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NON-AQUEOUS EMULSIONS AS VEHICLES FOR CAPSULE FILLINGS.

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ABSTRACT

New vehicles were developed based on non-aqueous emulsions. They may be classified as progress or supplimentation to the actual respectively conventional filling masses for soft gelatin capsules, but also for liquid or semi-solid hard gelatin capsule filling techniques.

IN-VITRO dissolution rate studies exhibit a clear superiority of PEG filling masses about oil-wax bases, which show extremely slow release rates.

But in the following corresponding IN-VIVO tests, which are carried out as urine recoveries, the whole loss of superio-

"Dedicated to Prof. Dr. H. Thies on his 80th birthday."

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rity of the PEG compounds is impressingly shown. On the contrary the PEG bases exhibit IN-VIVO the lowest recoveries, while the non-aqueous emulsions at least those with the Riboflavin indicate a tendency towards a more favorable gastrointestinal absorption.
These experiencies may therefore open an interesting way of attaining better bioavailabilities in certain cases with soft gelatin capsules as well as with hard gelatin capsules.

INTRODUCTION

Drugs to be filled into soft gelatin capsules are usually dispersed or dissolved before the filling procedure in liquid or semi-solid triglyceride-wax mixtures respectively in PEG 400/PEG 4000 mixtures. These two main types of capsule filling masses or vehicles are either extremely lipophilic or extremely hydrophilic, and therefore not in any case optimal.

To overcome the handicaps we first tried to add some water soluble carrier to drag the drug out of the lipophilic capsule filling masses. Finally some model drugs were were encapsulated after incorporation in non-aqueous emulsions. If there are to achieve biopharmaceutical advantages, must be proved by appropriate tests.

DEVELOPMENT AND COMPOUNDING OF THE CAPSULE FILLING MASSES

The two first mentioned compounds of the following are the mainly applied conventional vehicles for soft gelatin

capsules. They were the starting point on the way to the new non-aqueous emulsion type filling masses.

Compound 1:	Model Drug	30.0%
	Lecithin MC-Thin (Lucas Meyer, D-2000 Hamburg, Germany)	2.0%
	Wax Mixture[1]	15.0%
	Rapeseed Oil BP	53.0%
Compound 2:	Model Drug	30.0%
	Polyethylene Glycol 400 (PEG 400)	67.0%
	Polyethylene Glycol 4000 (PEG 4000)	3.0%

With the intention to gain better drug dissolution properties these conventional vehicles were changed by the addition of "drug-dragging" water soluble adjuvants in the following way:

Compounds	1 A	1 B
Model Drug	25.0%	25.0%
Glucose (Dextrose USP)	25.0%	-
Mannitol USP	-	25.0%
Lecithin MC-Thin	2.0%	2.0%
Wax Mixture[1]	10.0%	10.0%
Rapeseed Oil BP	38.0%	38.0%

1. The Wax Mixture is composed of 1 part of Yellow Wax NF, 1 part Soybean Oil hydrogenated, and 4 parts of Vegetable Oil partially hydrogenated.

The final step was the development of non-aqueous emulsions as capsule filling masses. For biopharmaceutical tests the following were selected:

Compound 3:	Model Drug	30.0%
	Sodium Cetostearylsulfate	1.8%
	1,2-Propylene Glycol USP	29.8%
	Klucel MF (Hydroxypropylcellulose, Hercules Inc., DE 19899)	2.5%
	Cetostearyl Alcohol NF	3.5%
	Rapeseed Oil BP	28.0%
	Soybean Oil hydrogenated	5.0%
Compound 4:	Model Drug	30.0%
	Pluronic F 68 (Poloxalkol, BASF-Wyandotte Corp., NJ 07054)	3.0%
	1,2-Propylene Glycol USP	28.5%
	Klucel MF (Hydroxypropylcellulose)	2.0%
	Glyceryl Monostearate NF	3.5%
	Rapeseed Oil BP	28.0%
	Soybean Oil hydrogenated	5.0%
Compound 5:	Model Drug	30.0%
	Pluronic F68 (Poloxalkol)	1.0%
	Cremophor EL (Polyethoxylated Castor Oil, BASF AG, D-6700 Ludwigshafen, Germany)	1.0%
	Polyethylene Glycol 400 (PEG 400)	29.5%
	Klucel MF (Hydroxypropylcellulose)	2.0%
	Lecithin MC-Thin	0.3%
	Rapeseed Oil BP	31.2%
	Soybean Oil hydrogenated	5.0%

These non-aqueous emulsions were prepared by mixing the hydrophilic and the lipophilic phases, previously dissolved by gentle heating.

The compounds 3 and 4 turned out to be "polyol/oil emulsions", while the compound 5 is an "oil/polyol emulsion" corresponding to W/O respectively O/W emulsions. As a rule the emulsions were composed by a polyol as the hydrophilic, by a triglyceride oil as the lipophilic liquid, by a more hydrophilic and a more lipophilic emulgator as well as a hydrophilic and a lipophilic thickening agent in order to stabilize the emulsions.

The model drugs were incorporated into the single compounds. After homogenisation and de-aeration by vacuum adequate doses were filled into hard gelatin capsules, since the filling of single soft gelatin capsules is rather intricate. By this way the non-aqueous emulsions proved themselves as very useful liquid or semi-solid filling bases for hard gelatin capsules.

Another complication in the case of soft gelatin capsules is the fact that in the moment the capsule formation and filling the shells still have a considerable high water content. In this period at least a part of the moisture is able to migrate into the non-aqueous capsule filling, and there possibly disturbs the emulsion balance. Only after the relatively protracted drying step the moisture content of the capsule shell in this respect is harmless. Hard gelatin capsules in contrast to this process are always filled after they have been dried. As a consequence of water migration into non-aqueous emulsions destabilisation may happen. Not only water but also a number of drugs may cause diverse influen-

ces on the stability of the emulsions. For this reason it is necessary to optimize each vehicle to each drug. In the case of these studies such compounds as vehicles were selected, that were expected to show nearly equal and sufficient stability in connection with all the model drugs to be used.

The hydrophilic phases of non-aqueous emulsions may consist of 1,2-Propylene Glycol, Glycerol, or Polyethylene Glycols. It is advisable, however, to use with preference Polyethylene Glycols in compounding capsule filling masses, since their little interaction trends towards gelatin are known. Due to their dissolving properties Propylene Glycol and Glycerol as ingredients for capsule fillings without complications, are only allowed in minor quantities.

IN-VITRO DISSOLUTION STUDIES

Sample Preparation

With four model drugs (Caffeine, Chloramphenicol, Salicylic Acid, and Sodium Salicylate) after passing an 80 mesh screen individually incorporated into the previously mentioned five different vehicles (compounds 1 - 5), the dissolution rate studies were arranged.

The single compounds were filled into hard gelatin capsules, wereby the average filling weight was 166.7 mg per capsule, and each capsule was containing 50 mg of the particular drug.

Apparatus

To determine the dissolution rates a flow-through cell with a volume of 20 ml and a glass sinter bottom[2] was em-

2. Manufacturer: Desaga, D-6900 Heidelberg, Germany

Results:

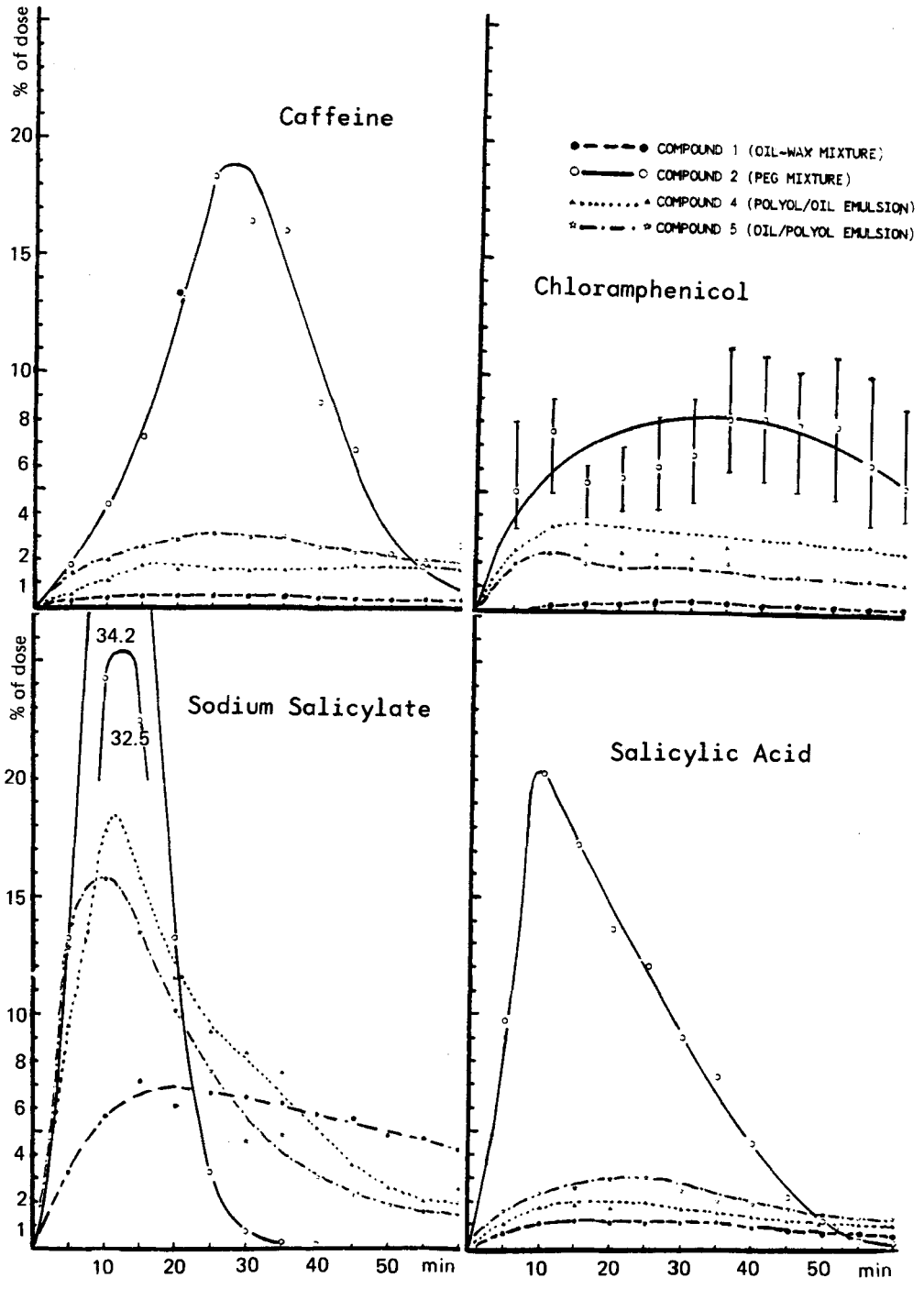

FIG.1: Summarizing survey of IN-VITRO results.

ployed. This method was given preference because of its more suitable differentiation known from literature (1, 2, 3, 4). For each determination one capsule at a time was fixed by small glass globules amidst the cell. The cell was continuously supplied with acceptor liquid (HCl solution, pH 3, 37 ± 1°C) at a flow velocity of 25 ml/min, as an open system. From each experimental batch three dissolution rate tests were conducted with one single capsule. In such a test serie lasting one hour, every five minutes samples were drawn, filtered through a membrane filter (Millex, pore size 0.8 µm, Sartorius, D-6048 Neu-Isenburg, Germany), and measured by an UV/VIS-spectrophotometer.

Results

The results obtained in the course of the previously described test series are summarized in FIG.1 and TABLE 1.

TABLE 1: Total release from the different compounds filled into hard gelatin capsules.

COMPOUND	Percental release of the applied dose of			
	Caffeine	Chloram-phenicol	Salicylic Acid	Sodium Salicylate
1	3.26	2.95	11.17	65.74
2	99.26	80.92	99.11	97.01
3	15.39	14.89	14.05	65.14
4	17.85	33.63	17.21	95.24
5	28.34	21.08	24.69	79.31
1A	6.77	2.59	9.57	55.59
1A+4	23.73	-	-	-
1B	4.77	3.01	10.53	51.79
1B+4	16.73	-	-	-

These results were obtained with the previously mentioned apparatus and method. The total release percentages of an one hour's period are calculated by adding all single values and taking the average. The release pattern according to the average single values of the five minute period samples of the compounds 1, 2, 4, and 5 are plotted in the graphs of FIG.1. Compound 1A and 1B means compound 1 with the addition of Glucose (A) respectively with Mannitol (B) as ingredients to help the drug coming out of the vehicle. Under this label the Glucose and the Mannitol are added in just the same quantity as the drug. Compound 1A+4 and 1B+4 means the addition of the "drug-dragger" in the fourfold amount compared to the drug.

IN-VIVO EXPERIMENTS

In order to ascertain if there are to recognize any trends of correlation with the previous IN-VITRO results finally some urinary excretion tests were carried out.

Volunteers

TABLE 2

	Body-weight	Height	Age	Sex
K.B.	83 kg	170 cm	53	M
B.D.	57 kg	170 cm	33	F
T.D.	73 kg	184 cm	32	M
I.P.	63 kg	171 cm	30	F
K.J.	41 kg	150 cm	24	F
J.S.	75 kg	180 cm	27	M

Preparation of the samples

As model drugs for these experiments Riboflavin and Salicylic Acid were added to the various compounds 1, 2, and 5. Then they were filled into hard gelatin capsules. Riboflavin was dosed with 30 mg per capsule, to ensure a linear absorption (5), and the Salicylic Acid with 100 mg per capsule. In both cases the relation drug to vehicle was kept at 1:2.

Determinations

Each volunteer took in the morning a continental standard breakfast, and a quarter of an hour later one capsule together with 200 ml of water. Particular attention was payed to keep the natural excretion of Riboflavin constant respectively controlled.

The single urine collecting periods were from 0 - 2, 2 - 4, 4 - 6, 6 - 8, and finally up to 24 hours. Acetic Acid was immediately added to the urine samples. Then they were stored in a refrigerator until determination. The Riboflavin and the Salicylic Acid in the urine samples were both measured by fluorophotometric methods. The Riboflavin according to that of the USP XX, the Salicylic Acid by an usual method as follows.

To 2.0 ml of urine 3.0 ml of HCl solution (35-37%) were added, and allowed to stand for 12 hours at 100°C. 1.0 ml of this probe was extracted two times for five minutes each with 5.0 ml of Chloroform, and the extract dried over Sodium Sulfate. Finally the samples were determined after sufficient centrifugation in a fluorophotometer (Perkin-Elmer 1000 M,

input filter 310 nm, output filter 447 nm) against blank urine.

The summarized results of these examinations are presented in TABLE 3.

The values of this survey are obtained by addition of the collecting period's results. The results of the single periods are averages of two readings each.

TABLE 3

	Total urine recovery in % of the applied RIBOFLAVIN within 8 hours			within 24 hours		
	Comp.1	Comp.2	Comp.5	Comp.1	Comp.2	Comp.5
K.B.	55.3	49.6	64.9	57.9	54.2	71.0
B.D.	45.1	27.6	48.6	53.3	32.1	52.9
T.D.	54.9	39.3	67.6	61.1	50.8	78.4
I.P.	45.4	47.4	48.2	62.3	47.4	48.6
average	50.2	41.0	57.3	58.7	46.1	62.7
	Total urine recovery in % of the appl. SALIC.ACID within 8 hours			within 24 hours		
	Comp.1	Comp.2	Comp.5	Comp.1	Comp.2	Comp.5
K.B.	16.6	17.7	12.0	16.6	17.7	12.0
B.D.	72.9	59.1	64.5	81.2	80.3	69.2
I.P.	22.5	26.9	23.0	43.2	45.9	43.4
K.J.	30.6	16.3	22.2	36.2	28.1	35.5
J.S.	88.0	76.6	86.5	128.6!	76.6	87.3
average	46.1	39.3	41.6	61.2!	49.7	49.5

DISCUSSION OF THE IN-VITRO AND IN-VIVO RESULTS

The IN-VITRO experiments in the first part of this paper show in an impressing way, that the model drugs all are released very fast and almost completely from the PEG mixtures. On the other hand, however, is their release from the conventional oil-wax capsule filling masses extremely poor.

The non-aqueous emulsions as new capsule vehicles exhibit release properties lying between the PEG and the oil-wax masses. Remarkable are the quite big deviations of some of the Chloramphenicol values. This may be due to the bad solubility properties or to interactions with the PEG. If there are in fact two peaks, as it is slightly indicated by the single points, or if these are artefacts is not yet clear, and is in the moment object of further experiments.

The most outstanding finding of the IN-VIVO tests is the apparently total loss of the PEG's release superiority. The PEG mixtures as capsule vehicles are obviously not able to convert their excellent IN-VITRO release properties into corresponding absorption effects. It is well known that solid dispersions of drugs in PEG for instance may enhance the bioavailability. But in this case, in the use as capsule vehicles, the relatively high excess of PEG seems to affect the ways of absorption unfavorable.

Unfortunately one value of Salicylic Acid showing more than 100% is unprobable, and it is suited to falsify a total column of results. But also one blank urine of the same volunteer was problematic, although he assured not having used other medicaments.

As far as the results, obtained with those few volunteers, may allow a fairly relevant conclusion this should be stated. The PEG bases present in almost all of the examined cases the lowest recoveries. The non-aqueous emulsions yield evident advantages with Riboflavin, with Salicylic Acid they seem at least to be not worse than the conventional oil-wax bases. If polyol/oil or oil/polyol emulsions are more suitable obviously depends on the hydrophilic-lipophilic properties of the concerned drug.

These results and considerations could be important experiences to realize improvements in bioavailability of certain drugs which are actually incorporated in oil-wax vehicles of soft or hard gelatin capsules, and which have real or supposed absorption handicaps.

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