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A COMPARATIVE EVALUATION OF FIVE COMMON SUSPENDING AGENTS USED IN DRUG SAFETY STUDIES

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ABSTRACT

Suspensions of three drugs at three concentrations (0.1, 1.0 and 10.0% w/w), prepared using five common suspending agents, have been evaluated for their suitability in drug safety studies. The suspending agents (methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose and gum tragacanth) were used in gels of similar viscosity. Sodium carboxymethylcellulose and hydroxyethylcellulose proved to be unsatisfactory in that drug assays for six of the nine suspension samples were outside the demanding limits set (±5% of theoretical). Methyl cellulose and hydroxypropylmethylcellulose were both considered to be equally satisfactory as the agent of first choice. Gum tragacanth performed slightly less well with the cationic drug used than the cellulose based agents. It is concluded that suspending agent gels should be of adequate viscosity to obtain satisfactory suspensions and that anionic

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suspending agents with the potential to interact with drugs are best avoided.

INTRODUCTION

Oral administration of drugs to animals for drug safety evaluation is an essential part of drug development. The formulations used for this type of study are selected on the basis of (i) toxicological inertness of formulating agent (ii) absence of potentiation of drug toxicity by formulating agent (iii) adequacy of absorption of drug under test (iv) simplicity of preparation (v) suitability for a wide range of test substances (vi) physical and chemical stability of formulation (vii) homogeneity of formulation and (viii) low level of microbiological organisms. Formulations are most commonly aqueous suspensions although suspensions in vegetable oils are also used.

The factors affecting the wetting of solids and the stability of the resulting suspensions to sedimentation have been extensively studied[1]. The initial wetting of the solid is likely to be poor in the case of hydrophobic materials resulting in poor dispersion. Both surfactants and hydrophobic polymers such as the suspending agents used in the study reported here can be used to aid the dispersion of hydrophobic solids.

To a first approximation the sedimentation rate of moderately dilute monodisperse suspensions (up to ca 10g solids per 100ml liquid) can be taken to depend primarily on particle diameter, the difference in density between solid and liquid phases and the viscosity of the liquid (2). For suspensions of <2g solids per 100ml liquid, sedimentation rate is proportional to the square of particle size. Solid surface-charge and particle-suspending agent interactions may also affect sedimentation rate.

The relationships between the rheological properties of some suspending agents and the physical stability of individual drug suspension have been investigated[2-5], as has the effect of these agents on the rate of drug dissolution in suspensions[6]. However,

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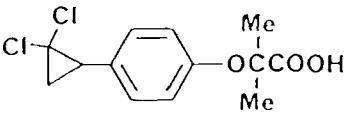
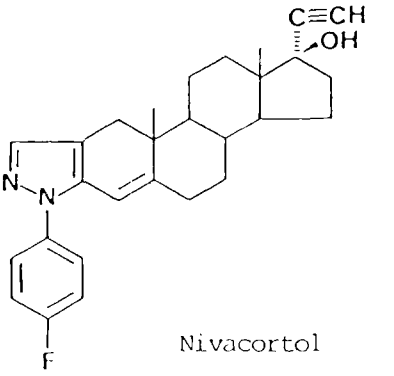
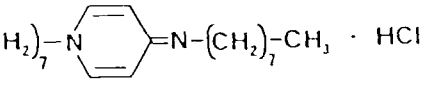


Ciprofibrate



Nivacortol



Pirtenidine

FIGURE 1
Structure of Drugs

comparison of different agents with a selection of drugs covering a range of differing physicochemical properties does not appear to have been reported previously. A survey of the literature from 1967 to 1988 by us shows that most recent studies of suspending agents have been concerned with their performance in pharmaceutical suspensions, where physical and chemical stability of many months is required, as compared to the 7 days stability often required in early stage toxicity testing.

It was therefore decided that it would be useful to compare the performance of suspending agents most commonly used in the UK pharmaceutical industry (C.S. Reed, unpublished data) with selected drug substances. This paper reports the comparison of the five most commonly used suspending agents with three drug substances, using three concentrations of each drug substance. The drug substances (Fig. 1) selected were ciprofibrate[7], an aralkyl propionic acid of fairly low water solubility and

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relatively high lipophilicity, nivacortol[8], a steroid with very low water solubility and high lipophilicity, and pirtenidine[9], a lipophilic but water soluble hydrochloride of a heterocyclic base. The densities of these drugs range from 0.98 to 1.38 g/cm^3, thus spanning the density of the suspending gel. Physicochemical data are given in Table 1.

MATERIALS

Suspending agents were supplied as follows:

Methylcellulose (MC) (batch no. T60643; grade M 450BP), Sodiumcarboxymethylcellulose (SCMC) (batch no. HTC0876; grade P75P), Hydroxypropylmethylcellulose (HPMC) (batch no. T50973; grade HPM 450BP) - Courtalds Chemicals, UK; Hydroxyethylcellulose (HEC) (batch no. D148; grade 250GR) - Hercules, UK; Gum tragacanth (GT) (batch no. PT2545; grade M/R) - Red Carnation Gum Co., UK.

Drug substances were synthesised by Sterling Research Group, Rensselaer, New York, USA and had a purity of >99.5%; melting points are given in Table 1.

METHODS

Determination of Density

Approximately 3g of drug sample or reference material (benzoic acid) was accurately weighed into a 25ml volumetric flask. Using a burette the flask was then filled to volume with cyclohexane (HPLC grade) which had previously been saturated with drug sample or reference material and filtered. The volume of the solid was calculated as 25 ml - (volume of cyclohexane added).

Determinations were made in duplicate and agreement within 1% was obtained. Using this method the density of benzoic acid was found to be 1.265 g/cm^3 at 22^{o}C as compared to a reported value of 1.266 at 15^{o}C[10].

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TABLE 1

Physicochemical Properties of Drug Substances

Drug	M.pt. °C	Water solubility (mg/ml)	$\log_{10} P$ [a]	Density (g/cm^3)	Particle diameter (um)
Ciprofibrate	183	167 at pH3.3	3.3	1.38	11.7 ± 6 [b]
Pirtenidine	c	8600 at pH7	2.96	0.98	d
Nivacortol	204	<10 at pH7	6.1	1.21	90% of particles <20

a - Log (octanol/water partition coefficient)

b - Volume median diameter $\pm$ standard deviation

c - Three polymorphic forms m.pt. 116, 129, 141°C

d - Waxy solid, wide particle size range

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Determination of Partition Coefficient

Partition coefficients (1-octanol/water) were calculated for ciprofibrate and nivacortol using the MEDCHEM program (version 3.530; Pomona College, Claremont, California, U.S.A.). The partition coefficient for pirtenidine was measured between 1-octanol and phosphate buffer (pH 7.0) using the shake-flask method and spectrophotometric analysis. The initial concentration of pirtenidine in the octanol was 1.1×10^{-3} M; the measurement was made in duplicate. Results are reported in Table 1.

Measurement of Particle Size

The particle size distribution of ciprofibrate was determined using a TA-II Coulter Counter fitted with a 140 um orifice tube. The Isoton II electrolyte (supplied by Coulter Electronics) was adjusted to pH 3.0 with dilute hydrochloric acid, presaturated with ciprofibrate and filtered before use.

The particle size distribution of nivacortol was estimated visually through a microscope of a magnification of X200-X400. Pirtenidine was a waxy solid forming crystalline aggregates and it was impractical to determine the particle size distribution.

Preparation of suspending agent gels

All suspending agent gels were prepared in distilled water using a Silverson Blender. Concentrations of suspending agents were selected to give viscosities matching those of a 0.25% w/w solution of gum tragacanth. Viscosities of 200ml batches of solutions at four concentrations of each of these suspending agents were measured using a Redwood No.1 Viscometer which measures viscosity under low shear conditions and plots of concentration against log (10) (viscosity) were found to be almost linear in each case. Concentrations required to give viscosities equal to those of the 0.25% w/w gum tragacanth solutions were derived using the linear regression equations relating concentrations to viscosity (Table 2). Two hundred ml batches of solutions of these calculated concentrations were prepared and viscosities were found to be as expected (Table 2). Two litre

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batches were then prepared for the suspending agent test and viscosities recorded (Table 2).

Preparation of Drug Suspension

All drug suspensions were prepared using the appropriate suspending agent gel using a Silverson Blender. The correct drug and suspending agent weights were blended for three minutes in a glass beaker prior to being dispensed into Beatson jars. It is recognised that the use of a Silverson Blender may have led to a reduction in drug particle size at this stage.

HPLC Analysis

Hewlett-Packard 1081B and Waters WISP 710B automated HPLC systems were used with 10 x 0.45cm i.d. columns and 20ul injections. In all cases linearity of peak height with sample concentration was determined using a reference solution (100%) and solutions of 50 and 150% of the reference concentration. All quantitation was based on the use of an external standard.

Ciprofibrate

HPLC analysis was on a 5um Hypersil ODS column using a 2ml/min flow rate and UV detection at 233nm. The mobile phase was acetonitrile : water (25 : 75 v/v) containing 5g/l ammonium acetate, adjusted to pH 6.0 by dropwise addition of acetic acid. The injection solvent was mobile phase. The reference solution contained 10 ug/ml ciprofibrate; the retention time was ca 4 min.

Pirtenidine

HPLC analysis was on a 5um Spherisorb nitrile column using a 2ml/min flow rate and UV detection at 280nm. The mobile phase was tetrahydrofuran : water (40 : 60 v/v) containing 5g/l ammonium acetate, adjusted to pH 6.0 by dropwise addition of acetic acid. The injection solvent was acetonitrile : water (30 : 70 v/v) and the reference solution contained 10 ug/ml pirtenidine in this solvent. The retention time of pirtenidine was ca. 5-6 min.

Nivacortol

HPLC analysis was on a 5um Hypersil ODS column using a flow rate of 2ml/min and UV detection at 262nm. The mobile phase was acetonitrile : ammonium acetate buffer (60 : 40 v/v) where the

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TABLE 2

Relationships Between Concentration and Viscosity at 20-25°C

$\log_{10}$ (viscosity (s)) = a + b (conc. (%w/w))

Suspending Agent	a	b	Correlation Coefficient	Equi-viscous concns[a]	Viscosity(s) 200ml batch	Viscosity(s) 2l batch
Methylcellulose (MC)	1.203	0.8544	0.994	0.75%w/w	63	69
Sodium carboxymethyl-cellulose (SCMC)	1.287	0.8899	0.997	0.58%w/w	63	66
Hydroxyethylcellulose (HEC)	1.187	1.06083	0.999	0.59%w/w	63	48
Hydroxypropylmethyl-cellulose (HPMC)	1.354	0.6173	0.990	0.75%w/w	63	69
Gum tragacanth (GT)	-	-	-	-	63	70

[a] Concentration required to give viscosity equal to 0.25% w/w gum tragacanth.

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acetate buffer was 5g/l ammonium acetate adjusted to pH 5.0 by addition of acetic acid. The injection solvent was mobile phase and the reference solution contained 10 ug/ml in this solvent. Retention time of nivacortol was ca. 5 min.

Sampling of Formulations

Each formulation analysed was shaken vigorously by hand and then sampled in duplicate whilst being stirred by means of a magnetic flea. The speed of rotation of the magnetic flea was sufficient to produce a vortex in the sample and was held constant for the sampling of each formulation. Samples were taken, using a 2ml glass syringe fitted with a veterinary needle, from the junction of the base and wall of each formulation container (100 ml glass Beatson jars) to maintain consistency of sampling. Samples were dispensed into previously weighed volumetric flasks of the appropriate volume which were re-weighed to determine an accurate sample weight. Samples were then analysed using the methods given above. Duplicate samples representing 100% of theoretical drug concentrations at the 0.1% w/w and 10.0% w/w strengths for each drug/suspending agent combination were analysed.

RESULTS AND DISCUSSION

Practical experience with gum tragacanth has shown that the grade of material purchased gives a suitable viscosity for formulating drug suspensions when used at a concentration of 0.25% w/w. Therefore this concentration, corresponding to a viscosity of 63-70 seconds, was used in this study and other suspending agents were used at concentrations expected to give this viscosity. Suspensions were considered satisfactory with regard to drug assay when assay results were within ± 5% of the theoretical value.

Suspending Agent Viscosity

The differences in viscosities of suspending agents recorded (Table 2) on the pilot 200ml batches (63-65 secs) and those

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recorded on the main 21 batches prepared at the same concentrations (66-70 secs excluding hydroxyethylcellulose) are probably due to the higher ambient temperature when the latter were prepared. Unlike the other cellulose based suspending agents, HEC was difficult to dissolve and prolonged heating was required to prepare the 21 batch of gel. This probably caused some degradation, resulting in a lower viscosity (48 secs) for the 21 batch than anticipated.

Analytical Methods and Drug Recovery

Recoveries of the three drugs from the four cellulose-based suspending agents were determined in duplicate from 0.1% and 10% w/w suspensions. In only one case (pirtenidine at 0.1% w/w in SCMC) was the average recovery outside the range 99.0-100.9%, namely 97.1%.

Analysis of reference samples of each of the three drugs on each day of analysis made at the beginning, middle and end of each analytical run gave results within the range 97.8-101.4% of theoretical for ciprofibrate, 96.8-101.4% for pirtenidine and 99.5-100.7% for nivacortol.

Comparison of Suspending Agents

Table 4 shows the number of formulations for each drug and suspending agent for which unsatisfactory assay results were obtained. From this it can be seen that MC gave no unsatisfactory results and HPMC only one. Comparable results might have been expected for HPMC and HEC which have similar structures but, as mentioned above, the viscosity of the HEC solution used was inadvertently lower than intended. This resulted in less stable suspensions which gave low assays in several cases (Table 4).

Results using MC and HPMC were essentially equivalent in that both gave acceptable formulations for all three drugs at each concentration, with the exception of 0.1% w/w pirtenidine in HPMC where an assay of just below 95% was obtained at day 1.

The strong interaction observed between SCMC and pirtenidine leading to agglomeration is typical of that occurring between

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TABLE 3

Drug Assay Results Expressed as % of Theoretical

		Ciprofibrate			Pirtenidine			Nivacortol		
Day	Conc. (w/v) Agent	0.1%	1%	10%	0.1%	1%	10%	0.1%	1%	10%
1	MC	100.8	99.1	97.1	97.6	96.3	97.5	101.5	98.6	100.3
1	SCMC	99.7	77.4	101.5	60.4	85.0	10.6	93.9	98.1	100.9
1	HEC	87.9	86.0	100.9	86.9	93.4	95.2	78.9	88.5	103.2
1	HPMC	100.6	98.2	97.7	94.8	96.7	97.1	102.7	102.0	98.9
1	GT	97.8	96.9	103.3	85.1	93.3	100.6	99.9	99.0	101.4
7	MC	100.6	101.1	102.3	103.4	97.0	97.5	101.8	100.9	100.8
7	SCMC	99.9	74.6	103.4	55.6	95.1	15.9	90.8	97.8	92.8
7	HEC	85.1	81.9	101.5	86.7	88.7	96.8	84.0	86.6	102.6
7	HPMC	100.4	101.0	103.6	95.5	95.9	99.2	102.9	102.5	102.8
7	GT	98.4	96.2	102.6	85.6	93.4	97.3	100.4	99.8	90.1

TABLE 4

Numbers of Formulations Failing to Meet Assay Criteria at day 1 and/or Day 7

AGENT	Ciprofibrate	Pirtenidine	Nivacortol
Methylcellulose	0	0	0
Sodium carboxymethyl-cellulose	1	3	2
Hydroxyethylcellulose	2	2	2
Hydroxypropylmethyl-cellulose	0	1	0
Gum tragacanth	0	2	1
Total number of formulations prepared	15	15	15

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anionic suspending agents and cationic drugs. Since many drugs are protonated at neutral pH, anionic suspending agents, including SCMC, are not suitable as standard suspending agents for preparing drug formulations.

Gum tragacanth is a complex mixture of polysaccharides containing D-galacturonic acid and various neutral species. The acid component could lead to interaction with basic drugs and may explain the results with pirtenidine, where GT proved to be a less satisfactory suspending agent than MC or HPMC. Further trials with a range of basic drugs would be needed to establish whether this is a typical result.

The microbiological status of drug suspensions is another factor influencing the selection of suspending agents. Results

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are to be reported in detail separately and confirm the widely held view that it is more difficult to achieve sterility or near sterility in GT suspensions than those based on semi-synthetic cellulose. However, it is demonstrated that with approriate treatment microbial populations can be reduced to acceptable levels.

Comparison of Drugs

i) Ciprofibrate

The 0.1% and 1.0% w/w formulations with HEC were both particularly unsatisfactory, with assays of <90% of theoretical, although the 10% formulation gave assays close to 100% at both day 1 and day 7. The low assays (86.0, 81.9%) with the 1% formulations were probably caused by sampling difficulties following very rapid settling caused by the low viscosity of the HEC solution.

Ciprofibrate at 0.1% w/w was completely solubilised by SCMC, as judged from visual inspection.

There were fewer unsatisfactory suspensions with ciprofibrate than the two other drugs showing that the high density of this compound (Table 1) was of no significance over the 7 day period of the test. This may have been partly related to the larger particle sizes of the other compounds.

ii) Pirtenidine

Pirtenidine at 0.1 and 1.0% w/w was completely solubilised by MC and HPMC and therefore satisfactory assays would have been expected for all four formulations but in fact the 0.1% w/w solutions in HPMC gave assays of ca 95% at day 1 and day 7. The solubilisation of the drug is related to its high water solubility and possibly to a strong dipolar interaction with the suspending agents. Agglomeration of pirtenidine caused by interaction with SCMC lead to totally unsatisfactory formulations and assays of only 10-16% were obtained with the 10% formulations.

The low density of pirtenidine ($0.98 g/cm^3$) lead to concentration of the drug at the surface, rather than sedimentation in four of the five suspensions at 10.0% w/w. Low assays of ca 85% of theoretical were obtained with 0.1% w/w pirtenidine in both HEC and GT although visually these suspensions appeared to be

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TABLE 5

Visual Assessment of Formulations

Suspending agent	Ciprofibrate (% w/w)			Pirtenidine (% w/w)			Nivacortol (% w/w)		
	(0.1)	(1.0)	(10)	(0.1)	(1.0)	(10)	(0.1)	(1.0)	(10)
MC	S	S,D	S,D	C	C	O	S	S,D	S,D
SCMC	C	U	S	A	A	A	S	A,D	S,D
HEC	S	U	S,D	S	S	O	S	U	S,D
HPMC	S	S,D	S,D	C	C	O	S	U	D
GT	S	S	U^+	S	A	U^+	S	S	S

S = Satisfactory suspension
C = Clear solution
U = Unstable suspension - rapid settling out
A = Agglomeration
D = Difficult to suspend at 7 days
U^+ = Suspended material came to surface
O = oily layer of pirtenidine on surface

satisfactory visually but only the 1.0% w/w concentration gave low assays.

iii) Nivacortol

Although all the nivacortol suspensions at 0.1% w/w concentration appeared to be satisfactory, those with SCMC and HEC gave low assays. At 7 days the suspension with SCMC needed vigorous manual agitation to achieve resuspension and the assay result remained low with precipitated solids, which account for the low assay obtained.

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All of the 10% w/w suspensions appeared to be satisfactory by visual inspection, and gave acceptable assays. However resuspension after 7 days proved very difficult by manual agitation, except for GT which was difficult and at this time low assays were obtained for the SCMC and GT suspensions.

The relatively high density of nivacortol ($1.2 g/cm^3$) would be expected to contribute to its sedimentation and lipophilic drugs of lower density would be expected to give more stable suspensions.

Visual Assessment of Formulations

In addition to drug assays, all formulations were examined visually at day 1 and day 7 and the main findings are summarised in Table 5. It can be seen that only a small proportion were considered satisfactory, with vigorous or very vigorous shaking being required to resuspend most formulations at 7 days. As discussed further below, visual impressions were not a very reliable guide to suspensions giving satisfactory assays.

CONCLUSIONS

It is important to select a concentration of suspending agent to give an adequate viscosity, particularly if the drug substances to be suspended have a density significantly different from 1.0 g/cm^3. The viscosity of 66-70 sec used in this study represents a reasonable compromise for drug safety testing in that at 7 days sedimented material could be resuspended, albeit with vigorous agitation, while this viscosity is sufficiently low to allow the use of a syringe for sampling and measuring doses of suspensions.

Heating during the preparation of the suspending medium is undesirable, at least for the cellulose based agents, as judged from the result obtained with HEC. Because of the practical difficulty of preparing a gel from the HEC, MC and HPMC were considered to be preferable alternatives. The use of anionic suspending agents such as SCMC is best avoided since neutral

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cellulose based and natural agents such as GT are readily available. From the limited data available it would appear that the MC and HPMC should be the agents of first choice since both performed well with all three drug substances, whereas there was evidence of an interaction between GT and the cationic pirtenidine at higher concentrations.

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