed a release rate of 76.01, 55.4, 55.5, 80.5, 69.8, 74.1, 60.5. Hence formulation A4 was optimized as the drug release was found to be highest i.e80.5in 7 hours.

Keywords: Capecitabine, Pronisomal gels, Anti-cancer, Breast cancer.

A R T I C L E I N F O

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1. Introduction

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two requisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through

various novel approaches in drug delivery. Approaches are being adapted to achieve this goal by paying considerable attention either to control the distribution of drug by incorporating it in a carrier system, or by altering the structure of the drug at molecular level, or to control the input of the drug into the bio-environment to ensure an appropriate profile of distribution.

Novel drug delivery system aims at providing some control, whether this of temporal or spatial nature or both of drugs release in the body. Novel drug delivery attempts to either sustain drug action at a pre-determined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ or target drug action by using carriers or chemical derivitazation to deliver drug to particular target cell type.

Niosomes

The traditional colloidal systems like micro-spheres and emulsions appeared in 1950's, out of which emulsions has been primarily used by the cosmetic industry in the topical delivery of cosmetic agents. In 1960's liposomes were discovered, and the introduction of liposomes in cosmetic market was in 1986 by company Dior. From a long time liposomes were considered as the main innovative contributors in the dermal area for both pharmaceutical and cosmetic products. Due to some drawbacks like high cost, variable purity of natural phospholipids and unstable nature, surfactant based vesicles 'Niosomes' came into existence. From early 1980's, Niosomes have gained wide attention by researchers for their use as drug targeting agents, drug carriers to have variety of merits while avoiding demerits associated with conventional form of drugs. Niosomes were studied as better alternatives to liposomes for entrapping both hydrophilic and hydrophobic drugs.

Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactants with or without incorporation of cholesterol or other lipids. Niosomes are widely studied as an alternative to liposomes. These vesicles appear to be similar to liposomes in terms of their physical properties. From a technical point of view, Niosomes are promising drug carriers as they possess greater stability and lack of many disadvantages associate with liposomes. These vesicular delivery systems have attracted considerable attention in topical drug delivery for many reasons. These penetration enhancers are biodegradable, non-toxic, amphiphilic in nature, and effective in the modulation of drug release properties. Their effectiveness is strongly dependent on their physiological properties, such as composition, size, charge, lamellarity and application conditions. In the present study it has been aimed at developing a proniosomal drug delivery system of Capecitabine by solvent evaporation technique. The objective of the present study is to enhance the dissolution release profile of Capecitabine. This was developed by using, span 80 and cholesterol as a carrier, surfactant, lipid respectively.

2. Materials and Methods

Materials:

Capecitabine (Gift sample from Dr.Reddy's Laboratories Ltd., Hyd), Cholesterol (S.D.Fine Chemicals, Mumbai.) Span 60(S.D.Fine Chemicals, Mumbai.), Methanol (Merck Specialities Pvt. Ltd., Mumbai.), Chloroform (Merck Specialities Pvt. Ltd., Mumbai.)

Methodology

Formulation of Proniosomes: Proniosomes were prepared by using slurry method (13). The composition of different proniosomal formulations is represented in (Table 4.3). In brief, accurately weighed amounts of lipid mixture comprising of span 60 and cholesterol as per formulation ratios were dissolved in 20ml of solvent mixture containing chloroform and methanol (2:1). The resultant solvent solution was transferred into a 250ml round bottom flask. The flask was attached to a rotary flash evaporator (Hei-VAP advantage/561-01300, Heidolph, Germany) and the organic solvent was evaporated under reduced pressure at a temperature of 45 ± 2^0C. The obtained proniosomes were stored in a tightly closed container for further evaluation.

Preparation of Gel:

Carbopol 934 was taken as polymer for the formation of Gel. 1% Carbopol was chosen for preparing gel. Weighed amount of Carbopol 934 was taken in a dry beaker and to this water was added and kept aside for swelling of carbopol for 3 hours. After complete swelling of carbopol, slowly stir with glass rod and to this add few drops of Tri ethanol amine (TEA) and this turns the preparation into gel. To tis gel the prepared proniosomes were added.

Evaluation

Morphological evaluation of prepared proniosome powders by Scanning Electron Microscopy

The surface morphology of the pro-niosomes was evaluated by scanning electron microscopy. The proniosome gel was placed on a cavity glass slide and few water was added drop wise along the side of the cover slip. The formation of vesicles was monitored through a microscope and photomicrograph was taken.

Percentage Drug Entrapment

The PDE of Capecitabine proniosomes was calculated after determining the amount of unentrapped drug by dialysis[38]. The dialysis was performed by adding the niosomal dispersion to a dialysis tube (donor compartment) and then dipping the tube into a beaker containing 200 mL of PBS pH 7.4 with 0.05% SLS (receptor compartment) on a magnetic stirrer, rotated at a speed of 80 to 120 rpm for 3 hours. After 3 hours, the solution in the receptor compartment was estimated for unentrapped drug at 304 nm by using a UV spectrophotometer[27].

$$Percent\ Entrapment = Total\ drug - Diffused\ drug / totaldrug X 100$$

***In vitro* diffusion study**:

In vitro dissolution study of proniosomal gel was perfomed by using franz diffusion cells by taking phosphate buffer 6.8 pH. The volume of diffusion medium used was 20 ml and maintained at a temperature of 37 ± 0.5ºC with paddle speed set at 50 rpm throughout the experiment. An aliquot of 5 ml was collected at predetermined time intervals 30 min, 1, 2, 3, 4, 5, 6, 7 hrs respectively and replaced with

fresh buffer to maintain constant volume[40]. Samples were analyzed for Capecitabine using UV-Visible spectrophotometer at 304 nm.

Fourier transforms infrared (FT-IR) spectroscopy

Infrared spectra of pure drug, and optimized proniosomal formulation were obtained using FT-IR spectrophotometer (Bruker, Alpha-T, Lab India) by the conventional KBr pellet method[13].

3. Results and Discussion

The encapsulation percentage obtained by different ratios of sorbitan fatty acid esters and lecithin were almost same with slight difference that is formulations having more of surfactant have encapsulation slightly higher than those with higher lecithin ratio. Table 8 shows the encapsulation percentage of different formulations.

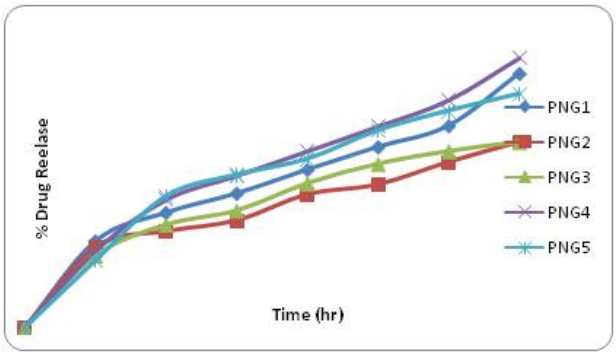

Figure1: In vitro drug release profile for Pro-Niosomal Gels

Release Kinetics:

The Release kinetics of the optimized formulations studied in in-vitro drug release are given in the tables .Different Kinetic model of the Formulations A2, A3, A4 and A5 are shown in the figure. To ascertain the drug release mechanism and release rate data of the various formulations, the data's were model fitted by Drug Kinetic Models. The models selected were Zero order, First order, Higuchi Matrix, Weibull, Korsemayer Peppas, Hixon-Crowell. The release pattern was found to be Zero Order and the best fit model was found to be Korsemayer-Peppas with 'n' value between 0.45 to 0.89 suggesting that the drug was released by non-fickian release mechanism or anamolous transport.

FT-IR:

The FTIR was performed for both pure drug and formulation, and the results clearly indicated that there is no incompatibility between pure drug and formulation.

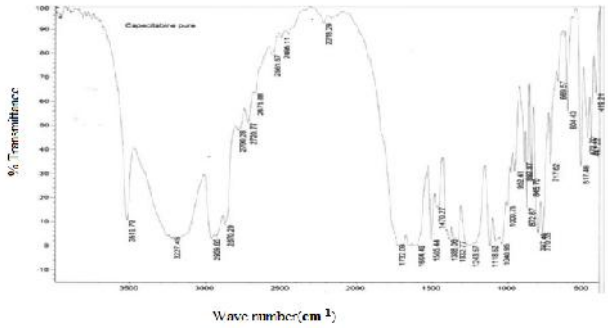

Figure 2

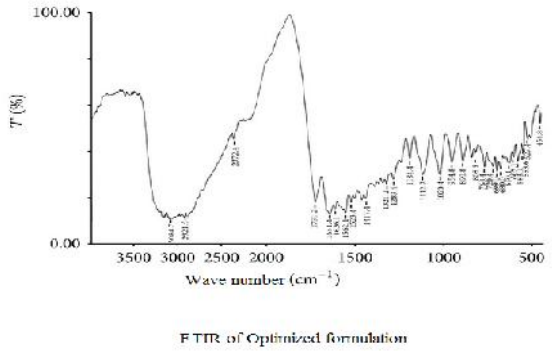

Figure 3

4. Conclusion

Studies were conducted with various levels of amount of cholesterol and span 60 to optimize proniosomal. All formulations were evaluated for the different Physico-chemical characteristics. Formulated proniosomes gave satisfactory results for entrapment efficiency. *In Vitro* drug release behavior was improved. There is no significant difference between the FTIR patterns of the optimized formulation of proniosomal gel and to that of the pure drug.

Table 1: Formulation of Proniosomes

Formulation code	Drug (Capecitabine)	Surfactant	Cholesterol	Solvent (2:1)
PNG1	**150**	Sapn 60	100	Chloroform and methanol
PNG2	**150**	Sapn 60	100	Chloroform and methanol
PNG3	**150**	Sapn 60	100	Chloroform and methanol
PNG4	**150**	Sapn 60	50	Chloroform and methanol
PNG4	**150**	Sapn 60	50	Chloroform and methanol

Table 2: Optical Parameters

Parameters (Units)	Values
	Capecitabine
λ max/ nm	304 nm
Linearity Range (µg/ml)	2-20
Slope, *b*	0.025X

Table 3: Encapsulation percentage of various Pro-Niosomal Gel Formulations

SL. No	Niosomal code	Encapsulation percentage (%)
1.	PNG A1	23.84 ±1.4
2.	PNG A2	59.50 ±2.3
3.	PNG A3	23.84 ±1.6
4.	PNG A4	28.84 ±2.0
5.	PNG F5	17.24 ±1.9

Table 4: Pro-niosomal gel formulations with various ratios of sorbitan fatty acid esters and lecithin

SL. No	Pro-Niosomal code	Ratios		Capecitabine (mg)	Cholesterol (mg)
		SPAN 40	Lecithin		
1.	A2	2	1	10	20
2.	A3	1	2	10	20
3.	A4	3	1	10	20
4.	A5	1	3	10	20

Table 5: Encapsulation percentage of different formulations

SL. No	Pro-Niosomal code	Ratios		Encapsulation percentage (Percentage)
		SPAN 40	Lecithin	
1.	A2	2	1	65 ±1.9
2.	A3	1	2	57.4 ±1.6
3.	A4	3	1	61.2 ±2.1
4.	A5	1	3	57.2 ±1.5

Table 6: *In-vitro* studies of different formulations

Time (Hr)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	25.84	24.04	21.47	22.89	20.06
2	34.33	28.72	30.72	38.17	39.28
3	40.1	31.96	34.98	45.3	45.63
4	47.22	39.72	43.14	52.64	50.36
5	54.01	42.69	48.94	60.05	58.87
6	60.34	49.4	52.74	67.92	64.77
7	76.01	55.4	55.5	80.5	69.8

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