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International Journal of Pharmaceutics 242 (2002) 381–384

international journal of pharmaceutics

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Note

Release profile of lidocaine HCl from topical liposomal gel formulation

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Received 14 January 2002; received in revised form 31 January 2002; accepted 4 February 2002

Abstract

Liposomal hydrogel formulations of lidocaine HCl, suitable for topical application, have been prepared and drug release properties in vitro have been evaluated. Liposomes composed of Soya lechitin and cholesterol, with lidocaine HCl, entrapped in the inner water compartment, were prepared by simple hydration method. Topical liposomal gel formulations were prepared by incorporation of liposomes into a structured vehicle (hydrogels of Carbopol 940 in concentration of 1.5, 1.75 and 2%). High percentage of encapsulated drug in liposomes has been obtained (over 70%). Liposomal gel formulations provided prolonged drug release rate. The concentration of gelling agent in a range 1.5–2.0% affected the release rate slightly. In vitro release data showed that release kinetic can be described as diffusion-controlled, while liposomes act as reservoir systems for continuous delivery of drug. Proposed formulations provided stable percentage of entrapped drug and drug release within an examination period of 3 weeks.

Keywords: Liposome; Lidocaine HCl; Topical application; Carbopol gel; Drug release; Stability

Liposomes have been investigated for many years as parenteral drug carrier systems, but only for approximately one decade, they have been considered for topical drug delivery, including ophthalmic and dermal treatments (Niesmann, 1992; Schreier and Bouwstra, 1994). With regard to the topical application, liposomes embedded in the topical dosage forms could provide a topical activity at the desired locus of action with little or no systemic activity. In general, they are deemed more effective and less toxic than conventional topical formulations, ointments, creams or lotions (Rollan, 1993; Reimer et al., 1997). Liposomal topical formulations may serve as a solubilizing matrix for poorly soluble drugs, penetration enhancers of the active ingredient into the skin, local depot (microreservoires) for sustained drug release as well as a rate-limiting membrane barriers for modulation of systemic absorption (Cromellin

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00221-1

and Schreier, 1994). In accordance to the above-mentioned, local anesthetics together with anti-cancer, antifungal and antibiotic agents are among the substances whose incorporation into liposomes satisfied all the requirements necessary for topical application and localized drug delivery (Lopez-Berestein and Fidler, 1989; Price et al., 1990; Schumahecher and Margalit, 1997).

The aim of this study was to evaluate the release profile of topical formulation containing lidocaine HCl loaded liposomes. Changes of the release profile during a period of 3 weeks storage were followed as well.

Liposomes were prepared with Soya lechitin (liquid state) and cholesterol, purchased from Soya protein and Galenika, Yugoslavia, respectively. Lidocaine HCl was obtained from Siegfried, Switzerland. Carbopol 940 (Alpha Pharma, Belgium) was used as gelling agent. All others chemicals used were of analytical grade.

Liposomes containing anesthetic agent lidocaine HCl were prepared by simple mixing method, vortexing the lipid dispersion in water (Schumahecher and Margalit, 1997). Lipid phase containing lechitin/cholesterol (9:1) was hydrated with a part of aqueous phase bearing total drug quantity (lipid/ aqueous phase ratio 7:19, drug/ lipid mass ratio 1:5). After 24 h, the rest of water was added, so final lipid/aqueous phase ratio was 7:33. Topical liposomal gel formulations (G1, G2, G3) were prepared by incorporation of liposomes in structured vehicle. The structured vehicles of Carbopol 940 were prepared by varying the concentration of gelling agent (1.5, 1.75, 2% of Carbopol 940).

Biopharmaceutical evaluations of prepared gel formulations were carried out by determination of the percentage of entrapped drug as well as drug release profiles.

Quantity of the entrapped drug in liposomes was determined indirectly, on a basis of free lidocain HCl in supernatant after dilution with purified water (1:10) and centrifugation, by mean of HPTLC method (plates Silica gel F_{254}, mobile phase cyclohexane:acetone:diethylamine = 80:10:10, UV detection at 254 nm, CAMAG).

Drug release studies on topical liposomal gel formulations were performed in vitro using dialyzing method (VanKel Enhancer Cell in Erweka DZT apparatus, hydrophilic membrane of regenerated cellulose). A weighed amount of liposomal gel formulations was poured into glass cell and dialyzed against purified water as a dialyzing medium, incubated at 32 °C. Quantity of the lidocaine HCl, released in dialyzing medium, was followed UV spectrophotometrically at 262 nm (Perkin Elmer, Lambda 16, USA) within a period of 24 h. Kinetic of drug release has been also estimated.

Changes of the percentage of liposome-asociated drug substance and drug release rate were registered within a period of 3 weeks storage on 4 °C in order to estimate the stability of the prepared topical liposomal formulations.

By use of simple vortex method under the proposed hydration conditions, high percentage of liposome-associated drug (over 72%) has been obtained. Regarding the drug release rate, similar drug release patterns were registered for all liposomal gel formulations (G1–G3). This indicates that the concentration of gelling agent in a range 1.5–2.0% affects the release rate slightly. Drug release profiles of liposomal gel formulation (G1, G2, G3) and corresponding hydrogels (H1, H2, H3) bearing lidocaine HCl are presented comparatively in Fig. 1. As expected, hydrogel formulations showed higher release rate of lidocaine HCl compared to liposomal gel formulations. Obviously, the encapsulation of lidocaine HCl into liposomes resulted in prolonged drug release rate. Kinetic parameters, obtained from the in vitro

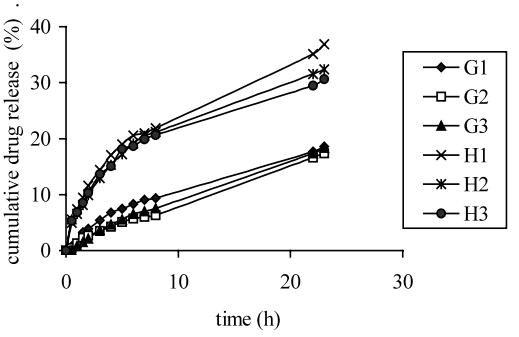

Fig. 1. Release of lidocaine HCl from different topical formulations (liposomal gel G1–G3 and hydrogels H1–H3).

Table 1
Kinetic parameters of drug release during the ageing period of 3 weeks

Sample	Higuchi diffusion model[a]		Zero order kinetic[b]	
	r	k (% $h^{-1/2}$)	r	k (% h^{-1})
G1				
Freshly prepared	0.997	4.45	0.994	0.62
After 1week	0.998	3.18	0.998	0.70
After 2 weeks	0.982	4.21	0.998	0.78
After 3 weeks	0.987	4.16	0.999	0.77
G2				
Freshly prepared	0.989	2.99	0.997	0.69
After 1 week	0.997	3.87	0.998	0.62
After 2 weeks	0.997	3.34	0.998	0.68
After 3 weeks	0.980	3.94	0.997	0.77
G3				
Freshly prepared	0.983	3.47	0.998	0.71
After 1 week	0.996	3.87	0.995	0.67
After 2 weeks	0.999	3.68	0.999	0.62
After 3 weeks		3.48	0.990	0.68
H1[c]	0.996	7.55	–	–
H2[c]	0.983	6.80	–	–
H3[c]	0.986	6.14	–	–

[a] 0–3 h.
[b] 3–24 h.
[c] 0–24 h.

drug release data (Table 1), showed that the release of lidocaine HCl from liposomal gel formulations in the first 3 hours followed the diffusion model of Higuchi (rate constant $k = 3$–4.45% $h^{-1/2}$), while the release after the 3rd h obeyed the zero order kinetic ($k = 0.62$–0.71% h^{-1}). This indicates that release kinetic can be described as diffusion-controlled, while a steady-state release, achieved after the 3rd h, suggests that liposomes act as a reservoir systems for continuous delivery of drug.

Follow-up of the percentage of encapsulated drug during ageing, indicated that the percentage of liposome-asociated lidocaine HCl in liposomal gel formulations remained stable (Fig. 2). Also, no greater changes of the release profile of lidocaine HCl from liposomal gel formulations G1–G3 were registered within a storage period of 3 weeks, as it can be seen in Table 1.

In conclusion, topical liposomal gel formulations containing anesthetic agent lidocaine HCl provided high percentage of entrapped drug which remained stable within an examination period of 3 weeks. Release rate of liposome-entrapped drug was prolonged, while steady-state release suggests that liposomes function as a drug reservoir systems.

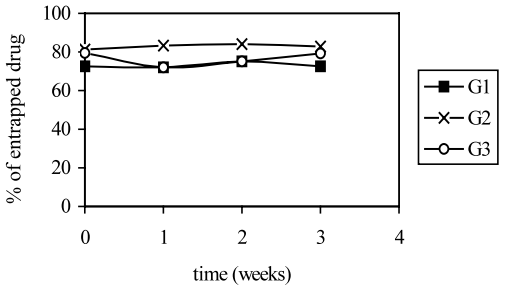

Fig. 2. Changes of the percentage of entrapped drug in different liposomal gel formulations during ageing

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