Acta Pharmaceutica Turcica
XLI (1) (9-13) 1999

EFFECT OF THE NATURE OF OIL, PRESENCE OF ELECTROLYTES, PHASE VOLUME RATIOS AND pH OF THE AQUEOUS PHASES ON THE *IN VITRO* RELEASE OF NIMESULIDE FROM MULTIPLE W/O/W EMULSIONS

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In vitro release characteristics of nimesulide encapsulated in internal aqueous phase of w/o/w multiple emulsions were investigated to see the effect of four formulation variables viz. the nature of oil phase, the presence of electrolytes in internal aqueous phase, phase volume ratios and the pH of the aqueous phases. The drug release rates were significantly affected by the above variables. The results indicated that optimization of the above variables is a prerequisite so as to obtain a desired delivery rate of the drug from multiple w/o/w emulsions.

Keywords: *w/o/w emulsion; Multiple emulsion; Nimesulide; In vitro evaluation; Formulation variables*

Introduction

Multiple emulsions are complex systems and are proved to be of use in prolonged drug delivery (1-3). Besides this, some other novel uses of w/o/w emulsion in medicine were also investigated: to treat overdose (4), to protect drugs, e.g. insulin, which is normally degraded when given orally (5) and to mask the unpleasant taste of drugs (6). The basic rationale for the use of w/o/w emulsions in prolonged delivery of drugs is that the drug contained in the internal aqueous phase has to partition between the aqueous phase and the oil phase prior to release at the site of administration (7). It has been reported that various release patterns can be obtained by adjusting the osmotic gradient between the two aqueous phases of the multiple w/o/w emulsions (7,8).

Based on the above facts, the present study was conducted to examine the *in vitro* release characteristics of nimesulide, a NSAID, under the influence of four different formulation variables. The study was conducted with an objective of achieving controlled and prolonged release formulation of Nimesulide with better compliance and lesser gastrointestinal problems associated with conventional therapy.

Materials and Methods

Nimesulide (Panacea Biotech.), heavy liquid paraffin I.P.(Reidel, India, Chem.) nimesulide suspension (Nimulid®, Panacea Biotech.), Span 80, Tween 80 and all the other chemicals were obtained commercially from India and were used as received. Instruments like magnetic stirrer, emulsifier and U.V. spectrophotometer (Japan Spectroscopic Co. Ltd., Japan) were used as and when required.

Each multiple w/o/w emulsion was prepared freshly on the day of evaluation in 50 ml total volume and contained 50 mg (1 mg/ml) of the drug in the internal aqueous phase only. The multiple emulsions were prepared by the two step emulsification process. The internal aqueous phase containing 50 mg drug was emulsified with the oil phase containing 15% w/w Span 80 by stirring at 2000 rpm for 5 min at 70°C to produce the primary (w/o) emulsion. The primary emulsion was reemulsified with external aqueous phase containing 1%v/v Tween 80 by

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Table.1. Formula of four different multiple emulsions.

Notation	Internal Aqueous Phase	Middle Oil Phase	External Aqueous Phase	Primary phase volume ratio	Secondary phase volume ratio
ME_{11}	Nm + PB (pH 7.4) + 15% v/v PG	HLP + 15% w/w span 80	5% v/v PG + PB (pH 7.4) + 1% v/v Tween 80	0.5	0.5
ME_{12}	Nm + PB (pH 7.0) + 15% v/v PG	HLP + 15% w/w span 80	5% v/v PG + PB (pH 7.2) + 1% v/v Tween 80	0.6	0.6
ME_{21}	Nm + 20% v/v PG + 2% w/v NaCl + PB (pH 7.4)	HLP + 15% w/w span 80	5% v/v PG + PB (pH 7.4) + 1% v/v Tween 80	0.6	0.6
ME_{22}	Nm + 20% v/v PG + 2% w/v Na_2CO_3 + PB (pH 7.4)	HLP + 15% w/w span 80	5% v/v PG + PB (pH 7.4) + 1% v/v Tween 80	0.6	0.6
ME_{31}	Nm + 20% v/v PG + 2% w/v NaCl + PB (pH 7.4)	HLP + 15% w/w span 80	5% v/v PG + PB (pH 7.4) 1% v/v Tween 80	0.6	0.6
ME_{32}	Nm + 20% v/v PG + 2% w/v NaCl + PB (pH 7.4)	Arachis oil + 15% w/w span 80	5% v/v PG + PB (pH 7.4) + 1% v/v Tween 80	0.6	0.6

Nm = Nimesulide
PB= Phosphate buffer
PG= Propylene Glycol
HLP = Heavy liquid paraffin

stirring at 1000 rpm for 3 min at room temperature. The details of the formulations are given in Table 1. The percentage calculation of electrolytes was done with respect to the total volume of the phase containing electrolyte.

In vitro Evaluation

The *in vitro* drug release studies were carried out over times upto 24 hours, in triplicate, in astandardized glass diffusion apparatus(8). The apparatus consists of a small donor compartment containing 10 ml of freshly prepared test emulsion and a larger stirred (100 rpm) compartment as a sink containing 250 ml of diffusion medium. The compartments were separated by a pretreated cellophane membrane (8) with a mean thickness of 0.025 mm. The whole apparatus was placed on an energy controlled hot plate of a magnetic stirrer and maintained at 37±0.2°C. The diffusion medium was phosphate buffer (pH 7.4) and was changed hourly till 7 hours. At the end of 7 hours, 750 ml of diffusion medium was placed in the receiver compartment and stirred till 24 hours. The emulsion in the donor compartment remained undisturbed. 1 ml aliquot samples at the end of each run was diluted suitably with phosphate buffer pH 7.4 and the absorbance was read at 393 nm in a UV spectrophotometer. The actual amount of drug released was computed from a calibration curve. The data were analyzed statistically applying students t-test. A value of $P<0.05$ was considered to be significant.

Results and Discussion

i) Effect of pH and phase volume ratios

The release profile of nimesulide from freshly prepared formulations ME_{11}, hav ing different pH of the aqueous phases and also different primary an secondary phase volume ratios (PPVR and SPVR respectively) are shown in Fig.1. It was observed that formulation ME_{12} gave higher cumulative percent of drug release (25.17%) in

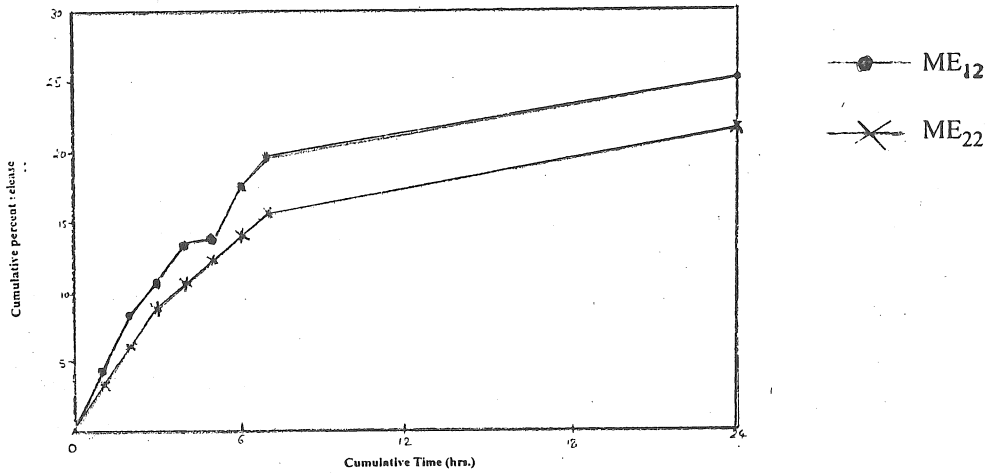

Fig.1. *In-vitro* release profile showing combined effect of the pH of the aqueous phase and different primary and secondary phase volume ratio on release of Nm from different multiple w/o/w emulsions

24 hours as compared to fomulation ME_{11} (21.53%). The reason for the higher drug release from formulation ME_{12} and lower drug release from ME_{11} was attributed to the following fact. The primary an secondary phase volume ratio of the formulation ME_{12} was 0.6 each whereas in formulation ME_{11} it was only 0.5 each. The drug nimesulide in poorly water soluble (0.01 mg/ml). Because of the higher phase volume ratio in ME_{12} , more amount of internal aqueous phase was available to drug for solubilization, and it was only the solubilized drug which was available for diffusion through the oil layer. Different pH of the two aqueous phases in these two emulsions might also be contributing as the drug has higher solubility at higher pH.

The statistical analysis proved these two formulations to be significantly different from each other, in terms of rate and extent of drug release at each hour of study.

ii) Effect of Electrolytes

From the release profile (Fig.2) of formulations ME_{21} and ME_{22} containing 2% w/v each of NaCl and Na_2CO_3 respectively, it was observed that the presence of electrolytes and its nature significantly effected the drug release. The drug release were increased in presence of electrolytes. The cumulative percent of drug release were 32.05% and 49.28% from ME_{21} and ME_{22} respectively as compared to 25.17% from ME_{12} which contained no electrolyte. The increase in drug release was attributed to change of osmotic gradient across oil layer due to presence of NaCl and Na_2CO_3 in internal aqueous phase. Under the influence of osmotic gradient, the external aqueous phase molecules migrate towards the internal aqueous phase. Due to this migration, the internal aqueous phase volume increases which results in higher amount of drug solubilization and thinning of oil film . More amount of drug in solubilized from and thinning of oil film results in higher drug release. Further the Na_2CO_3 provides, in formulation ME_{22}, an alkaline pH leading to higher drug solubilization and hence higher drug release as compared to formulation ME_{11}. Statistical analysis

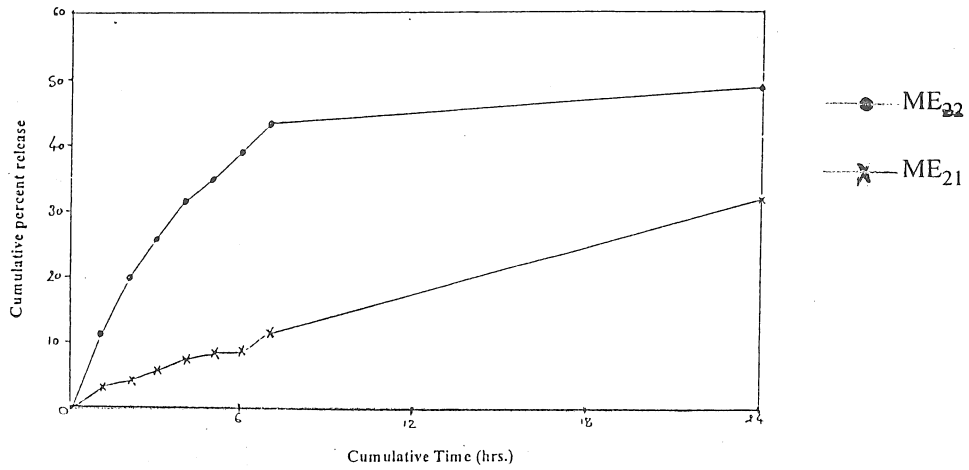

Fig.2. *In-vitro* release profile showing effect of additives on release of nimesulide from different multiple w/o/w emulsions

proved them to be significantly different at each hour of study ($P<0.05$).

iii) Effect of Nature of Oil Phase

The release profile of formulation ME_{31} and ME_{32} shown in Fig.3. proved that the nature of oil phase also effects the release of drug. Nimesulide, being more soluble in arachis oil, results in higher cumulative percent release from formulation (ME_{32}) prepared with

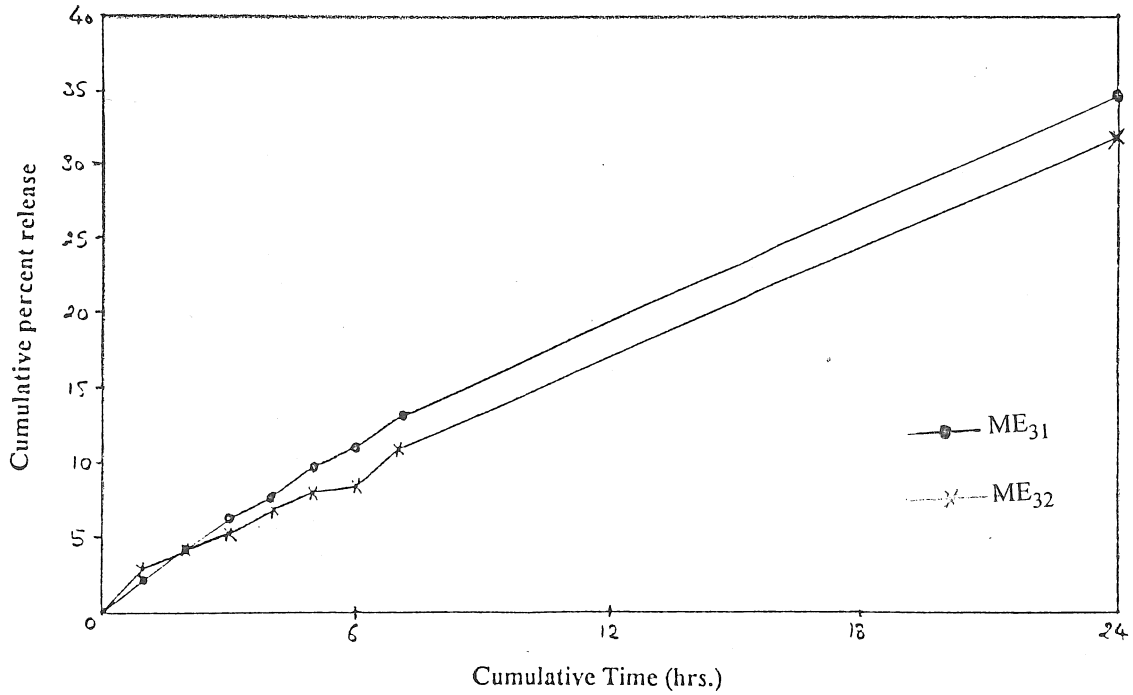

Fig.3. In-vitro release profile showing the effect of the nature of oil phase on release of Nm from multiple w/o/w emulsion

arachis oil (34.88%) as compared to the formulation ME_{31} prepared with heavy liquid paraffin (drug release 32.05%) in which the drug was less soluble. High viscosity of heavy liquid paraffin also contributes to slower release from ME_{31}.

Conclusion

Based on above results, it was concluded that if the formulation variables, like nature of oil phase, pH aqueous phases, phase volume ratios and.presence and nature of electrolytes are optimized together, then the release characteristics of nimesulide from multiple w/o/w emulsion can be obtained as desired.

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Accepted: 04.06.1998