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RECTAL ABSORPTION OF PHENYTOIN IN RABBITS FROM POLYETHYLENE GLYCOL SUPPOSITORIES

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ABSTRACT

Various suppositories containing phenytoin and phenytoin sodium were formulated with different polyethylene glycol combinations. The three formulae that had the best **in vitro** release rate were administered to rabbits. Phenytoin was well absorbed from the suppositories, and the results show that rectal administration of phenytoin can be an alternative to oral administration.

INTRODUCTION

Phenytoin is one of the drugs preferred in the treatment of many types of convulsive disorders. Phenytoin has a low water solubility which together with unique pharmacokinetic characteristics makes it liable to bioavailability problems [1].

For the treatment of epilepsy, oral administration of anticonvulsants is commonly practised to achieve systemic steady state concentrations. In some pathological conditions however, oral administration is inconvenient or even impossible. The rectal administration of valproic acid resulted in steady state plasma concentrations. Adequate data on rectal absorption of phenytoin are not available [2]. Moolenaar **et al.** [2] reported that no appreciable plasma concentrations of phenytoin could be measured after rectal administration of a lipid base suppository containing phenytoin. Rectal absorption of phenytoin were recorded, especially in the first 30 minutes after administration of a solution of phenytoin[2].

In this present study, the **in vitro** release of phenytoin from different combinations of PEG-bases and a surfactant (Myrj® 59) were investigated to determine the **in vitro** release characteristics of phenytoin from suppositories. From the results of the **in vitro** study the formulae with the best drug release were selected for **in vivo** evaluation.

MATERIALS & METHODS

Materials

Phenytoin and phenytoin sodium (Parke Davis); Polyoxyl 59 stearate (Myrj® 59) (ICI, South Africa); Polyethylene Glycol (PEG 1000, 1500, 4000 & 6000) (BDH, England).

Apparatus

Erweka DT 6R - Dissolution apparatus (Erweka, Heusenstamm, West Germany), Abbott Tdx - automated analytical apparatus (Abbott laboratories, Irving, Texas, U.S.A.)

Table 1

Composition of the different suppository formulae

Formula	Base	P : S
1	PEG 1000:1500:4000 (1:2:1)	1 : 0
2	PEG 1000:1500:4000 (1:2:1)	1 : 1
3	PEG 1000:1500:4000 (1:2:1)	1 : 2
4	PEG 4000:6000 (2:1)	1 : 0
5	PEG 4000:6000 (2:1)	1 : 1
6	PEG 1000:1500:4000 (1:2:1)	1 : 0
7	PEG 4000:6000 (2:1)	1 : 0

P = Phenytoin (formula 1, 2, 3, 4 & 5)
P = Sodium phenytoin (formula 6 & 7)
S = Surfactant (Myrj® 59)

Preparation of suppositories

The suppositories were prepared by fusing the active ingredient with the molten PEG base. The formulae containing Myrj® 59 were prepared by mixing the phenytoin with the Myrj® 59 and this solution was fused with the molten PEG base, and poured into 1g suppository moulds. The weight of each suppositories was adjusted to exactly 1g. Each suppository contained 100mg of phenytoin as either phenytoin (free acid) or phenytoin sodium (corrected for sodium). The composition of the different formulae are given in table 1.

In Vitro release rate

Dissolution studies were done to select the formula with the best **in vitro** release rate of the drug. The release rate of phenytoin and phenytoin sodium from the suppositories were determined with the dissolution apparatus 1 of the United States Pharmacopeia XXI. According to Palmieri [3] this method showed plausible and reproducible results when water soluble suppository bases were used. The rotating speed of the basket was set at 50 r.p.m's. The dissolution medium was 1000cm^3 phosphate buffer adjusted to a pH of 12. At this pH the solubility of phenytoin is optimum and therefore the release rate of the phenytoin is only a function of the suppository base. The dissolution medium was kept at 37 ± 5 °C. At each interval an aliquot was withdrawn by a filtered pipette and replaced by an equal volume of the dissolution medium at 37°C. Each dissolution was repeated six times. The phenytoin concentrations in the samples were determined by an ultraviolet light absorption spectrophotometric method described by Mura **et al** [4].

In Vivo release rate

The bioavailability of phenytoin from the three suppositories with the best **in vitro** release rate were determined. Twenty New Zealand white rabbits of the same age, sex and ± weight (1,76kg ±0,175), were used for the investigation. The rabbits were fasted 24 hours before the experiments, while water was allowed **ad libitum**. The rabbits were anaesthetised with halothane (fluothane®), and kept under sedation with a ventilation bag filled with oxygen and halothane (2%). After the administration of the suppository the rectum of the rabbit was closed off with a metal clamp to keep the molten suppository mass inside the rectum. Blood samples were taken at predetermined intervals and the plasma concentration of the phenytoin in the samples were determined by a fluorescent - polarisation technique (Abbott TDx apparatus)[5].

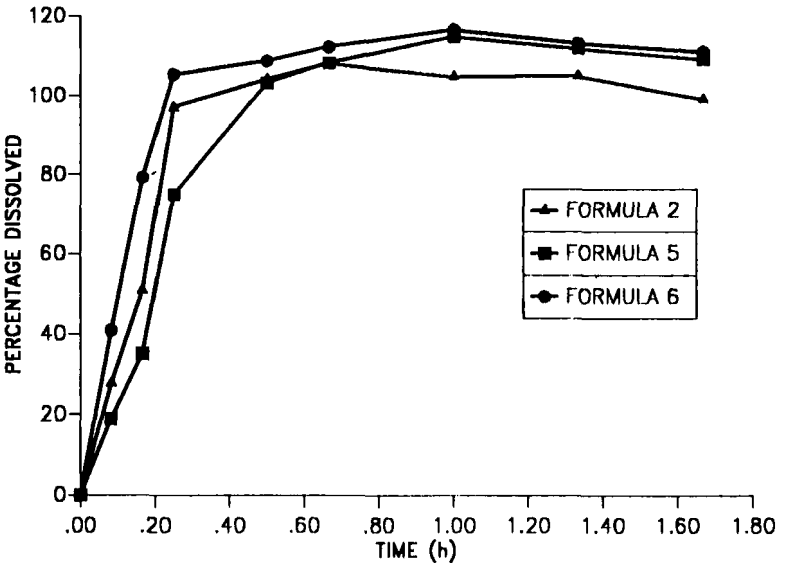

FIGURE 1

Dissolution curves of the percentage phenytoin dissolved of the three formulae with the best release rate.

RESULTS & DISCUSSION

In Vitro study

In figure 1 the dissolution curves of formula 2,5 and 6 are given. To discriminate between the dissolution properties of the different suppository bases the area under the dissolution curve (AUC) was determined. The AUC is a single value that can be easily obtained to compare the dissolution profiles of the formulae. The AUC was calculated by the trapezoidal rule from 0 to 100 min.

The results indicate that the PEG blend (1000,1500 and 4000) gave the best phenytoin release. The Myrj® 59 concentration that showed the best enhancement of phenytoin release is 10% (1:1). It also showed that sodium phenytoin was released faster than phenytoin from the

Table 2

Area under the dissolution curves of the seven suppository formulae

Formula	AUC	CV*
1	57,101	6,570
2	65,489	1,479
3	55,354	4,147
4	59,590	0,950
5	65,096	1,897
6	73,347	4,340
7	48,807	5,133

*CV = Coefficient of variance

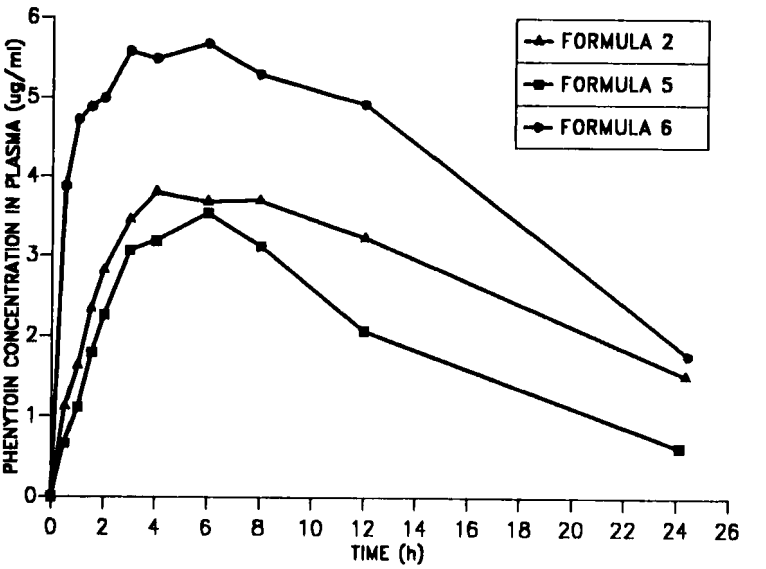

FIGURE 2

Mean phenytoin concentration in the plasma of five rabbits, of formula 2,5 and 6.

Table 3.

Bioavailability parameters of formula 2, 5 & 6.

Formula	AUC	Cmax	tmax	MRT
2	93,09	3,94	7,53	22,19
	(23,34)*	(0,96)	(3,44)	(14,00)
5	61,37	3,55	6,41	13,93
	(10,21)	(0,36)	(0,88)	(3,13)
6	124,30	7,01	6,31	14,73
	(9,89)	(0,89)	(4,09)	(3,99)
IV	235,84			6,13
	(54,70)	---	---	(0,89)

* Standard deviation is between brackets

1000, 1500 and 4000 PEG blend. Formula 2, 5, and 6 had the largest AUC and were selected for the **In vivo** evaluation.

In Vivo release study

In figure 2 the mean phenytoin concentrations in the plasma of five rabbits are given for formula 2, 5 & 6.

From the phenytoin concentration in the plasma, the maximum phenytoin concentration in the plasma (C_{max}) the time of maximum concentration (t_{max}) the area under the curve (AUC 0 - 24h) and the mean residence time (MRT) were calculated. The calculations were done with a SAS program[5], and a noncompartmental method were used to determine these parameters (see table 3).

The results showed that the PEG blend(1000,1500 and 4000) gave the best absorption, while the sodium salt of the drug gave the fastest absorption.

Conclusion

Phenytoin's low water solubility is the biggest single draw back in its bioavailability. This problem can partly be avoided by using suppositories made of water soluble bases, like PEG and by using a surfactant like Myrj® 59 in the formulation. This combination showed that rectally administered phenytoin might be an alternative for oral or intravenous phenytoin administration. This study therefore clearly indicate that rectal administration of phenytoin are a alternative, to oral administration but the clinical effectiveness will have to be verified in humans.

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