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IN VITRO RELEASE OF DICLOFENAC SODIUM FROM MULTIPLE EMULSIONS; EFFECT OF LOCATION OF DRUG AND pH OF THE AQUEOUS PHASE

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Multiple w/o/w and o/w/o emulsions of diclofenac sodium were prepared and studied to see the effect of location of drug in one or more phases along with change of pH of the external aqueous phase of the w/o/w and aqueous phase of o/w/o emulsion. The rate and extent of drug release were affected by pH of the aqueous phase and also by the location of the drug in w/o/w and o/w/o emulsions. Among all the multiple emulsions evaluated, the maximum rate and extent of drug release were observed from a w/o/w emulsion containing equal amounts of drug in both the aqueous phases with pH 8 of the external aqueous phase, and a control o/w/o emulsion which contained total amounts of drug only in the internal oil phase without any pH adjustment of the aqueous phase.

Keywords : *Multiple emulsions; Water-oil-water (w/o/w) emulsions; Oil-water-oil (o/w/o) emulsions; Diclofenac sodium (DS); Controlled drug release*

Introduction

Multiple emulsion systems have the potential for unlimited use, ranging from controlled and prolonged delivery of drugs (1-3), cosmetic applications (4), food applications (5) and protection of labile drugs (6). Their spherical vesicular structure and the selective permeability of the interfacial barriers make them useful in controlled and prolonged delivery of drugs. The greatest advantage with multiple emulsions is the ability to manipulate the rate and extent of drug release using various methodologies. We had earlier made a series of investigations (7-9) to see the *in vitro* release characteristics of pentazocine under the influence of various parameters.

Diclofenac sodium (DS) is a weak acid (NSAID) and it was thought possible that its release characteristics may be altered by changing the pH environment within the multiple emulsion. Also, different release profiles may be obtained by varying the proportion of the drug in one or more phases. Based on the above facts, the present study was undertaken to investigate the effect of location of drug along with pH change of the aqueous phase on *in vitro* release of DS and with an objective of achieving controlled and prolonged release formulation of DS. This was expected to perform therapeutically much better than conventional formulations of DS.

Materials and Methods

DS, a gift sample from Torrent Laboratories Pvt. Ltd., India, and all the chemicals of analytical reagent grade were used as received.

All the multiple emulsions were prepared by the well established two-step emulsification technique. Multiple w/o/w emulsion was prepared by emulsifying 8 ml of drug solution in distilled water (DW) with 12 ml of liquid paraffin containing 5% v/v Span 80 at 4000 rpm for five minutes. The resultant 20 ml w/o emulsion was further emulsified in the second step with 30 ml DW containing 1 % v/v Tween 40 at 2000 rpm for three minutes. This gave 50 ml of control w/o/w emulsion (**A**) containing 50 mg of the drug. Some more multiple emulsions, $w_{10}/o/w_{40}$ (**C**) $w_{20}/o/w_{30}$ (**D**), $w_{25}/o/w_{25}$ (**E**), $w_{30}/o/w_{20}$ (**F**) and $w_{40}/o/w_{10}$ (**G**) were also prepared. The number in the subscript in w/o/w emulsions indicates the amount (mg) of drug present in that particular phase of emulsion. Similar to the above emulsions, other emulsions, $w_{10}/o/w_{40}$

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(Ce8) $w_{20}/o/w_{30}$ (De8), $w_{25}/o/w_{25}$ (Ee8), $w_{30}/o/w_{20}$ (Fe8) and $w_{10}/o/w_{14}$ (Ge8) were prepared in which pH of the external aqueous phase was changed to eight. These emulsions were prepared similar to that of the control emulsion except that the proportionate amounts of the drug were dissolved in DW of first and second step emulsification and in latter emulsions, DW was replaced with Sorenson's phosphate buffer of pH 8(10).

Multiple o/w/o emulsion was prepared by emulsifying eight ml of drug suspension in liquid paraffin containing 2% v/v Span 80 with twelve ml of DW containing 5% v/v Tween 40 at 4000 rpm for five minutes. The resultant 20 ml O/W emulsion was further emulsified with 30 ml liquid paraffin containing 2% v/v Span 80 at 2000 rpm for three minutes. This gave 50 ml of the control emulsion B containing 50 mg of the drug.

Some more multiple emulsions, $o_{10}/w/o_{40}$ (H) $o_{20}/w/o_{30}$ (I), $o_{25}/w/o_{25}$ (J), $o_{30}/w/o_{20}$ (K) and $o_{40}/w/o_{10}$ (L) were also prepared. Other multiple emulsions, in which the pH of the middle aqueous phase was changed to eight, $o_{10}/w/o_{40}$ (Hw8) $o_{20}/w/o_{30}$ (Iw8), $o_{25}/w/o_{25}$ (Jw8), $o_{30}/w/o_{20}$ (Kw8) and $o_{40}/w/o_{20}$ (Lw8) were also prepared. Again, the number in subscript in o/w/o emulsions indicates the amount (mg) of drug present in that particular phase of emulsion. These emulsions were prepared similar to control o/w/o emulsion **B** except that proportionate amount of drug was suspended in the oils of the first second step and in the latter set of emulsions DW was replaced with Sorenson's phosphate buffer of pH 8.

In vitro Studies

All the above emulsions were evaluated *in vitro*, in triplicate, till seven hours, according to a previously reported buffer change method (7). Ten ml of freshly prepared emulsion was placed in the donor compartment which separates the receptor compartment with a pre-treated 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 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. Pre-warmed (37±0.2°C) buffer (250 ml) solutions 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 analyzed spectrophotometrically at 280 nm. Released drug content was computed from a calibration curve of DS. Diffusion coefficient values were also calculated for all the emulsions (11).

Results and Discussion

The release profiles of DS from both sets of w/o/w emulsions, with and without pH change of the external aqueous phase, are given in figs. 1 and 2. Diffusion coefficients for individual emulsions are also mentioned.

A complex pattern of drug release has been observed from different w/o/w emulsions with pH 8 in the external aqueous phase. Control emulsions **C** and **G** gave a similar rate and extent of drug release but the same two emulsions, when adjusted to pH 8 (i.e. **Ce8** and**Ge8**), gave an appreciably different rate and extent of drug release and **Ce8** delivered the drug maximally. Similarly, control emulsions **D** and **F** provided

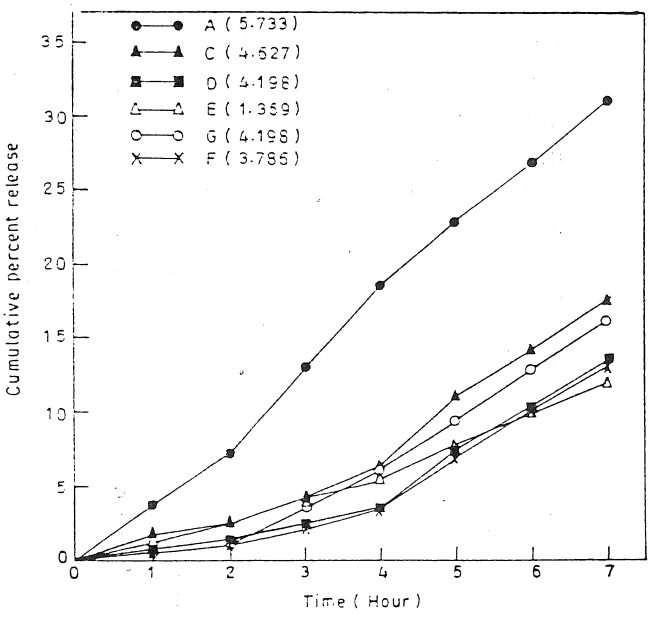

Fig.1. In vitro release profiles showing the effect of location of drug (DS) without pH change of external aqueous phase on release of DS from W/O/W emulsions. Diffusion coefficient values ($x10^{-5}$ cm^2/s) are given in the legend within parenthesis

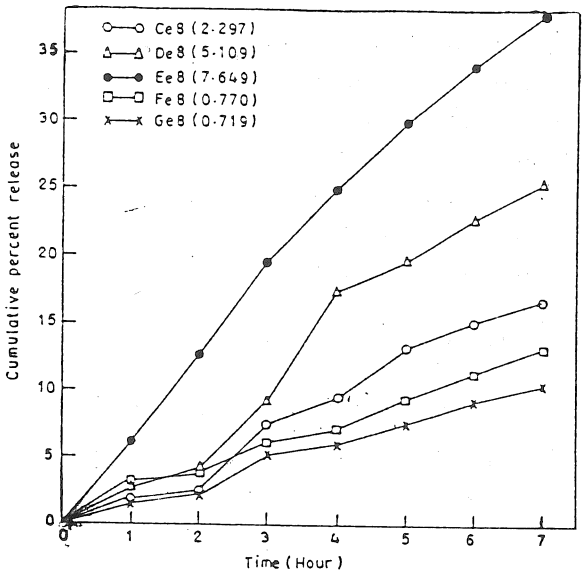

Fig.2. In vitro release profiles showing the effect of location of drug (DS) with pH change of external aqueous phase on release of DS from W/O/W emulsions. Diffusion coefficient values (x10^{-5} cm^2/s) are given in the legend within parenthesis

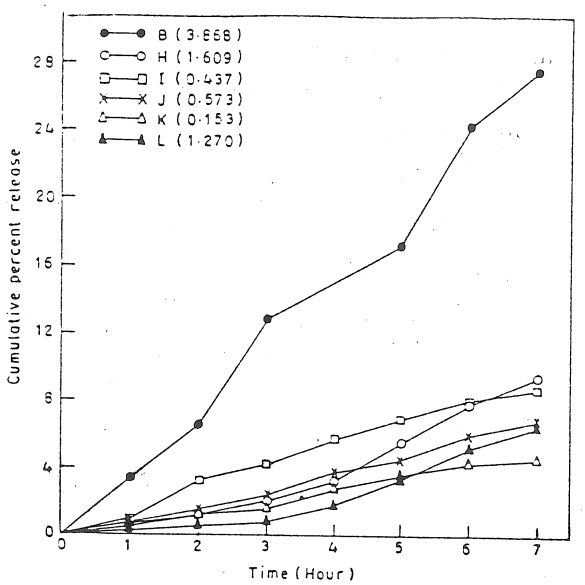

Fig.3. In vitro release profiles showing the effect of location of drug (DS) without pH change of middle aqueous phase on release of DS from O/W/O emulsions. Diffusion coefficient values (x10^{-5} cm^2/s) are given in the legend within parenthesis

almost similar rate and extent of drug release but emulsions **Fe8** and **De8** different largely in their drug release performance. Emulsion **De8** not only gave a linear release but also a much higher extent of release than emulsion **Fe8**. The interesting result was observed with emulsion **Ee8** which exhibited the highest rate and extent of drug release with a linear release profile followed by drug release from emulsion E. Thus, the results described above clearly indicate that multiple w/o/w emulsions with different proportions of the drug located in internal and external aqueous phase provided higher rate and extent of drug release when the external aqueous phase was maintained at pH 8. This was attributed to the fact that pH 8 in the external aqueous phase is a favourable environment for drug to diffuse from internal to external phase because of higher solubility of drug at pH 8. Thus, emulsion Ee8 appears to be the best formulation as it provides maximum extent of drug release and at a controlled rate.

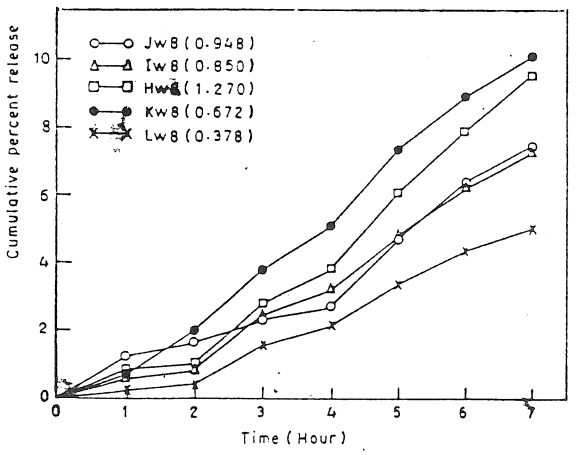

Fig.4. In vitro release profiles showing the effect of location of drug (DS) with pH change of middle aqueous phase on release of DS from O/W/O emulsions. Diffusion coefficient values (x10^{-5} cm^2/s) are given in the legend within parenthesis

The release profiles of DS from both sets of o/w/o emulsions, with and without pH change of the middle aqueous phase, are given in figs 3 and 4. Diffusion coefficients for individual emulsions

are also mentioned.

Drug release observed from the o/w/o emulsions with pH 8 in the aqueous phase were also of complex type. The rate and extent of drug release observed from emulsions **J** and **Jw8** were always similar indicating thereby that pH of the aqueous phase had negligible effect. Similar observations were made with emulsions **H** and **Hw8**. Also, they provided the maximum extent of drug out of all the o/w/o emulsions tested in the series and was attributed to the presence of large amount (40 mg) of drug in the external oil phase. Emulsions **L** and **Lw8**, however, gave a complex pattern of drug release profiles with lower extent than **H** and **Hw8** emulsions which was attributed to lower amount (10 mg) of drug located in external oil phase.

As shown in figs 3 and 4, emulsion **Iw8** always gave lower extent of drug release than the control emulsion **I** whereas, emulsion **Kw8** always gave a higher extent of drug release than control emulsion **K**.

Thus, from the above discussions, it is evident that the desired rate and extent of drug release from multiple w/o/w and o/w/o emulsions can be obtained by varying the proportion of the drug in the innermost and outermost phases. Moreover, pH 8 was found to be suitable for providing linear and controlled drug release in case of w/o/w emulsions only. More useful information might be derived from the *in vivo* studies of these emulsions being under investigation.

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