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"A COMPARATIVE STUDY OF THE EXTENSIBILITY AND BIO-AVAILABILITY OF TOPICAL PREPARATIONS OF GLYCOL SALICYLATE"

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SUMMARY

Test on the extensibility of semi-solid preparations assist in the selection of the ideal excipient for each active substance. This is due to the fact that, among other things, the possibility of establishing chemical pharmaco-excipient bonds, that will increase the consistancy of an ointment, and subsequently decrease the liberation of medicaments, influence the said parameter.

INTRODUCTION

Extensibility studies carried out on semisolid pharmaceutical forms reveal questions of interest, being indicative of both the correct preparation of the formula and the stability of the topical preparation.

This property is affected not only by the proportion of drug and excipient, but also by the possible formation of chemical links between them, which, although usually weak, increase the consistency of ointments, thus diminishing the liberation of the drug from the excipient.

Thus, the principal aim of this study is to find the ideal excipient for glycol salicylate (MSEG), using extensibility studies established for different topical preparations of MSEG and their respective vehicles using planimetric methods.

At the same time we intend to establish the possible correlation between the results obtained from this property and the differing bioavailability of this active substance in the preparations under study.

MATERIALS

2.1.- MATERIALS

Manual type RANVIER microtomo

Petri dish (50 g)

Set of weights (100, 150, 300 and 500 g)

Olimpus camera

Roll of black and white DURST-DA 900 films

Unicon-50 filter

Negra 17.8 x 24 papers

Staedtler-Mass 927 planimetre

2.1.- TOPICAL PREPARATIONS OF GLYCOL SALICYLATE (prep. MSEG) 5 % w/w PREPARATIONS IN THE FOLOWING EXCIPIENTS.

2.1.1.- Oleoaqueous emulsion (O/W)

Sedefos^{R} 75	18 p
Vaseline oil	10 p
Propilenglycol	28 p
Sodium p-hydroxybenzoate	q.s.
Distilled water, sufficient to produce	100 p

2.1.2.- Anhydrous-hidrosoluble excipient (PEG)

Poliethylene-glycol 400	71.0 p
Poliethylene-glycol 4000	28.5 p

2.1.3.- Aqueous gel (GEL)

Carbopol^{R} 934	3.7 p
Glycerine	25.0 p
Alcohol 96 %	28.0 p
Trietanolamine (pH = 6.8)	q.s.
Distilled water, sufficient to produce	100 p

METHOD

We prepared the measuring base by the method described previously by various authors (1), and modified by us in earlier studies (2, 3), using a manual microtome, 5 cm in diameter, with an absolutely flat base, a 1.2 cm screw-hole with 0.69 mm thread.

After placing the micrometric screw in the correct position, it was filled with the preparation to be studied, -- and air bubbles in the preparation were eliminated by raising the screw to its mid-position, thus avoiding possible errors of measurement.

Finally the screw was raised to the zero position, at the same level as the base, and a cylinder containing 0.31 - c.c. of the sample product was obtained, on which were placed successively the Petri dish, and the weights in the following order: 100, 150, 300 and 500 g, at intervals of 60 seconds.

This study was carried out at a constant temperature of 25°C and 48 hours after the preparations of each formula.

3.1.- MEASUREMENT TECHNIQUES

Extensibility was evaluated by a technique proposed (3) and perfected in our previous studies (4); after each period of 60 seconds photographic plates were taken of the extensibi

lity of each sample, at a lens-sample focal distance of 22 cm, under light from a constant source at constant intensity. After developing and printing the plates (at a constant 7.8 x - magnification) the planimeter was fixed, together with the -- prints, to a completely flat surface; the perimeter of each - sample was then read off.

RESULTS

To evaluate the results, after measuring the perimeter five times with each weight, we subtracted the weight, as far as the statistical data is corcerned, of the Petri dish (50g) since as we demonstrated in previous studies (4) not all of - its weight exerted the required pressure on the sample.

In tables 1,2 and 3 average results, showing the extensibility of excipients and corresponding MSEG preparation, as well as statistical comparison of this data, are given.

At the same time, variance of the extensibility of -- groups of MSEG oinments (table 4) and individual comparison between pairs of groups (Scheffé's test) (table 5).

DISCUSSION

Drug solid in anhydrous excipient oinments, for all weights, that no significant difference in extensibility was found (6). It was precisely this excipient which showed --

TABLE 1.- Extensibility of PEG and corresponding MSEG preparation.

WEIGHTS	EXTENSIBILITY ($\bar{x}$) PEG / MSEG Prep.		EXPERIMENTAL MARGIN OF ERROR	t_8
100	2.21	1.58	1.2×10^{-3}	28.174
150	2.52	1.84	4.0×10^{-4}	53.758
300	3.05	2.25	2.9×10^{-3}	23.489
500	3.34	2.26	1.4×10^{-3}	44.844
t (8, 0.001) = 3.355				
P 0.01				

TABLE 2.- Extensibility of GEL and corresponding MSEG preparation.

WEIGHTS	EXTENSIBILITY ($\bar{x}$) PEG / MSEG Prep.		EXPERIMENTAL MARGIN OF ERROR	t_8
100	3.89	3.03	0.01	13.598
150	3.91	3.32	2.5×10^{-3}	18.657
300	3.93	3.66	3.0×10^{-3}	7.730
500	3.95	3.81	2.9×10^{-3}	4.110
t (8, 0.001) = 3.355				
P 0.01				

TABLE 3.- Extensibility of O/A and corresponding MSEG preparation.

WEIGHTS	EXTENSIBILITY ($\bar{x}$) O/A	/ MSEG Prep.	EXPERIMENTAL MARGIN OF ERROR	t_8
100	4.54	4.09	5.8×10^{-2}	2.942
150	4.68	4.20	8.5×10^{-3}	8.232
300	4.83	4.40	1.6×10^{-2}	5.309
500	4.99	4.67	0.242	1.022

t (8, 0.001) = 3.355

P 0.01

TABLE 4.- Variance of the extensibility of groups of MSEG oinments.

WEIGHTS	F
100	697.37
150	733.19
300	138.70
500	410.37

F (2.12, 0.01) : 6.93

P 0.01

TABLE 5.- Scheffé's test.

	PREPARATIONS		
	GEL / PEG	PEG / OA	GEL / OA
F(100)	230.94	692.01	123.42
F(150)	282.26	717.73	99.79
F(300)	57.78	134.35	15.91
F(500)	165.23	399.45	50.86
F (2.12, 0.01) : 6.93			
P 0.01			

least extensibility in all test, and this extensibility was statistically unchanged by the addition of the active substance. Other authors (2) have achieved similar results on - adding boric acid, zinc or sulphur to this type of excipient, adducing the low extensibility of the vehicle itself which is not altered by the addition of other substances.

Significant difference in extensibility was found in -- MSEG in anhydrous excipient oinment (table 1), for all --- weights. This is consistency, with the formation of chemical links between drug and excipient, and to a certain extent, -- with liberation (7), diffusion (8, 9) or biopharmaceutical -- (10) test. The test referred to, carried out on the same preparations, have liberated doses at t = 180 minutes of · 98.44 %

and 84.29 % respectively in emulsion and aqueous gel excipient, as against 28.45 % of the initial dose in the anhydrous excipient.

Urinary excretion of the drug was also investigated, giving results at t = 33 hours of 36.09 % (aqueous gel), 26.67 % (O/A emulsion) and 20.86 % (anhydrous excipient).

Howerer, after individual comparison between the groups (table 5), we demonstrated that all preparations are significant. We believe that this result is important, since it is close to those mentioned in the previous paragraph; that is, to the results of the liberation mechanics test, which implies similar kinetic behaviour, as is demonstrated by quantitative data on diffusion and urinary excretion (8, 10).

CONCLUSIONS

After analysing these results we may conclude this - study with two observations:

* There is a significant difference between the extensibility of the preparations studied and their repective vehicles, independently of the physical state of the active -- substance and of the physico-chemical system used to blend - them.

* The extensibility of semi-solid preparations could - confirm the results obtained in bio-availability or transference studies, when they are carried out together.

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