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INVESTIGATION OF NIOSOMES CONTAINING ANTI-INFECTIVE DRUG FOR DERMAL APPLICATION

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ABSTRACT

Clarithromycin is macrolide antibiotic used as against various susceptible bacteria. In the present study erythromycin was entrapped into niosomes by ether injection technique with the optimization of various process parameters. The niosomal formulations were prepared using a polymer Span 80 and Cholesterol in different ratio (2:1, 2:2, 3:1, 3.5:1, 4:1, 4.5:2). Dicetly phosphate (DCP) was added in the niosomal formulation. The niosomal formulation was used to formulate topical gel and evaluated for various parameters such as pH, spreadability, Rheological study and *In vitro* release in diffusion cells. All the formulations were found to release clarithromycin in a controlled manner for a prolonged period over 8 hours. It was observed that niosomes prepared using an span 80 and cholesterol in 4.5:2 ratio exhibited the best release profile and able to sustain the drug release for 8 hours. The results demonstrate that the entrapment of drug into niosomes leads to prolongation of drug release, enhanced drug retention into skin and improved permeation across the skin after encapsulation.

KEYWORDS

Clarithromycin, Niosomes, Particle size and Injection method.

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INTRODUCTION

In the past few decades considerable attention has been focused on the development of new drug delivery systems. Controlled release concept and technology have received increasing attention in the face of growing toxicity and effectiveness of drugs when administered or applied by conventional methods. Topical drug delivery is a route for systemic treatment. The skin is the body's largest organ. It is home to up to three million micro-

organisms per cm2, which feed on its scales and secretions[1].

Niosomes increase drug efficacy as compared with that of free drug. An ideal drug delivery system deliver drug at the rate dictated by the need of the body over period of treatment and it channel the active entity solely to the site of action. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs[2,3].

Many formulation of anti infective drug of clarithromycin are available such as ointments, creams, tablets and also in the form of injections for i.v and i.m route. But these conventional dosage forms of oral drug delivery system faces many problems. These drugs has poor bioavailability due to high hepatic first pass metabolism thus leading to low systemic circulation[4].

Clarithromycin, relatively short half life (3-4 hr) in plasma and has potential to be delivered by transdermal route. They undergo presystemic metabolism and excreted by renal route and about 20-30% excreted unc unchanged by oral route and have a very short half life 3-4 hours. They are having low protein binding. They require dosing frequently. Moreover, for the dermal infection such as mycobacterium chelone induced skin infection can be best treated by formulation of clarithromycin in the form of niosomal gel that may deliver locally and release the drug for a prolonged period of time. Niosomes loaded with drugs for dermal application show interactions with epidermal tissue without exerting immediate or strong systemic action[5,6].

Clarithromycin is macrolide antibiotic which may be either bacteriostatic or bactericidal depending on the sensitivity of the microorganism and the concentration of the drug. The present study is based on the hypothesis that incorporat ion of clarithromycin into niosomes will improve the amount and time of drug retention within the skin. Niosomes characteristics such as lamellarity, lipid composition and tructure surface charge and size and physiochemical nature of drug itself may affect follicular deposition of drugs[7].

In topical preparation it has advantage that increase the contact time with the applied tissue. They may serve as a solubilization matrix as local depot for sustained release or permeation enhancers of dermally active compounds or as a rate-limiting membrane barrier for the modulation of systemic absorption of drugs via the skin[8].

Therefore, in the present work attempt was made to formulate noisome containing anti-infective drug for dermal application which brings about site specific targeting, less side effects, improved bioavailability, less dosing frequency and thus achieving better patient compliance.

MATERIAL AND METHODS

Materials

Clarithromycin was purchased from Mylan Lab., Hyderabad. Span 20, Span 60, Span 80 was purchased from Loba Chemie, Mumbai, India. All the chemicals and reagents were used of analytical grade.

Methods

Formulation of niosomes containing anti infective drug for dermal application

The Niosomes containing anti infective drug for dermal application were prepared by ether injection method[9,10].

Preparation of drug loaded niosomes

Niosomes were formulated by ether injection method as follows: The surfactants, cholesterol and drug were first dissolved in suitable organic solvent. The prepared organic phase was then added to aqueous phase. In brief thus the surfactant and cholesterol along with clarithromycin and dicetyl phosphate were dissolved in 10ml diethyl ether. Thus the dissolved organic solution containing drug were injected drop wise through 24 gauge needle into preheated 20ml phosphate buffer of 7.4, which is magneticaly stirred and maintained at 650C for 45 min. Stirring was continued until all ether evaporating to get drug loaded niosome.

Preparation of carbopol gel

Sufficient quantity of carbopol 934 (1% w/w) was weighed and sprinkled onto warm distilled dissolved in 100ml of distilled water and it was placed for two hours. The measurement of pH of each formulation was done in triplicate and average

values were calculated. Ingredients like propylene glycol (10 % w/w) and glycerol (30 % w/w) were added subsequently to the aqueous dispersion with continuous stirring. The dispersion was neutralized to pH 6 using 1 % w/v of sodium hydroxide solution and the final weight was adjusted with distill ed water. The prepared gel was sonicated for 15 minutes and kept overnight to remove air bubbles.

Preparation of clarithromycin niosomal gel

Niosomal gels were prepared using the same formula. For this purpose equivalent amount of niosomes containing 100mg drug (separated from the unentrapped drug) was mixed into the 1% (w/w) carbopol gel with an electrical mixer (25rpm, 2 min).

Evaluation of drug loaded niosomal gel

Visual Inspection

The prepared formulations were inspected visually for their colour, homogeneity, consistency, grittiness and phase separation.

Measurement of pH

The pH of formulations was determined by using digital pH meter[11].

Spreading co-efficient

Spreading co-efficient was measured on the basis of 'Slip' and 'Drag' characteristics of niosomal gel. An excess of niosomal gel (about 2gm) under study was placed on this ground slide. Niosomal gel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The hook was provided in the second glass slide. Weight of one gram was placed on the top of the two slides for 5 min to provide a uniform film of niosomal gel. The time (in sec) required by the top slide to separate from ground slide was noted. A shorter interval indicates better Spreading coefficient[12].

Rheological study

The viscosity was determined using a Brookfield viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 07. The formulation whose viscosity was determined and added to the beaker was allowed to settle down for 30 min. at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the centre of niosomal gel and jar rotated at a speed of 50rpm for 10 minutes. The viscosity reading was noted down[13].

Drug content determination

Weigh accurately 1gm of niosomal gel and it was dissolved in 100ml of methanol. The volumetric flask was kept for 2 hours and shaken well the solution was passed through the filter paper and filtered. The absorbance was measured spectrophotometrically at 207nm after appropriate dilution[14].

***In vitro* drug release studies**

The release of clarithromycin from niosomes and niosomal gel was determined using the membrane diffusion technique, 1ml of niosomal suspension were placed in a beaker containing 25ml of Phosphate buffer pH 7.4 as the dissolution medium maintained at 37±0.5°C. The medium was stirred at 100rpm. Aliquots (5ml) of samples were taken at 5sec time intervals, and the same volume of fresh phosphate buffer was replaced. Samples were filtered, diluted suitably and analysed using UV/Visible spectrophotometer (V-630, JASCO, Japan) at λmax 207nm. The cumulative percentage drug release was calculated and plotted against time (sec)[15].

RESULTS AND DISCUSSION

Visual Inspection

The transdermal films formulated with different polymer concentration were found to be flexible, smooth, opaque, sticky and homogeneous.

Measurement of pH

It was determined as per the procedure given in methodology and found to be pH 7.1. Hence, it does not cause any irritation to skin and safe for dermal use.

Spreading co-efficient

Spreadability was determined as per given in methodology. Spreading coefficient was found to be in the range of 15.83 ± 0.04 to 15.91± 0.05 g.cm/sec for gels prepared.

Rheological study:

The viscosity of the formulated batches were determined using a Brookfield viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 07 and viscosities of the niosomal gel was found to be in the range of 28913±0.155 to 28917±0.132cps.

Drug content determination

The percentage drug content in various formulations ranged from 80.00 % - 95.00 % and the drug content was found to be in the limit.

***In vitro* Release studies**

The drug release from the formulation depends upon the type of polymer used. When the concentration of cholesterol was high in F2 then drug release was retarded and in formulations with low cholesterol concentration the percentage of drug release was high. Increasing cholesterol content markedly reduces the efflux of the drug. Inclusion of cholesterol fills the pores in vesicular bilayers and abolishes the gel liquid phase transition of niosomal systems resulting in niosomes that are less leaky. Cholesterol in the formulation acts as a membrane stabilizing agent and help to control drug release. The entire amount of drug was not released from the niosomes. This may be due to entrapment of drug in lipophilic region. Difference in the drug release may be due to vesicle size, lamellarity and membrane fluidity as a function of chain length of surfactant and cholesterol content.

Table No.1: Composition of niosomal formulations with loaded drug

S.No	Formulation code	Clarithromycin (mg)	Dicetylphosphate (mg)	Span 80: cholesterol
1	F1	100	10	2:1
2	F2	100	10	2:2
3	F3	100	10	3:1
4	F4	100	10	3.5:1
5	F5	100	10	4:1
6	F6	100	10	4.5:2

Table No.2: Drug release profiles of various niosomal gel formulation

S.No	Formulation code	% Cumulative drug release*
1	F1	74.563 ±0.612
2	F2	66.766 ±0.519
3	F3	72.085 ±0.984
4	F4	72.958 ±0.888
5	F5	71.438 ±0.866
6	F6	76.410 ±1.005

*Each reading is an average of 6 determinations

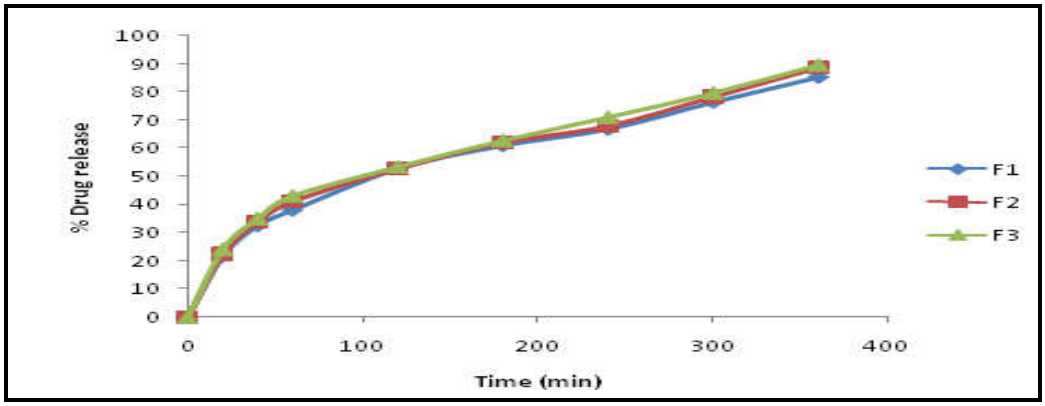

Figure No.1: Cumulative percentage of drug release F1 to F3

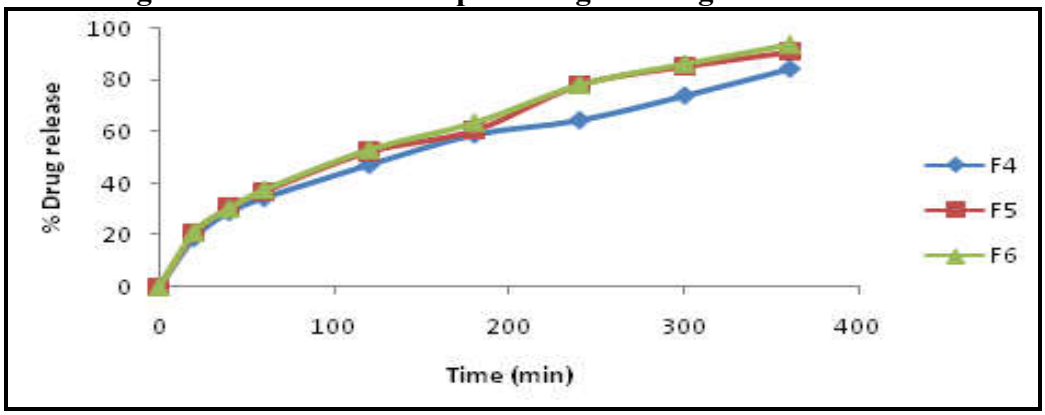

Figure No.2: Cumulative percentage of drug release F4 to F6

CONCLUSION

The present work of niosomes of clarithromycin were formulated and were found to be satisfactory in terms of its appearance and made to optimize various formulations F1 to F6. Clarithromycin niosomes were prepared by ether injection method using magnetic stirrer. Six formulations (F1, F2, F3, F4, F5 and F6) of niosomes were prepared using clarithromycin, span 80 and cholesterol in ratios (2:1, 2:2, 2:1, 3:1, 3.5:1, 4:1, 4.5:2) respectively. 100mg of clarithromycin was used in each formulation. The pH of the niosomal gel (F6) was found to be 7.1, spreadability of 15.87gcm/sec, viscosity of 28915cps, The percentage drug content in various formulations ranged from 80.00 % - 95.00 %. *In vitro* drug release have revealed that the formulation were suitable for the topical dermal application Hence the optimized formulation F7 showed better drug release kinetics in a prolonged period of time and found to be effective against Staphylococcus aureus. Further detailed investigations and in vivo studies need to carried out to compare in vitro-in vivo correlation need to be established to guarantee the efficacy of the formulation and it can be a promising tool in the treatment of skin infection.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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