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Formulation and *in vitro* Evaluation of Topical Liposomal Gel of Triamcinolone Acetonide

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ABSTRACT

Triamcinolone acetonide is a glucocorticoid that it is used in treatment of skin inflammatory diseases. liposomes can increase the deposition of drugs within the skin at the site of action and reduce side effects of drug. The aim of the present study was to formulate and evaluate liposomal vesicles loaded with triamcinolone acetonide. liposomes containing triamcinolone acetonide were prepared using thin film method. The quantities of lecithin and cholesterol were changed to enhance the encapsulation of the drug. Carbomer 940 was used as gel base and four different gel formulations including hydroalcoholic gel, MLV liposomal gel, SUV liposomal gel and blank MLV gel containing free drug were prepared. The release profile of triamcinolone acetonide was determined using dialysis membrane method. Liposomes were also characterized by optical microscope and their particle size was also determined. Formulation containing lecithin: drug: cholesterol (100: 10: 10) having about 90.05 percent encapsulation was selected as the best formulation and the results of release showed SUV liposomal gel has the most regular and the least interaction between the drug and polymer. Results of particle size determination showed 50% of MLV and SUV liposomes had diameter below 33.80 µm and 22.09 µm, respectively. The results of characterization of the vesicles indicated the potential application of triamcinolone acetonide loaded liposome as carrier system.

Key words: triamcinolone acetonide, liposome, thin film, gel.

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INTRODUCTION

Transdermal drug delivery has many advantages over the other traditional routes of administration. But, the barrier nature of the skin is a significant obstacle for most drugs to be delivered into and through it. Many researchers have been investigated the liposomes as drug delivery systems that can improve transdermal drug delivery. Liposomes are spherical vesicles with concentric phospholipid bilayers [1]. The results of some studies have been indicated that liposomes can increase the deposition of drugs within the skin at the site of action and reduce its absorption into blood [2, 3]. Lipid bilayered membrane encloses an aqueous core that hydrophilic drugs get entrapped in the central aqueous core of the vesicles while lipophilic drugs get entrapped within the bilayered membrane [4]. Drugs encapsulated in liposomes can be transported without rapid degradation and minimum side effects to the recipients [5]. Liposomes have many advantages such as, biocompatiblity and biodegradablity, prolonging release of active pharmaceutical agents, ability to entrap lipophilic and hydrophilic drugs, protecting encapsulated agents from metabolic processes, nontoxicity, penetration enhancing and slow drug release [6-10].

Triamcinolone acetonide is a glucocorticoid that it is used in treatment of allergic reactions, asthma, rhinitis and other inflammatory diseases. Mechanism of action of the drug is control of the synthesis of prosteglandins and leukotrienes [11].

The aim of the present study was to prepare and evaluate topical liposome gel formulation of triamcinolone acetonide and to study their in vitro release behavior.

MATERIALS AND METHODS

Egg lecithin and vitamine E (alpha tocopherol) were purchased from Merck, Germany. Cholesterol and triamcinolone acetonide were obtioned from BDH, England and Sicro, Italy respectively. Carbomer 940 was purchased from Antwerpen, Belgium. All of the solvents were of analytical grade.

Experimental

Preparation of liposome

Liposomes were prepared by thin film method. Briefly egg lecithin, cholesterol, vitamin E (as antioxidant) and 10 mg triamcinolone acetonide were dissolved in 5ml chloroform. The quantities of lecithin and cholesterol were changed to enhance loading drug in liposomes (table 1). Then the mixture was evaporated in a rotary evaporator (Heidolph, WB2000, Germany) at 150 rpm for 30 min. The thin film formed in the round-bottomed flask was hydrated with phosphate buffer saline for 30 min. Glass ball was used for dispersion of liposome [1, 10].

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Table 1: Effect of lipid composition on encapsulation efficiency of triamcinolone acetonide liposomes

Formulation NO.	Compositions ratio (mg) (lecithin:drug:cholesterol)	Entrapment efficiency (%)	Formulation NO.	Compositions ratio (mg) (lecithin:drug:cholesterol)	Entrapment efficiency (%)
1	100:10:5	75.80	7	125:10:10	58.83
2	100:10:10	90.05	8	125:10:20	47.85
3	100:10:20	78.71	9	150:10:10	47.97
4	100:10:40	53.19	10	150:10:20	44.90
5	100:10:60	69.49	11	200:10:10	48.53
6	100:10:80	67.19	12	200:10:20	45.35

Preparation of SUV liposome

SUV liposomes were obtained by sonication of MLV liposome in an ultrasonic bath ($F_{s,}$ Germany) 30 min at room temperature.

Determination of triamcinolone acetonide entrapment in liposomes

The liposomal suspension was centrifuged at 20000 rpm for 30 min. The supernatant was removed and the liposomes were disrupted with ethanol 70% and the quantity of drug was measured using a spectrophotometer (Bio-tek Kontron, 922, England) at 239 nm.

Particle size determination

The average diameter of liposomes was determined using a particle sizer (Malvenrn, Xlongbed ver.2.15, England) at 25 ˚C.

Microscopy

liposomes were examined by optical microscope (Olympus, R4, Japan) to determine the shape and lamellarity of vesicles (magnification x 200).

Preparation of liposomal gel

Carbomer 940 (1%) was added slowly to a PBS buffer solution (pH 7.4), under constant stirring by a paddle stirrer. For gel preservation, methyl paraben (0.2%) was added. Then teriethanolamine was added for achieving neutral pH and clearing of the gels. After addition of the full amount of solid material, the gels were allowed to swell under moderate stirring. Four different formulation gel including hydro-alcoholic gel, MLV liposomal gel, SUV liposomal gel and blank MLV gel plus the drug were prepared (table 2).

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Table 2: Different gel formulations of triamcinolone acetonide.

F_1	hydroalcoholic gel
F_2	MLV liposomal gel (containing lecithin 100 mg: drug 10 mg: cholesterol: 10 mg)
F_3	SUV liposomal gel (containing lecithin 100 mg: drug 10 mg: cholesterol: 10 mg)
F_4	blank MLV liposome gel plus the drug

Stability evaluation of liposomal gels

The liposomal formulations were stored in refrigerator for 3 months to evaluate color and appearance. 1 gr of each sample was dispersed in 100 ml distilled water and pH was determined using a pH meter (Coring, 7, England).

In vitro drug release studies

In vitro triamcinolone acetonide release from the liposomes was measured using dialysis membrane method. 1 g of each formulation was put in a dialysis bag (Medicell International England). The receptor phase was contained ethanol 20% and phosphate buffer saline (pH 7.4) was stirred continually using a magnet stirrer at 37˚C. An aliquot of 2.5 ml of samples were withdrawn from each batch at definite time intervals (15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min) and replaced with the same amount of ethanol and phosphate buffer saline to maintain sink condition. Then, the concentration of released drug was monitored using a UV spectrophotometer at 239 nm.

Statistical analysis of data

The reported release data were analyzed by Jim fit program [12] and compared and plotted using Excel Microsoft. $P>0.05$ was considered as significant difference.

RESULTS AND DISCUSSION

As mentioned before, for determination of entrapment efficiency, the quantities of lecithin and cholesterol were changed to enhance loading drug in liposomes. At first, the quantity of cholesterol was changed (formulation No.1-6). Then the quantities of cholesterol (10 and 20 mg) that had high encapsulation, was selected as a constant value and the quantity of lecithin was changed (table 1). Formulation number 2 (containing lecithin: drug: cholesterol ratio of 100: 10: 10) having about 90.05% encapsulation was selected as the best formulation ($P< 0.05$). Results of particle size determination showed 50% of MLV and SUV liposomes had diameter below 33.80 µm and 22.09 µm, respectively. According to the results of particle size, sonication is an important parameter in preparation of SUV liposomes. Also the results of microscopy indicated the SUV liposomes may be obtained by sonication of MLV liposome in a bath sonicator (fig 1a and 1b).

It has been previously reported that sonication time is an important parameter in the liposome preparation, and also increasing the time of sonication is necessary to decrease the

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polydispersity [13]. Also, loading of essential oil of *Eucalyptus camaldulensis* in liposomes, showed that homogenization is another factor that can significantly affected the liposomal particle size [14].

According to the results, release of drug from all of the formulations followed zero-order kinetics. The results showed that the release from SUV liposomal gel has the most regular and showed the least interaction between the drug and polymers (table 3, fig 2). The drug release from hydroalcoholic gel had the most irregularity and the highest interaction (table 3, fig 2). Also similar results obtained from MLV liposomal gel and the blank formulation indicated that a high percentage of the drug may be attached to external layer of liposomes (table 3, fig 2).

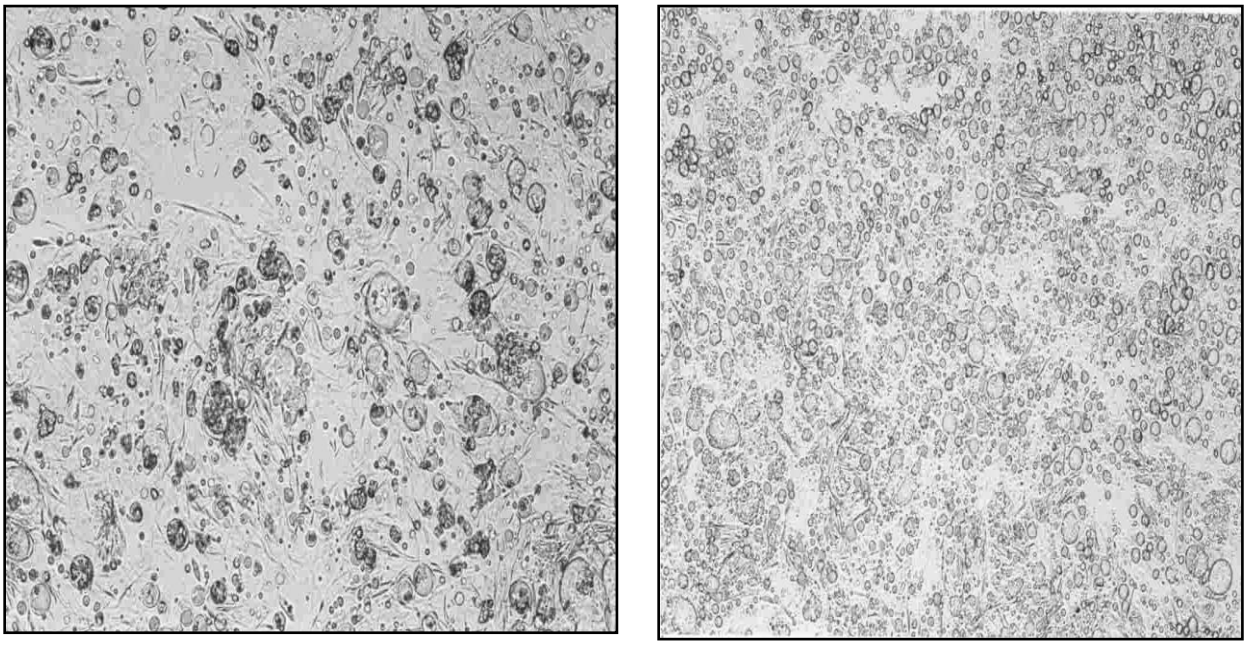

Fig 1: a) Image of MLV liposomes of triamcinolone acetonide b) Image of SUV liposomes of triamcinolone acetonide (200 X).

The stability of the vesicle dispersions was monitored for 3 months and the results indicated that there was no significant change in the appearance and color of the samples during the storage.

Triamcinolone acetonide is a glucocorticoid and is useful for treatment of inflammatory diseases. However, there is a tendency to reduce its use due to its complicated pharmacokinetic characteristics [11]. Many studies have been reported for improvement of tissue distribution and targeting of glucocorticoids drugs by using nano drug delivery system such as liposome and solid lipid nanoparticle (SLN). Ghanshyam *et al* in 2011 have been investigated the formulation and characterization SLNs dry powder inhaler containing triamcinolone acetonide and the results showed SLNs are suitable carriers for incorporating the drug [11].

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Table 3: The percentage release of different formulation gel of triamcinolone acetonide.

Time (min)	Release of hydroalcoholic gel (%)	Release of MLV liposomal gel (%)	Release of SUV liposomal gel (%)	Release of blank MLV liposome gel plus the drug (%)
15	0.68±0.56	5.81±0.84	5.81± 4.78	6.66±0.97
30	4.75±2.14	8.99±0.27	9.85±4.68	7.83±1.03
45	6.91±2.56	12.43±0.58	12.66±4.45	9.59±1.24
60	9.49±1.83	14.99±0.77	19.16±3.30	14.59±2.62
90	13.22±1.63	21.12±1.09	27.58±3.47	19.20±2.30
120	17.49±1.59	27.51±1.03	37.33±3.09	25.53±2.57
150	22.75±1.56	33.69±1.66	44.00±4.54	31.77±3.39
180	25.84±1.79	39.69±1.66	53.70±6.52	38.59±3.63
210	31.20±2.91	45.26±1.90	61.39±8.47	45.37±3.68
240	37.38±2.71	51.90±1.70	69.49±11.20	53.71±4.90
270	42.40±2.20	58.59±2.07	76.72±11.29	60.86±5.84
300	48.15±1.49	69.91±2.38	83.90±11.17	67.87±5.82

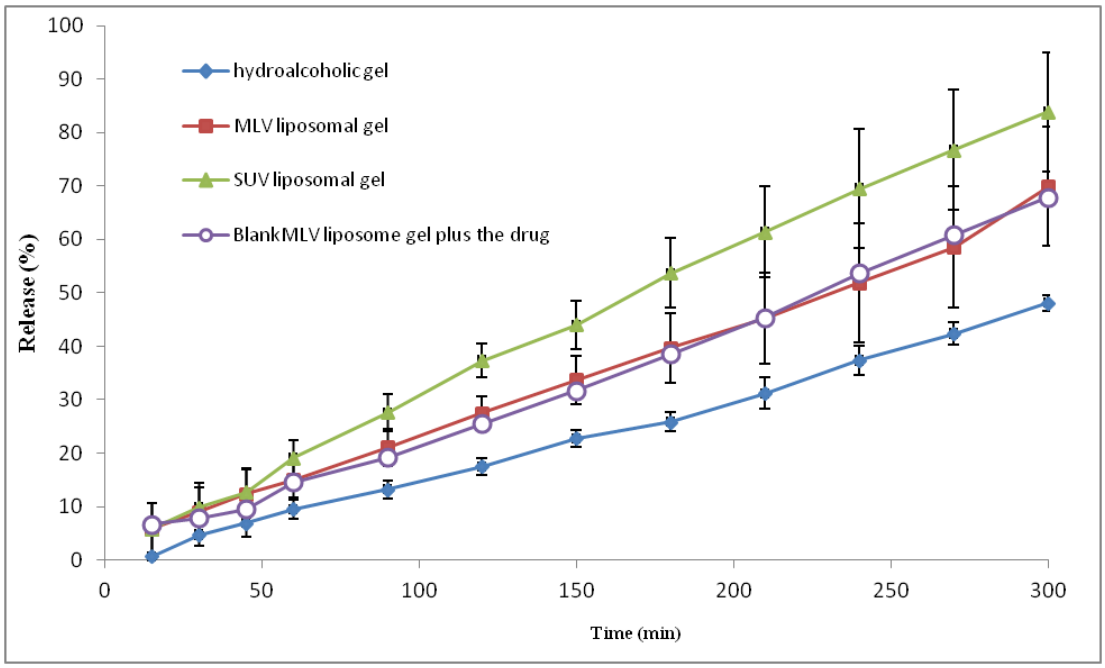

Fig 2: The percentage release of triamcinolone acetonide from different gel formulations

Topical application of liposome vesicles has many advantages over the conventional dosage forms. It has been suggested that the formulated liposomes may be applied to the skin as gel. It has been previously showed that the liposomal gel of Lidocaine HCL may perform therapeutically better effects than the conventional formulation [15]. Samani *et al* in 2009 showed that cyproterone acetate containing liposomes had 74±6.11% loading efficiency and the liposomal formulation has better penetration potential than conventional cyproterone acetate formulation [7]. Agarwal *et al* in 2002 have evaluated the miconazol (MCZ) nitrate loaded topical liposome *in vitro*. The results have shown the entrapment of MCZ in liposome

can facilitate localized delivery of the drug [10]. Also, formulation of celecoxib loaded liposomes and the study of their release behavior indicated that the potential advantages of celecoxib loaded liposome as carrier system [13].

CONCLUSION

According the results of the present study, incorporation of triamcinolone acetonide in liposome in proper amounts and incorporation of liposomes in gel formulation has many advantages over the conventional dosage forms, including prolonged and controlled release topical dosage delivery.

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