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Enhancing properties of surfactants on the release of carbamazepine from suppositories

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Summary

The effect of surfactants on physicochemical properties and on the release characteristics of carbamazepine from fatty suppositories was investigated in vitro. Four surfactants, polyoxyethylene 50-stearate (Simulsol M^R), polyoxyethylene 23-lauryl ether (Brij 35^R), polysorbates 20 and 80, were examined as adjuvants. The dissolution rate was enhanced by all surfactants used. The dissolution rate at 30 min increased from 54% without surfactant, to 100% with polysorbate 80 (2%). The liquefaction time could be the limiting factor for the dissolution rate of carbamazepine. The better solubilising effect of polysorbate 80 can be due to the better incorporation capacity of its micellae.

Introduction

The rectal route of administration is not often used with psychiatric drugs (Chaumeil et al., 1990). Intravenous and rectal dosage forms of carbamazepine are not commercially available, but they could be of great value when oral therapy has to be stopped. The rectal administration of carbamazepine has been reported in humans, using suspensions (Graves et al., 1985; Neuvonen and Tokola, 1987; Brouard et al., 1990) or suppositories (Johannessen et al., 1984). Carbamazepine is quite insoluble in water. Its rectal absorption is limited by its dissolution rate because only the solubilized drug can be absorbed (Moolenar and Schoonen, 1980).

In order to increase the rate of dissolution of carbamazepine, polyoxyethylene 23-lauryl ether, polysorbates 20 and 80, and polyoxyethylene 50-stearate were incorporated into suppositories including carbamazepine.

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Materials and Methods

Materials

Carbamazepine was supplied by Ciba-Geigy, Rueil-Malmaison, France (granulometry of carbamazepine was 50 to 200 μm).

Witepsol H15^R (Atlas-Chimie, Paris, France) was used as a suppository base, to obtain approx. 1 g suppositories. The melting point of this excipient was 34.5°C and its hydroxyl index was less than 15.

In order to increase the rate of dissolution of carbamazepine, the different surfactants used were polyoxyethylene 50-stearate (Simulsol M^R, Seppic, Paris, France), polyoxyethylene 23-lauryl ether (Brij 35^R, ICI, Clamart, France), polysorbates 20 and 80 (Montanox 20 and 80^R, Seppic, Paris, France). The surfactants' concentration range, their hydrophilic-lipophilic balance (HLB), and their ethylene oxide index are summarized in Table 1.

Methods

Preparation of the suppositories

Eleven formulae were manufactured, containing 200 mg of carbamazepine with or without surfactants.

All the suppositories were prepared by the melting method, using a metal mould. Surfactant, then carbamazepine were incorporated in the Witepsol H15^R liquid mass at 40°C. After cooling at 20°C, the suppositories were stored at 4°C to avoid the development of polymorphic forms and cracking.

TABLE 1

Concentration range, hydrophilic-lipophilic balance (HLB), and ethylene oxide groups of polyoxyethylene 50-stearate, polyoxyethylene 23-lauryl ether, and polysorbates 20 and 80

Surfactants	Concentration range (%)	HLB	Ethylene oxide groups included
Polyoxyethylene 50-stearate	2	17.9	50
Polyoxyethylene 23-lauryl ether	0.25–2–5	16.9	23
Polysorbate 20	0.5 –2–5	16.7	20 mol/mol
Polysorbate 80	0.5 –2–5	14.9	20 mol/mol

Physicochemical tests

Twenty suppositories of each formula were used to measure the weight variations, according to the European Pharmacopeia assay. The homogeneity was controlled with a whole suppository and with a half suppository cut either longitudinally or transversely. The carbamazepine content was determined by a spectophotometric method: six suppositories from each formula were individually melted and dissolved in 100 ml of an ethanol/hexane (60 : 40 v/v) mixture. After dilution in ethanol (1 : 50 v/v), the absorbance was measured by spectrophotometry (Spectronic 1001^R Bausch et Laumb, Bioblock Scientific, France) at 285 nm. A standard curve of carbamazepine was constructed at 285 nm. The suppository base and the surfactants had no absorption at this wavelength. The melting point was measured by the open capillary tube method according to the European Pharmacopeia assay. Three suppositories of each formula were used.

The liquefaction time was determined using the Suppotest ST3^R apparatus (Sotax-Osi, Paris, France) at 37 ± 0.5°C. Three suppositories for each formula were used.

The hardness was measured by the resistance to crushing (Erweka, SBT, Euraf, France). Three suppositories for each formula were used. The disintegration time was evaluated according to the European Pharmacopeia assay. The dissolution assay was carried out with the rotating basket apparatus (Dissolutest^R, Prolabo, Paris, France). The basket used was a parallel bar basket (Palmieri, 1981). Carbamazepine is quite insoluble in water, so the dissolution medium was 1 l of 30% ethanol v/v to respect 'sink conditions'. The temperature was 37 ± 0.5°C and the agitation rate was 100 rpm. Samples were automatically realized with a peristaltic pump (Ismatec IPS 12^R, Bioblock Scientific Illkirsch, France), every 2 min during the first 10 min, then every 10 min during the following 110 min. The percentage of the carbamazepine release was automatically determined by spectro-

photometry at 285 nm. The evaluated parameter was the release at 30 min (begining of the steady-state).

Results

Physicochemical tests

The weight variations were in conformity with the European Pharmacopeia for each formula, with a standard deviation of less than 5%.

Considering the drug content uniformity test, the difference between the mean of each formula and the theoretical value was less than 10%. All standard deviations were less than 5%.

The disintegration times were less than 10 min, and the hardness was greater than 5.4 daN for all formulae.

The results obtained for the melting point, the liquefaction time and dissolution rate at 30 min are summarized in Table 2.

The melting point was decreased when the percentage of polysorbate was increased, from 35.1°C to 34.3°C for polysorbate 20 and 33.5°C to 32.8°C for polysorbate 80. The higher liquefaction time (7.3 min) and the lower dissolution rate (54%) were obtained with the formula without surfactants.

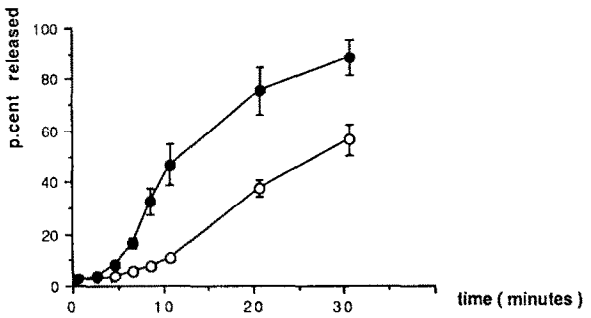

Fig. 1. Dissolution rate of carbamazepine 200 mg suppository. (○———○) Without surfactant, and (●———●) with polyoxyethylene 50-stearate (Simusol Mr) 2% ($n = 6$).

In vitro release

The dissolution rate was improved by all surfactants used (Figs 1–4). The dissolution rate at 30 min increased from 54% without surfactant to 100% with polysorbate 80 (2%).

TABLE 2

Melting point, liquefaction time and dissolution rate of carbamazepine 200 mg suppositories after 30 min, with or without surfactants (m, mean; Δ max, difference between maximal and minimal value; SD, standard deviation); melting point and liquefaction time: n = 3, dissolution rate, n = 6

		Melting point (°C)		Liquefaction time (min)		Dissolution rate after 30 min %	
		m	Δ max	*m*	Δ max	*m*	SD
No surfactant		35.0	0.2	7.30	0.45	54	6.4
Polyoxyethylene 50 stearate	2%	33.9	0.4	5.98	0.31	86	7.3
Polyoxyethylene 23 lauryl ether	0.5%	33.8	0.5	6.40	0.22	66	9.1
	2%	34.4	0.5	6.47	0.17	80	8.2
	5%	34.6	0.4	6.12	0.62	63	5.6
Polysorbate 20	0.5%	35.1	0.5	6.36	0.05	77	6.5
	2%	34.9	0.5	6.54	0.57	91	7.1
	5%	34.3	0.1	6.28	0.19	84	4.0
Polysorbate 80	0.5%	33.5	0.7	5.84	0.27	96	2.6
	2%	33.4	0.5	5.54	0.28	100	1.6
	5%	32.8	0.5	4.91	0.15	98	2.7

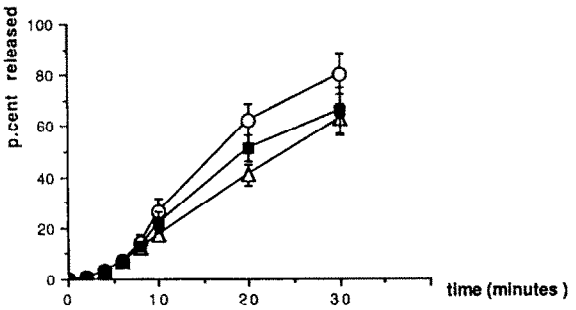

Fig. 2. Dissolution rate of carbamazepine 200 mg suppository containing polyoxyethylene 23-lauryl ether (Brij 35®, (■———■) 0.5% (○———○) 2%, and (△———△) 5% ($n = 6$).

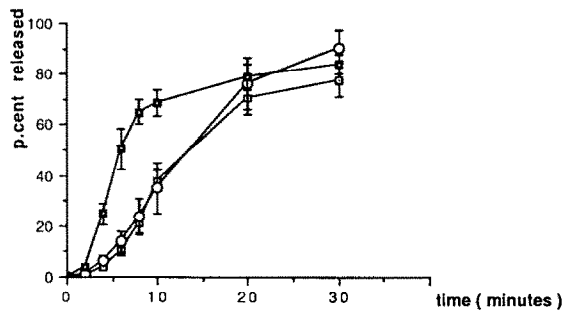

Fig. 3. Dissolution rate of carbamazepine 200 mg suppository containing polysorbate 20 (□———□) 0.5%, (○———○) 2%, and (■———■) 5% ($n = 6$).

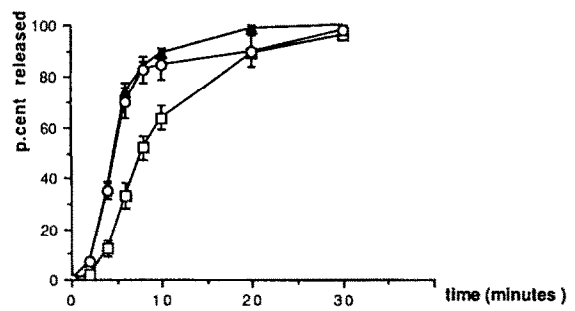

Fig. 4. Dissolution rate of carbamazepine 200 mg suppository containing polysorbate 80 (□———□) 0.5%, (▲———▲) 2%, and (○———○) 5% ($n = 6$).

Discussion

In vitro, polysorbate 80 was the most efficient dissolution enhancer of carbamazepine (Fig. 4). Its liquefaction time was the shortest and its melting point the lowest (Table 2). The formula without surfactant showed the lowest dissolution rate (Fig. 1), the longest liquefaction time and one of the highest melting point values (Table 2). Other formulae showed intermediate dissolution rates, intermediate liquefaction time and melting points (Figs 1–3 and Table 2). The liquefaction time is influenced by different parameters such as the hardness of the suppositories, the hydrophilic character of the base, and especially the melting point (Zuber et al., 1988). The liquefaction time could be the limiting factor of the dissolution rate of carbamazepine in this study.

A surfactant with a high HLB is hydrophilic, so it enhances the moisturising of lipid excipients by the dissolution medium. The increase in hydrophilic character of the lipid base could reduce its affinity for a lipophilic substance (Zein El Din et al., 1987). Our results are in disagreement with this hypothesis: our experiment showed that the surfactant with the lower HLB was the most efficient.

Micellar solubilisation could be another explanation, if the critical concentration for micelle formation was reached. Polysorbates 20 and 80 contain the same hydrophilic chain: 20 mol of ethylene oxide per mol of sorbitol (Table 1). The difference between their enhancing activities on the release was due to their lipophilic chain. Polysorbate 80 is an oleic ester (C18) whereas polysorbate 20 is a lauric ester (C12). The solubilizing properties of such a surfactant are influenced by its structure. The size and the number of micellar aggregates of the surfactant increase when the length of its chain becomes higher (Djimbo and Moes, 1986). Micelles of polysorbate 80 could then have a better incorporation capacity of active materials because of their longer lipid chain.

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