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INFLUENCE OF ENHANCERS ON THE PHYSICOCHEMICAL PROPERTIES AND ON THE RELEASE OF SUPPOSITORIES OF CLOMIPRAMINE HYDROCHLORIDE

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ABSTRACT

The clomipramine hydrochloride shows a low rectal bioavailability (28 p.cent).The suppositories were manufactured with a semi-synthetic glyceride as the excipient : Suppocire NAI 10.

Two groups of enhancers could be distinguished in vitro:

Sodium salicylate at 0.1 p.cent, Sodium dioctylsulfosuccinate at 0.5 p.cent, Sodium lauryl-sulphate, 0.1 p.cent, Polyoxyethylene 2,3 lauryl ether at 1 and 2 p.cent, which didn't induce any influence on the clomipramine HCl dissolution time.

Sodium salicylate at 0.5,1,5,10 p.cent, Polysorbate 20 at 0.5 p.cent, Polysorbate 80 at 0.5 and 2.0 p.cent, which induced a decrease of the clomipramine HCl release rate.

Some ex vivo assays were carried out, using a rat rectal mucosa. In these conditions, Polyoxyethylene 2.3 lauryl ether 1 p.cent and Polysorbate 80 at 2 p.cent induced an increase of the clomipramine HCl absorption. (9.80 p.cent to 16.25 p.cent)

These experiments showed in one hand that it was impossible to choose one or several enhancers among the assayed ones, using only the measure of the physicochemical properties of the suppositories containing an active materials as soluble as the clomipramine HCl, in the other hand the ex vivo assays could be useful to study the optimization of the formula by the use of several enhancers.

INTRODUCTION

Clomipramine hydrochloride, tricyclic antidepression drug, showed great individual pharmacokinetics variations.

The short passive digestive absorption time (lower than one hour) and the slow elimination kinetics by the urinary tract (the blood half life is about 17 to 28 hours) were are in favour to a rectal administration.

The aim of our study was the research of a rectal form of clomipramine hydrochloride with some enhancers in order to increase its absorption.

The influence of some enhancers such as polyoxyethylene 2,3 lauryl ether, polysorbates 20 and 80 (1, 2), sodium salicylate (3,4,5,6,7,8,9,10), and sodium dioctylsulfosuccinate was studied on the rectal absorption of the clomipramine hydrochloride in vitro and ex vivo.

MATERIALS

The clomipramine HCl was supplied by Ciba Geigy, France

The suppositories formulations were manufactured using a semi-synthetic glyceride (suppocire NAI 10, Gattefossé Ets, France) to obtain 1 g suppositories. This excipient was chosen among several semi synthetic glycerides during a previous study (11). The melting point of this excipient was 34,5°C and the hydroxyl index was less than 15 in order to release quickly the clomipramine HCl, because the partage coefficient was in favour to the water phase.

The type and the concentration range of the enhancers were comprised between 0.1 and 5.0 p.cent (table 1). The formulations were expressed in percent of the total suppository mass.

The particle size of the clomipramine HCl and the solid enhancers was comprised between 40 and 100 µm.

Thirtheen formulations containing 50 mg of clomipramine HCl, were used for the in vitro assays.

Six formulations containing 12 mg of clomipramine HCl, were used for the ex vivo studies. After preliminary assays this dosage was chosen according to ours conditions.

METHODS

Preparation of the suppositories

The suppositories were prepared by melting the suppository base at 50°C and adding the drugs into the liquid mass. They were filled either

TABLE 1

Enhancers used into the clomipramine HCl suppositories.
(AINS:non steroid antiinflammatory drug)

Enhancers class	Enhancers type	French Pharmacopea IXème édition	Range of concentrations in vitro	Range of concentrations ex vivo
AINS (2,5,6,7, 10,11)	Sodium salicylate (Prolabo, Paris)		0,1 0,5 1 5 10	0,1 0,5 1
ionic (3,11, 12,14) surfactants	Polyoxyéthylène 2,3 lauryl ether (Brij * 35) (ICI, Clamart France)		1 2	1
	sodium lauryl sulphate (Ets Gattefossé, Lyon France	Xème édition	0,1	
	sodium Dioctylsulfosuccinate (Prolabo, Paris)	Xème édition	0,5	
non ionic surfactants	Polysorbates 20 et 80 (Tweens* 20 et 80 (ICI,Clamart, France)	IXème édition	0,5 (Tween 20	
			0,5 2 (Tween 80)	2

into 1 g suppository metallic mould for the in vitro study and into the low part of an hard gelatine capsule of 0.3 ml volume for the ex vivo study. The mass was kept at ambiant temperature to solidify to avoid polymorphic forms and cracking. Suppositories without clomipramine HCl, were prepared under the same conditions to be used as reference control.

Physicochemical tests

The formulas with and without enhancers were submitted to the following assays.

The weight variations and the disintegration time were measured according to the European Pharmacopeia assays (2nd edition). For the disintegration time, an automatic apparatus was used (Erweka, Euraf, France)

The melting point was measured by the open capillary tube method, the liquefaction time was determined by the Krowczynski manual method.

The spreading area was calculated according to the watch glass method (12) with a digital planing apparatus (AOTT, Kempten, RDA).

The homogeneity was verified on the entire suppository and with half suppository, cut either longitudinally either transversally.

The clomipramine HCl content was determined by a titrimetric method using perchloric acid 0.1N in acetic anhydride / acetic acid (10/50) with methyl violet as indicator after dissolution at 60°C.

The hardness was measured by the resistance to crushing (Erweka, SBT, Euraf, France)

The stability of the clomipramine HCl, was studied after extraction with methanol by thin layer chromatographie on silicagel plates using benzene / ethyl acetate / ethanol / ammoniac (50/50/10/5). The revelator was the potassium dichromate at 0.05 p.cent in sulfuric acid.

Kinetics of clomipramine chlorhydrate release

In vitro studies

The dissolution assay was carried out at 37.0 ± 0.5°C with purified water as dissolution medium. The Guyot Hermann cells, equipped with a cellophane membrane (porosity 0.023 µm, Visking, Polylabo Block, France) was immersed in 200 ml of a receptor medium to respect sink conditions. The suppository was put on this membrane with 2 ml of purified water to simulate the presence of the rectal liquid.

Ex vivo studies

The clomipramine HCl absorption was studied on a isolated rat intestine used as a dialysis membrane according to the IZGU and GUNGOR'S technic (13).

Some " Sprague - Dawlay " male rats of 250 g weight (laboratoire Janvier , Le Genest France) were fasting 24 hours before the assay to avoid any feces in the intestine tractus. After beheading the rats and the excision of the rat intestine, the last five centimeters of the intestine were cut out 2 centimeters before the anus. These rectal samples were washed out three time successively with Tyrode solution and stored during the experiment time into a pH 7.4 buffer ." Suppository " containing 12 mg of

clomipramine HCl, was introduced with 1 ml of a pH 7.4 phosphate buffer (French Pharmacopeia IX ^{ed}) and the tips were ligatured with a coton thread. The isolated intestine was put into 50 milliliters of pH 7.4 phosphate buffer at 37 ± 0.5°C shaked on a magnetic agitator.
In the in vitro and the ex vivo studies, the samples were made at 5,10,15,30, 60,90,120 min and analysed by ultraviolet spectrophotometry (Perkin Elmer 550, OSI, France) at 252 nm. The excipient did not interfere in the dosage ; for the enhancers the difference beetween the optic density (DO) was made comparatively with suppositories without clomipramine HCl. Six assays by formulations were made, the Mann-Whitney statistic test was used to compare in vitro and ex vivo kinetics.

RESULTS

Physico chemical tests

The results were shown in the tables 2 and 3.
The hardness was always greater than 4.8 daN.
The disintegration time and the liquefaction time, less than 10 min, were short.
The melting point was lower than 35°C

In vitro release

The results have shown that 40 at 78 p.cent of the clomipramine HCl was released in 90 min (tables 4,5,6)
Two types of enhancers could have been distinguished:

* The enhancers didn't influencing the clomipramine HCl release (fig. 1) Brij 35 at 1 p.cent and 2p.cent, sodium dioctylsulfosuccinate at 0.5 p.cent, sodium lauryl sulphate at 0.1 p.cent and sodium salicylate at 0.1 p.cent

* The enhancers decreasing the clomipramine HCl release (fig.2) sodium salicylate at 0.5 p.cent, 1 p.cent, 5 p.cent, 10 p.cent, Tween 20 at 0.5 p.cent and Tween 80 at 0.5 p. cent and 2.0 p.cent.

Ex vivo release

The results were shown in tables 7 to 9
The clomipramine HCl formulations without enhancers released 9.80 p.cent of the drug at 90 min ; with the enhancers, the results varied between 6.75 to 16.25 p.cent at 90 min. Tween 80 and Brij 35 gave the highest results. The sodium salicylate at all concentrations decreased the clomipramine HCl rates. The fig. 3 and 4 showed the linear kinetics of the clomipramine HCl release.

TABLE 2

Results of the physicochemical tests of formulas with clomipramine HCl (C) and with different percents of sodium salicylate (S).

Formulas tests	C	S 0,1 %	S 0,5 %	S 1 %	S 5 %	S 10 %
Melting point (°C)	35	33,5	33,5	34,0	33,5	34,5
Disintegration time (min)	10	9	7	7	10	10
Liquefaction time (min)	6	8	8	6	7	6
Spreading area (mm^2)	1500	1560	1590	1570	1300	1286

TABLE 3

Results of the physicochemical tests with different concentrations ranges of enhancers.

B = Brij 35, SLS = sodium lauryl-sulphate,

DOSS = sodium dioctylsulfosuccinate,

SLS = sodium lauryl-sulphate - TS = Tween

Formulas tests	B 1 %	B 2 %	SLS 0,1 %	DOSS 0,5 %	TS20 0,5 %	TS80 0,5 %	TS80 2 %
Melting point (°C)	35	35	34,8	34,8	34	34	33,5
Disintegration time (min)	6,5	7,0	8	8	9	8	9
Liquefaction time (min)	7,5	8,5	9	10	12	10	10
Spreading area (mm^2)	1395	1405	1470	1375	1470	1270	1180

TABLE 4

Dissolution rates of clomipramine chlorhydrate from suppositories containing different enhancers

C = clomipramine HCl alone, B = Brij 35, DOSS = sodium dioctylsulfosuccinate, SLS = sodium lauryl-sulphate)

SD = Standard déviation

FORMULAS Time (min)	5	10	15	30	45	60	75	90
C p.cent release	3,40	8,60	13,20	21,40	33,20	46,00	52,00	71,60
SD	1,5	2,25	3,25	2,0	1,5	2,5	1,5	1,5
B2 % p.cent release	3,74	9,23	14,08	22,59	32,25	44,82	48,39	68,48
SD	1,00	1,25	1,25	2,5	2,5	2,5	1,25	2,5
B1 % p.cent release	2,90	9,19	14,56	19,40	33,20	51,15	52,00	78,52
SD	1,5	2,0	2,5	1,25	4,5	2,5	2,5	2,5
DOSS 0.5%	2,90	7,35	11,61	18,31	32,57	44,72	44,32	64,07
SD	1,0	1,25	1,5	2,0	2,0	2,5	2,0	2,0
SLS 0.1%	3,07	6,93	11,38	22,52	21,01	32,77	40,13	70,36
SD	1,25	2,5	3,5	4,0	5,0	2,5	5,0	2,5

DISCUSSION

In vitro with a water soluble drug such as the clomipramine HCl, the enhancers don't increase the release but change the kinetics profiles.

Ex vivo the Brij 35 at 1 p.cent and the Tween 80 at 2 p.cent increase the clomipramine HCl release up to 60 p.cent but don't differ themselves. Nevertheless, the sodium salicylate at all concentrations ranges decrease or doesn't modify the clomipramine HCl release ($p < 0.01$).

TABLE 5

Dissolution rates of clomipramine HCl from suppositories containing (TS) Tween 80 and 20 at different concentrations
SD = standard deviation

FORMULAS Time (min)	5	10	15	30	45	60	75	90
TS80 2 % p.cent release	2,60	6,80	9,80	20,40	29,60	38,40	39,40	40,60
SD	1.0	1,0	1,25	1,5	1,5	1,5	2,0	2,0
TS80 0,5 % p.cent release	5,20	10,60	15,00	25,00	32,60	37,60	40,60	42,40
SD	1,0	1,5	1,25	2,00	2,0	2,0	1,25	1,25
TS20 0,5 % p.cent release	4,60	12,00	15,80	29,00	33,80	37,00	42,20	43,20
SD	1,0	2,0	1,2	2,00	2,5	2,5	2,5	2,5

Physicochemical tests.

The melting points showed a very low decrease according to the reference formulation without enhancers (35°C) However, it only allowed to estimate a particular stadium of the melting called beginning melting. Fantelli and Setnikar (14) have notified great variations between the beginning melting point and the mass melting point so that it could decrease the drug release. The increase of the clomipramine HCl release was in relation to one excipient with a low melting point. So the formulations containing enhancers seemed to be in favour to a better clomipramine HCl release.

The disintegration and the liquefaction times didn't differ themselves and didn't be necessary in relation to a low or a high melting point.

The spreading area measures showed that the addition of high percentages of sodium salicylate at 5 p.cent and 10 p. cent or surfactants decreased the spreading area, probably due to the increasing of the viscosity for the

TABLE 6

Dissolution rates of clomipramine HCl from suppositories containing different concentrations of sodium salicylate
SD = standard deviation

FORMULAS Time (min)	5	10	15	30	45	60	75	90
0,1 % p.cent release	4,60	7,40	12,00	23,00	32,40	42,80	53,60	66,00
SD	1,25	2,0	2,00	1,5	2,0	1,5	2,5	2,5
0,5 % p.cent release	2,20	5,80	8,80	16,40	28,00	24,00	48,00	51,30
SD	1,0	1,0	1,25	1,25	2,0	2,0	2,0	2,5
1 % p.cent release	2,60	5,60	8,20	16,60	26,60	37,20	41,60	49,20
SD	1,25	1,25	2,5	2,00	2,0	1,5	2,0	1,5
5 % p.cent release	2,82	5,64	8,47	17,03	26,03	34,02	42,20	51,0
SD	1,0	1,3	1	1,5	2,0	1,8	1,5	1,9
10 % p.cent release	2,87	5,50	8,30	16,4	25,00	32,9	42,3	50,0
SD	1,4	1,6	1,5	1,6	1,6	1,5	1,5	2,0

sodium salicylate and the increasing of the mass cohesion for the surfactants.

In vitro release

* linear kinetics

The clomipramine HCl released in the formulation without enhancers was a linear one (eq.1). The linear kinetics showed that the clomipramine HCl released was according to a diffusion phenomenon (t = time)

p.cent of clomipramine HCl release : 0. 163 + 0. 7518t r = 0.99 (eq.1)

The clomipramine HCl suppositories with sodium salicylate at all

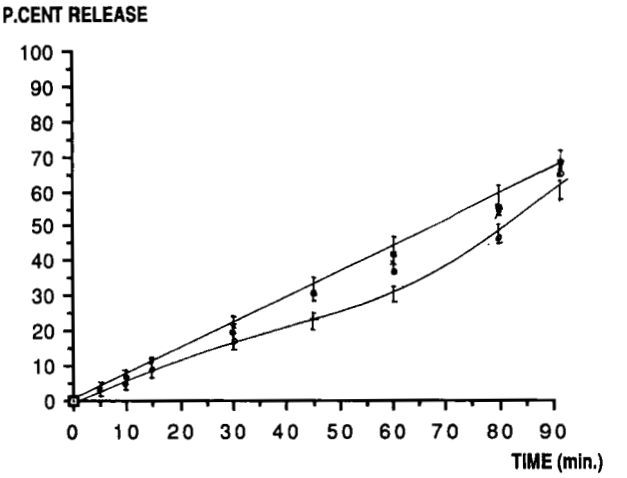

FIGURE 1

Enhancers didn't influencing the clomipramine HCl release (in vitro)

• clomipramine HCl., * Brij 35 1 p.cent + Brij 35 2.p.cent,
o sodium dioctylsufosuccinate 0.5 p.cent,
x sodium lauryl-sulphate 0.1 p.cent,
- sodium salicylate 0.1 p.cent

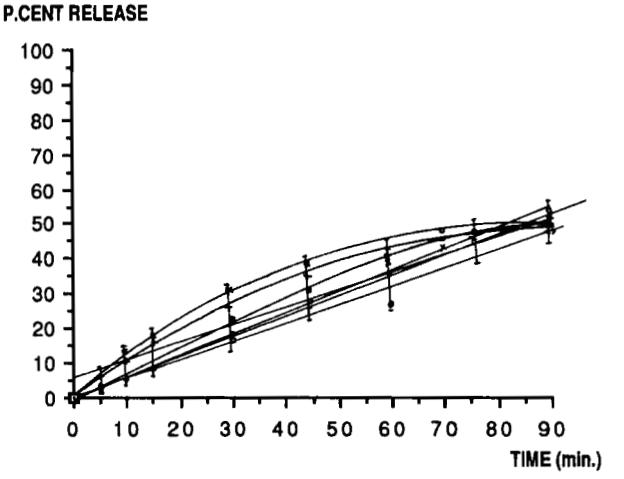

FIGURE 2

Enhancers decreasing the clomipramine HCl release (in vitro)

▪ clomipramine HCl., o sodium salicylate 0.5 p.cent, x 1.0 p.cent,
- 5.0 p.cent, <> 10.0 p.cent, * Tween 20 0.5 p.cent,
+ Tween 80 0.5 p.cent, ▪ 2.0 p.cent

TABLE 7

Percentage of the clomipramine HCl release from the formulas without enhancers (ex vivo). SD = standard deviation

Time (min)	5	10	15	30	45	60	75	90
p.cent release	0,93	0,70	2,98	3,80	4,80	7,40	9,43	9,80
SD	0,71	0,67	1,62	1,21	0,44	1,5	1,4	1,09

TABLE 8

Influence of sodium salicylate (S) 0.1 p.cent 0.5 p.cent and 1. p.cent on the clomipramine HCl release (ex vivo). SD = standard deviation

Time (min)	5	10	15	30	45	60	75	90
S 0,1 % p.cent release	0,50	0,25	0,50	0,75	2,50	4,50	5,75	6,75
SD	0,38	0,14	0,33	0,35	0,53	0,53	1,30	1,24
S 0,5 % p.cent release	0,37	1,00	0,87	2,10	3,12	4,87	5,62	7,00
SD	0,17	0,35	0,53	0,53	1,59	1,94	1,59	2,47
S 1 % p.cent release	1,25	1,60	1,50	3,08	5,00	5,30	7,66	8,16
SD	0,54	0,38	0,25	0,28	0,66	0,94	1,01	0,52

TABLE 9

Influence of the surfactants (Brij 35 1 p.cent B, Tween 80 2p.cent TS,) on the clomipramine HCl release (ex vivo). SD=standard deviation

Time (min)	5	10	15	30	45	60	75	90
B 1 p.cent release	0,95	1,62	1,95	6,05	9,58	13,06	14,62	16,25
SD	0,51	0,99	0,32	0,95	0,88	0,94	1,32	1,23
TS 2 p.cent release	0,62	0,62	1,55	6,00	9,25	11,85	13,65	14,45
SD	0,14	0,25	0,37	1,47	1,62	1,51	1,67	1,24

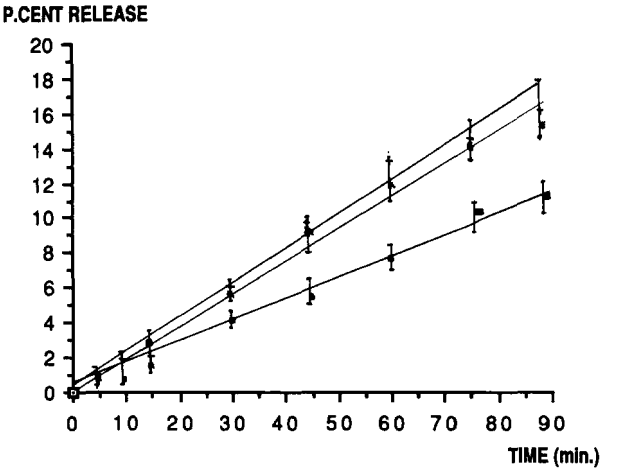

FIGURE 3

Enhancers increasing the clomipramine HCl release (ex vivo)
▪ clomipramine HCl., * Tween 80 2.0 p.cent, + Brij 35 1.0 p.cent

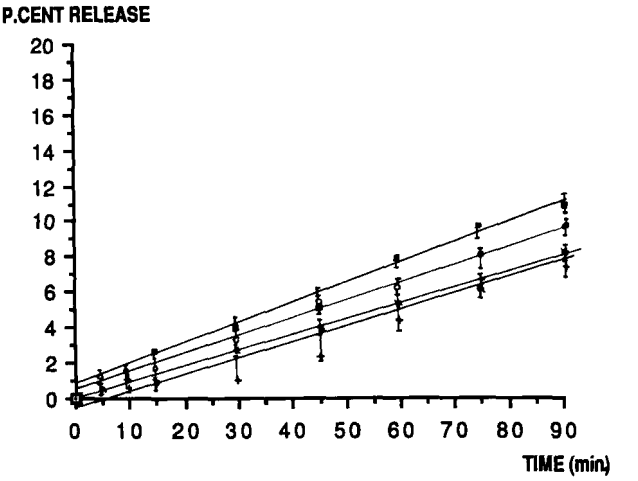

FIGURE 4

Enhancers decreasing the clomipramine HCl release (ex vivo)
▪ clomipramine HCl.
sodium salicylate + 0.1 p.cent, * 0.5 p.cent, o 1 p.cent

concentrations showed a linear kinetic according to a diffusion phenomenon (eq. 2,3,4,5,6)

p.cent of clomipramine release with :

sodium salicylate 0.1 p.cent = 0.8335 + 0.7125 t r = 0.99 (eq.2)
sodium salicylate 0.5 p.cent = - 0.5474 + 0.5724 t r = 0.97 (eq.3)
sodium salicylate 1.0 p.cent = 0.2585 + 0.5622 t r = 0.99 (eq.4)
sodium salicylate 5.0 p.cent = 0.0040 + 0.5647 t r = 0.99 (eq.5)
sodium salicylate 10.0 p.cent = 0.1483 + 0.5749 t r = 0.99 (eq.6)

The sodium salicylate could react upon semi synthetic glyceride by its free doublets such as phenolic hydroxyle (15). It could be bound by some charges like sodium ion which could be appear after pulverizing the drug. Sodium salicylate could increase the hydrophilous tendance of the suppository mass so that it could decrease the clomipramine HCl release. Sodium salicylate at 0.1 p.cent didn't are in a sufficient concentration to decrease the clomipramine HCl release.

The clomipramine HCl with the Brij 35 and the sodium dioctylsulfosuccinate showed a kinetics release according to a diffusion phenomenon (eq.7,8,9)

p.cent of clomipramine HCl release with :

Brij 35 1 p. cent = - 0.8786 + 0.8120 t r = 0.98 (eq.7)

Brij 35 2 p. cent = 1.7115 + 0.6997 t r = 0.99 (eq.8)

sodium dioctylsulfosuccinate 0.5 p.cent = 0.2829 + 0.6775 t r = 0.99 (eq.9)

* non linear kinetics

Sodium lauryl-sulphate showed a kinetic release with the clomipramine HCl in three parts. The first one could correspond to a quick release of the clomipramine HCl from the surface area of the suppository, the second phase to a diffusion phenomenon, the third one with the highest slope, to the whole disintegration of the suppository (eq.10).

p.cent of clomipramine HCl release with :

$SLS = 5.611 + 1.686\ t - 0.0363t^2 + 2.989\ e^{-4t3}$ r = 0.99 (eq.10)

The clomipramine chlorhydrate with Tween 20 and 80 showed a kinetic release in two steps. The first one according to a diffusion phenomenon, the second one corresponding to the steady state where the release was a function of the remaining clomipramine HCl in the suppository mass (eq.11,12,13)

p.cent of clomipramine HCl release with :

Tween 20 0.5 p.cent = $1.9055 + 0.9863\ t - 0.006\ t^2$ r = 0.99 (eq.11)

Tween 80 0.5 p.cent = $1.5619 + 0.9308\ t - 0.0054\ t^2$ r = 0.99 (eq.12)

Tween 80 2.0 p.cent = $- 2.8761 + 0.9795\ t - 0.0055\ t^2$ r = 0.99 (eq.13)

These results were according with Othman and Muti's studies (16) who showed that sodium lauryl-sulphate at 0.1 p.cent didn't modify the kinetics release of indomethacin suppositories rather than Tween 80 decreased of 55 p.cent indomethacin release. Tweens could have been able to react upon the suppository excipient increasing the mass cohesion and slowing the drug release.

Ex vivo release

All the kinetics of the clomipramine HCl release were linear, according to a diffusion phenomenon accross isolated intestine membrane (eq. 14 to 19).

p.cent of clomipramine HCl release alone :

= 0.3978 + 0.1111 t r = 0.98 (eq. 14)

p.cent of clomipramine HCl release with :

sodium salicylate 0.1 p.cent = -0.6737 + 0.0815 t r = 0.98 (eq. 15)

sodium salicylate 0.5 p.cent = -0.0788 + 0.0776 t r = 0.99 (eq. 16)

sodium salicylate 1.0 p.cent = 0.6215 + 0.0866 t r = 0.99 (eq. 17)

Brij 35 1.0 p.cent = -0.0342 + 0.195 t r = 0.99 (eq. 18)

Tween 80 2.0 p.cent = -0.2453 + 0.1818 t r = 0.98 (eq. 19)

In vitro we showed that the sodium salicylate (> 0.1 p.cent) could decrease the release of the clomipramine HCl by a physicochemical reaction with semi synthetic glyceride.

Ex vivo the same results were observed because the dissolution time was the limiting factor of the release.

Surfactants alter the drug absorption from rectal mucosa, by two mechanisms : the drug - surfactants interaction and the direct action of the surfactant on the rectal mucosa. Surfactants (Brij 35 and Tween 80) may also be capable of modifying the properties of biological membranes by solubilization of membrane components and increase the protein release. Intercellular lipids are assumed to play an important role in maintaining the barrier function to polar subtances. The surfactants would probably interact with these lipids and increase the permeability of rectal mucosa, though the detailed mechanisms remain unsolved (17).

CONCLUSIONS

In vitro, Brij 35 at 1 p.cent and Tween 80 at 2.0 p.cent didn't modify the kinetics release of the clomipramine HCl, because it is a very water soluble drug. The ex vivo method allowed to classify the different enhancers. This was explained by the presence of biological mechanisms of the enhancers on the proteins and the intercellular lipids of the rectal mucosa. It is really necessary to complete an in vitro assay with an ex vivo method for water soluble drug before the study on the men.

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