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PROLONGED TISSUE LEVELS OF PENTAZOCINE FROM MULTIPLE W/O/W EMULSIONS IN MICE

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ABSTRACT

Multiple W/O/W emulsions containing pentazocine were prepared and tested in virtro and in vivo. The in vitro results indicated a well controlled and higher drug release from the W/O/W emulsions than the W/O emulsion. The in vivo data showed prolonged tissue levels of pentazocine after oral administration of W/O/W emulsions to mice in comparison to acqueous drug solution and W/O emulsion.

INTRODUCTION

Multiple emulsions have high potential for controlled and prolonged delivery of drugs (1-5). The present study was undertaken to assess the suitability of W/O/W emulsions as prolonged release formulation of an analgesic drug pentagocine which requires frequent administration to patients in conventional dosage form.

MATERIALS

Pentazocine and all other chemicals were obtained commercially and were either of pharmacopoeal or analytical reagent grade.

METHODS

50ml of each formulation, which contained a total of 40mg and 100mg of drug for in vitro and in vivo studies, respectively, was prepared freshly on the day of evaluation.

Suffix 'd' in emulsions indicates the presence of drug in that particular phase. The aqueous drug solution was prepared by dissolving pentazocine in minimum volume of 0.1N HCl solution, adjusting the pH to 5.0 with 0.1N NaOH solution and diluting to 50 ml with distilled water.

The simple Wd/O emulsion was prepared by stirring 20ml of an aqueous drug solution with 30 ml of liquid paraffin containing 1% v/v Span 80 at 4000 r.p.m. for 5 minutes with a stirrer.

Multiple W/O/W emulsions were prepared by a two-step emulsification method (5) with modification. Wd/O/W emulsion was prepared by emulsifying 8ml of an aqueons drug solution with 12 ml of liquid paraffin containing 1% V/V Span 80 by stirring at 4000 r.p.m. for 5 minutes and by reemulsifying this with 30 ml of distilled water containing 2% V/V Tween 40 by stirring at 2000 r.p.m. for 5 minutes. Wd/Od/W and Wd/O/Wd emulsions were also prepared similarly except that half of the total drug was added to each corresponding phase prior to emulsification. The in vitro and in vivo evaluation of each formulation was done by our earlier reported method (3).

Tissue-to-blood partition coefficient (Kp) values were calculated (6) by using the following formula:

$$Kp = \frac{\text{AUC for Tissue}}{\text{AUC for Blood}}$$

where, AUC is the area under concentration -time curve.

RESULTS AND DISCUSSION

In Vitro Release of Pentazocine: The cumulative percent release of pentazocine from different emulsions are shown in Table 1. The results indicate that location of drug in one or more phases of W/O/W emulsions and pH of the desorbing solution had a marginal effect on drug release. In comparison to simple Wd/O emulsion, which gave a negligible drug release, multiple W/O/W emulsions exhibited significantly higher drug

TABLE 1

In Vitro Release of Pentazocine from Different Emulsions

Emulsion	Mean* Cumulative Percent Release							
	pH of the Receptor Fluid							
	1.4	4.5	5.8	5.8	7.0	7.0	7 .4	7.4
	Time in Hours							
	1.0	2.0	3.0	4.0	5.0	6.0	7.0	7.5
Wd/O	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Wd/O/W	6.7	9.7	12.1	14.0	15.7	17.2	18.3	18.8
Wd/Od/W	6.6	9.7	12.1	14.2	15.9	17.4	18.7	19.2
Wd/O/Wd	6.6	9.7	12.1	14.0	15.9	17.5	18.9	19.5

* Mean of three observations.

release. The negligible drug release from the Wd/O emulsion is because of higher viscosity of Wd/O system and also because the ionized drug molecules could not pass freely through the oily phase. The higher release from W/O/W emulsions may be due to lower viscosity of these systems. It was also thought that the resistance offered by the oily phase to the diffusion of the charged species of the drug from internal to external aqueous phase in W/O/W emulsions is overcome by the pulling force exerted by the external aqueous phase on the charged species of drug in the internal aqueous phase. This factor causes more diffusion of the drug from W/O/W emulsions than the Wd/O emulsion in which no such pulling force is operative.

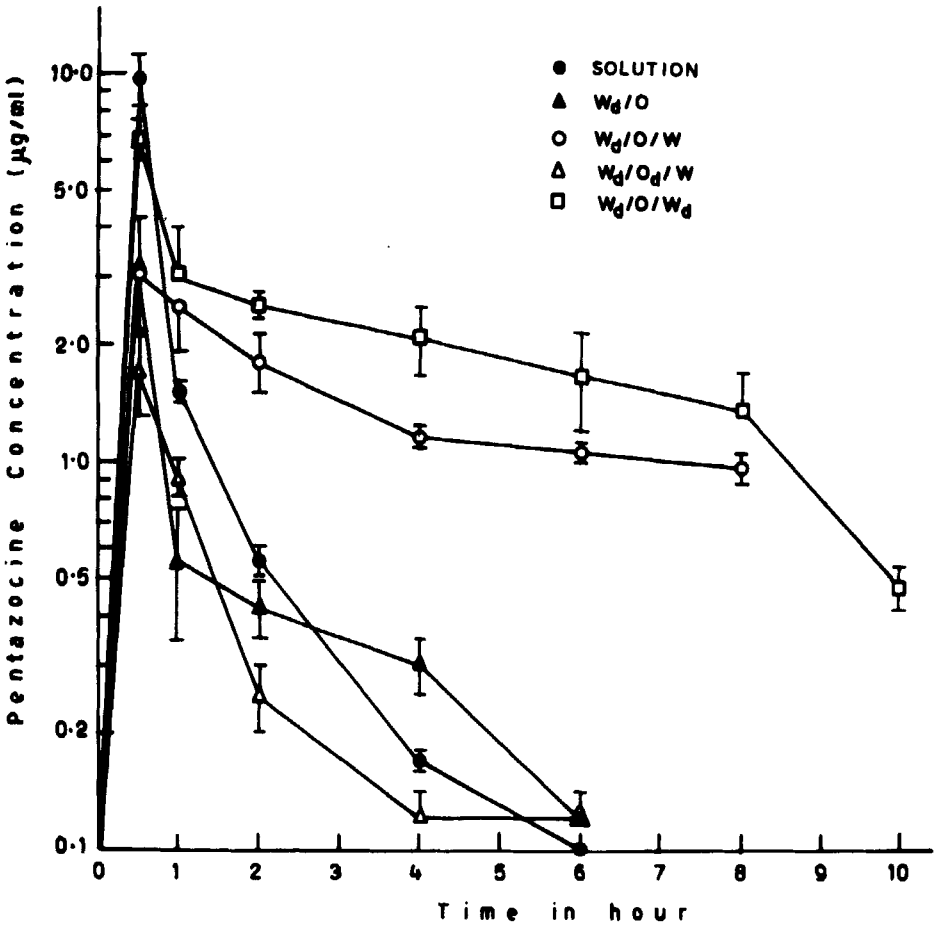

FIG. 1 - PROFILES OF AVERAGE BLOOD CONCENTRATIONS OF PENTAZOCINE AFTER 2 mg/ml ORAL ADMINISTRATION OF FIVE DIFFERENT FORMULATIONS TO MICE (n=3). DATA ARE EXPRESSED AS MEAN ± SEM.

Tissue Levels of Pentazocine in Mice : Fig. 1 and Table 2 demonstrate pentazocine levels in blood and tissues, respectively, at different time intervals after oral administration of various formulations to mice. Although drug concentrations in all the four tissues reached peak levels at half hour from

TABLE 2

Mean±SEM Tissue Levels (mcg/g) of Pentazocine after Oral Administration of Five Different Formulations to Mice (n = 3 for each data)

Formulation	Tissue	Time in Hours 0.5	1.0	2.0	4.0	6.0	8.0
Solution	Li	37.23±6.29	8.65±0.00	3.10±0.50	1.10±0.08	0.10±0.00	-
	Lu	56.45±8.68	22.05±1.52	6.18±0.88	1.40±0.10	1.00±0.15	-
	Ki	62.57±8.72	23.96±2.48	5.78±0.48	1.58±0.28	0.68±0.15	-
Wd/0	Li	17.72±2.84	10.65±0.05	2.47±0.25	1.50±0.00	0.23±0.03	-
	Lu	31.42±4.32	17.15±2.25	6.52±0.52	2.28±0.28	1.40±0.00	-
	Ki	37.87±3.21	14.33±1.52	6.87±1.17	2.30±0.34	0.38±0.08	-
Wd/0/W	Li	17.83±2.49	5.80±0.25	2.22±0.43	1.25±0.00	0.70±0.00	0.43±0.02
	Lu	34.40±4.18	14.90±0.32	2.63±0.35	1.80±0.48	1.20±0.11	1.12±0.12
	Ki	27.63±3.55	9.35±0.02	3.58±0.66	2.45±0.43	1.52±0.18	1.20±0.12
Wd/0d/W	Li	12.40±0.90	6.42±0.18	0.86±0.09	0.68±0.11	0.40±0.03	-
	Lu	32.35±3.58	14.72±1.14	2.72±0.13	2.20±0.40	0.95±0.00	-
	Ki	23.15±4.03	11.25±2.01	1.67±0.18	0.75±0.00	0.20±0.00	-
Wd/0/Wd*	Li	53.45±7.22	22.83±3.98	3.87±0.52	0.97±0.16	0.92±0.16	0.87±0.09
	Lu	46.20±8.02	23.72±2.70	8.70±0.35	3.27±0.59	2.00±0.27	1.40±0.10
	Ki	65.83±9.80	19.75±0.15	4.53±0.52	2.82±0.48	2.25±0.41	1.80±0.39

- Not Determined. Li - Liver, Lu - Lung, Ki - Kidney
* Tissue Livels at 10 Hours : Li - 0.86±0.10, Lu - 1.00±0.07, Ki - 0.60±0.02

all formulations, the decline in drug concentration was faster with solution and Wd/O emulsion.

Multiple Wd/O/W and Wd/O/Wd emulsions provided prolonged drug levels in each tissue. This is because of the controlled migration of the drug from the internal to external aqueous phase and subsequently to the absorption site. Due to presence of half of the total drug as solution in the external aqueous phase, Wd/O/Wd emulsion gave higher peak tissue drug level in comparison to Wd/O/W emulsion. Multiple Wd/Od/W emulsions exhibited a faster decline in tissue drug levels probably because it contained half of the total drug as suspension in the oil phase.

The Kp values for Wd/O/W and Wd/O/Wd emulsions (li-2.1,3.5; Lu-3.9, 4.1; Ki-3.5, 4.3; respectively) were markedly lower than for the solution and Wd/0 emulsion (li - 4.4, 7.1; lu - 8.0, 13.2; Ki - 9.0, 12.4; respectively), which points towards negligible drug accumulation in tissues from the multiple Wd/O/W and Wd/O/Wd emulsions.

CONCLUSIONS

The evidence presented in this reported led us to conclude that multiple W/O/W emulsion system can be utilized as potential prolonged release dosage form of pentagocine.

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