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MECHANISMS OF DRUG RELEASE CONTROL BY OSMOTİC ADDITIVES FROM MULTIPLE W/O/W EMULSIONS CONTAINING DICLOFENAC SODIUM

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Mechanisms by which the release of drug could be controlled by certain osmotic additives from multiple w/o/w emulsions were studied Multiple emulsions containing diclofenac sodium in the innermost aqueous phase were prepared by the two step emusification technique. The effect of osmotic additives like glucose, ascorbic acid, sodium chloride, glycerin, lactose and sodium citrate were studied in two different concentrations, 1% and 3% for their effect of drug release. It was found that the extent of release was lower for all the additives at both the concecntration except 3% ascorbic acid, which gave a higher release than the control emulsion, which did not contain any additive. Diffusion coefficients of the drug were calculated for all the emulsions.

Keywords : *Water-oil-water (w/o/w) emulsions; Multiple emulsions; Diclofenac sodium (DS); Osmotic additives; Diffusion coefficient*

Introduction

Multiple emulsions, both o/w/o and w/o/w, have the potential for unlimited uses because of the fact that the spherical vesicular structure of the internal dispersed phase being similar to that of liposome lipid vesicles and the selective permeability of the liquid membranes. The basic rational for the use of multiple emulsions as a means for controlled and prolonged delivery of drugs is that the drug contained in the internal dispersed droplets is forced to partition itself through several phases prior to its release at the absorption site.

It is apparent that the various partition and diffusion coefficients and the strength of liquid crystal membrane, which is a structure formed by oil, water and emulsifier molecules at both the interfaces, control the release of the drug from the multiple emulsions. Therefore, it is possible to achieve a controlled as well as a prolonged release of the drug from the multiple emulsion system by controlling the rate-limiting partition or diffusion coefficients, by varying the composition of the liquid crystal membranes or interfacial barriers, or by including some additives in one of the phases of the multiple emulsion systems.

Various investigators (1-7) including the present author have studied on release characteristics of different drug molecules from both w/o/w and o/w/o emulsions under the influence of various other parameters. In these studies, a series of multiple w/o/w emulsions of diclofenac sodium (DS) with other additives like sodium chloride, glucose, lactose, glycerin, ascorbic acid and sodium citrate in two different concentrations (1% and 3% w/v) were prepared and studied with respect to their release profiles as compared to a control multiple emulsion without any additive. The purpose of this study was to elucidate the various mechanisms by which the so-called osmotic additives modify the drug release.

Materials and Methods

Diclofenac sodium (DS) was obtained as a gift sample from Torrent Laboratories Pvt. Ltd.,

India. All the other chemicals were of analytical grade and were used as received.

Apart from control w/o/w multiple emulsion (A) which did not contain any additive, some more w/o/w emulsions were prepared in which the internal aqueous phase contained two different concentrations (1% and 3% w/v) of six different additives namely, sodium chloride (A1a, A1b), glucose (A2a, A2b), glycerol (A3a, A3b), lactose (A4a, A4b), ascorbic acid (A5a, A5b) and sodium citrate (A6a, A6b). The percentage calculation of each additive was done with reference to the total volume of multiple emulsion prepared. The 50 ml of Emulsion A was prepared by emulsifying 8 ml of aqueous drug solution containing 50 mg DS with 12 ml of liquid paraffin containing 5% v/v Span 80 at 4000 rpm for 5 minutes (first-step). The resultant 20 ml w/o emulsion was further emulsified in the second step with 30 ml distilled water containing 1% v/v Tween 40 at 2000 rpm for 3 minutes. In case of emulsions containing additives, the additive (500 mg for 1% w/v and 1500 mg for 3% w/v) was added to the drug solution before the first step and then the two-step emulsification was followed similarly as in case of control emulsion A. Formation of all the emulsions was confirmed by microscopic observation.

In vitro Studies

All the above emulsions were evaluated *in vitro*, in triplicate, till seven hours by according to a previously reported buffer-change method (5). A 10 ml of freshly prepared emulsion was placed in the donor compartment, which separates the receptor compartment, by a pretreated cellophane membrane (thickness-0,025 mm). The receptor compartment was placed on a magnetic stirrer with an energy-controlled hot plate which maintained the temperature of the diffusion media at 37±0.2°C. A teflon-coated iron rod (3.3 cm X 0.4 cm), placed at the bottom of the receptor compartment, was rotated at 100 rpm to equilibrate the diffused drug in the diffusion medium. A 250 ml quantity of pre-warmed (37±0.2°C) buffer solution of increasing pH, i.e., pH 1.9, 4.5, 6.0, 7.0 and 7.4, were used periodically in the receptor compartment as diffusion media. Samples were collected at each hour and were analysed spectrophotometrically at 280 nm. Released drug content was computed from a calibration curve of DS. Diffusion coefficient values for all the emulsions were also calculated (8).

Results and Discussion

In vitro release profiles of DS from various w/o/w emulsions are shown in Figs. 1 and 2. Diffusion coefficient value for each emulsion is also given in legends of Figs. 1 and 2. Drug release observed in the presence of additives were compared with drug release from w/o/w emulsion without any additive (control emulsion).

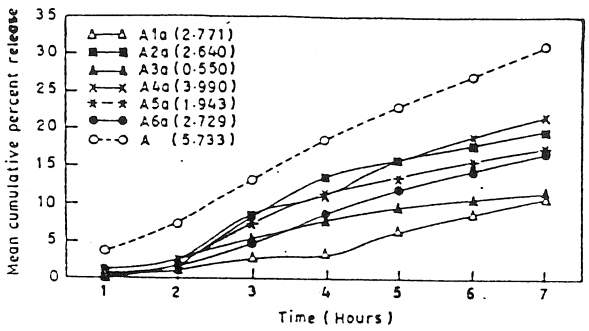

Fig. 1. In vitro release profiles of DS from w/o/w multiple emulsions showing the effect of osmotic additives at 1% concentration. Diffusion coefficient values (x10^{-5} cm^2/s) are shown in the legend within parenthesis.

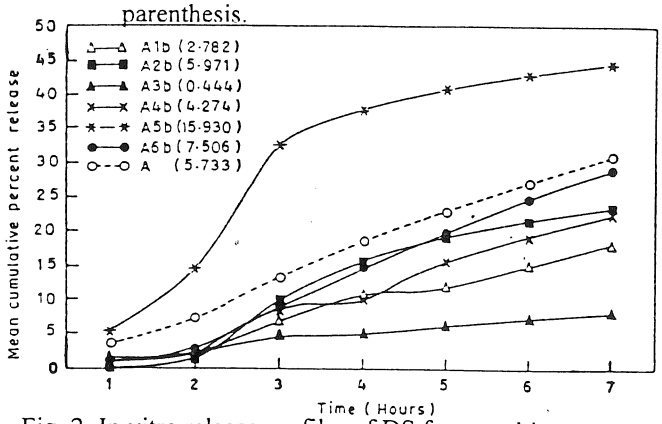

Fig. 2. In vitro release profiles of DS from multiple w/o/w emulsions showing the effect of osmotic additives at 3% concentration. Diffusion coefficient values (x10^{-5} cm^2/s) are shown in the legend within parenthesis.

Except 3% ascorbic acid, both concentrations of all the other additives reduced the overall extent of drug release in comparison to control w/o/w emulsion. The rate and extent of drug release was enhanced significantly by the presence of 3% ascorbic acid as compared to control. In the presence of 3% ascorbic acid, w/o/w emulsion exhibited a triphasic drug release profile-an initial slow release followed by a steep increase and then another slow but constant and controlled drug phase. The w/o/w emulsion containing 1% and 3% w/v glucose also provided an almost similar type of triphasic drug release. On the other hand, all the other additives, at both the concentrations, provided a biphasic drug release profile –an initial slow release followed by a fast (an almost linear) release phase of the drug. The rapid release of the drug was observed only after two hours in each case. The biphasic release profile in general could be explained as follows : since the drug, DS, is least soluble in acidic solution, acidic pH of the diffusion media used during initial hours of the *in vitro* study resulted in lower release of drug. On the other hand, the higher pH of the diffusion media, in which DS is more soluble, used during later hours of the study resulted in higher quantum of drug release. Drug released constantly in the second phase because the drug diffused in a controlled manner from the internal phase of the w/o/w emulsion.

The decreasing or increasing effect of additives on the drug release from w/o/w emulsions is directly dependent on the concentration of the additives. Emulsion containing 3% glycerol gave lower drug release than 1% glycerol probably because of an increase in the vicosity of the system at the higher concentration of glycerol. This can be verified by the fact that the diffusion coefficient of DS is also reduced by half at 3% concentration as compared to at 1% concentration of glycerol.

Enhancing or decreasing effect of individual additive on drug release can be explained on the basis of osmotic pressure gradient which develops between the two aqueous phases of w/o/w emulsions because of the presence of the additive in the internal aqueous phase. Development of osmotic gradient leads to the migration of water molecules from the external aqueous phase resulting in the swelling of the internal dispersed droplets. Since the viscosity of such a system is directly proportional to the volume fraction of the dispersed phase, the viscosity of the system increases and therefore, a lower drug release than the control was observed in the presence of both concentrations of additives excepting 3% ascorbic acid. What is intriguing however, is the fact that the diffusion coefficient actually has increased at higher concentrations of the additives with a corresponding increase in the percent cumulative release. This contradicts the previous statement, because at higher concentrations of the additives, more influx of the external phase is expected, leading to higher viscosity and hence a lower diffusion coefficient of the drug. This phenomenon may be explained as probably at 3% concentrations, there develops, relatively, such a high osmotic gradient between the two aqueous phases that continuous influx of water from external to internal phase and subsequent swelling of the internal vesicles (droplets) occurs. This can result in thinning or even the rupture of the intermediate oil phase which ultimately leads to increase in drug release and diffusion coefficient.

The most interesting release was shown by multiple emulsion containing 3% ascorbic acid. It alone gave a mean

cumulative percent release higher than the control. The diffusion coefficiient of DS from this multiple emulsion was of the order 2-10 times more than that from the other emulsions containing other additives. This again may be explained by thinning or rupture of the oil phase but a look at the isoosmotic concentrations of various additives (9) revealed a different picture. A 5.05% solution of ascorbic acid is isoosmotic with 0.9% sodium chloride solution, which is isoosmotic with 3.02% sodium citrate solution. The fact that glucose, which has an isoosmotic concentration of 5.51%, evokes only half the percent cumulative percent release as that of ascorbic acid complicates the picture further. Thus, a simple explanation of increasing of viscosity or thinning of the oil phase might not suffice. There might be another possible explanation for the observed phenomenon.

This explanation was concerned with the pH of the internal phase in the presence of additives. While the pH of internal aqueous phase in presence of additives (except ascorbic acid) ranges from 5.8 to 7.8 (9), a solution of ascorbic acid is predominantly acidic. DS is a weak acid with a pKa value of 4.0. Thus, the percent of DS ionized in the presence of ascorbic acid was expected to be very low as compared to in the presence of other additives. During the first hour, the pH of the receptor fluid was acidic. Thus, althouh there was a higher partition of the unionized drug into the oil phase, the drug still found an unfavourable receptor environment for partitioning into it. Change of receptor fluid to alkaline pH leads to release of the entire drug, partitioned in the oil phase, into the receptor fluid. The third slow phase of the triphasic release profile might be attributed to the fact that the drug concentration in the internal dispersed phase was reduced at the end of the second rapid release phase (because of more rapid release of drug during the second phase) which ultimately resulted in lower concentration gradient. Thus, the drug was released rather slowly but with a constant rate during the third phase.

From the above finding it can be concluded that using various additives in the innermost aqueous phase, one can modify and thus achieve the desired optimum rate and extent of release of DS from multiple w/o/w emulsions. Either a biphasic or a triphasic release can be obtained by using different additives at different concentrations.

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