Table 3. Effect of viscosity on fill weight variation at room temperature.

Viscosity cP	Material	Fill wt mean mg	(% c.v.)
108	PEG 400	253	(0·3)
370	7·5% w/w hydrogenated castor oil in liquid paraffin	250	(0·4)
1452	10% w/w hydrogenated castor oil* in liquid paraffin	260	(0·8)
5000	2% hydroxyethyl-cellulose† in water	251	(0·3)
270 000	3% hydroxyethylcellulose in water	250	(1·2)

* Thixcin R (Abbey Chemicals Ltd).
† Natrosol 250MR (Hercules Ltd).

Capsule shell weight variation is relatively large and introduces error into the calculation of fill weight variation, further evaluation of the system components was therefore carried out using tared containers.

The reservoir, pump and dosing nozzle were isolated from the Zanasi and fill weight variation of a variety of filling materials was evaluated under various temperature and air pressure conditions. The variables examined and results obtained are illustrated in Tables 2 and 3, all filling materials, except those using PEG, exhibit non-Newtonian flow.

Fill weight variation is shown to be excellent under all operating conditions and filling materials of widely differing viscosity and flow properties can be dosed with great precision.

Conclusion

The system of filling liquids into hard gelatin capsules as described has been shown to be versatile, capable of operating over a wide range of temperature and filling material viscosity and to be relatively insensitive to minor variations in operating conditions. The excellent fill weight uniformity achieved indicates that good drug content uniformity can also be obtained as demixing and segregation will not occur in well stirred solution and suspension formulations. The uniformity of the filling material and the reliability of volumetric dosing of liquids indicates that unlike conventional solid dose form manufacture the individual control of unit weight is unnecessary.

The system is suitable for pilot scale or small scale production batches and any intermittent motion powder fill capsule machine can be similarly modified at reasonable cost. Changeover from powder to liquid filling can be completed in less than 30 min avoiding the need for dedicated machines, and scale-up to multi-station machines can be achieved by increasing the number of pumps.

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Communicated July, 22 1983

The prolonged retention of sodium cromoglycate in the rabbit eye

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The retention of sodium cromoglycate in the rabbit eye over a 6 h period following its administration in two different vehicles is reported. When formulated as a dispersion in a hypo-allergenic acetylated lanolin/paraffins base, prolonged retention was observed. Thus, the concentration of sodium cromoglycate in the tears, conjunctiva and cornea 6 h after administration equalled or exceeded the concentration obtained with an aqueous solution 1 h post-instillation.

Recently Lee et al (1983a) reported on the disposition of topically-applied 2% sodium cromoglycate aqueous solutions (I) in the rabbit eye over 2 h. In a subsequent report (Lee et al 1983b), the effect of several different vehicles on the disposition of 4% sodium cromoglycate in the rabbit eye was studied over 4 h. These latter vehicles were an absorption base containing hypo-allergenic acetylated lanolin (Modulan) in paraffins (II), an oleaginous base comprised of polyethylene and mineral oil (Plastibase) (III) and a water-soluble base consisting of 15% polyvinyl alcohol (Polyviol) in water (IV). Formulations (II) and (III) were found to be superior to (IV) in terms of sodium cromoglycate concentration in the tear pool and the several ocular tissues examined (conjunctiva, cornea, iris-ciliary body and aqueous humor) 4 h post-instillation. A comparison of these two studies, which were carried out sequentially using rabbits from the same source, showed that the concentration of sodium cromoglycate in the tear pool 2 h following the instillation of 25 mg of (II) was 375 μg ml^{-1} (s.e.m. ≈ 113) while that from 25 μl of (I) was 68 ± 29 μg ml^{-1}. The data also suggested that, even after taking into account the difference in concentration

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Table 1. Effect of formulation on the retention of sodium cromoglycate in the tear pool, conjunctiva and cornea of the rabbit[a].

	Sodium cromoglycate concentration[b]					
	tears, μg ml^{-1}		conjuctiva, μg g^{-1}		cornea, μg g^{-1}	
Time, h	Formulation (I)[c]	Formulation (II)[d]	Formulation (I)	Formulation (II)	Formulation (I)	Formulation (II)
0·5	2144 ± 1056 (7)[e]	2724 ± 586 (14)	26 ± 16 (5)	172 ± 33 (14)	15 ± 4 (6)	69 ± 9 (14)
1·0	322 ± 108 (7)	2663 ± 469 (50)	11 ± 3 (6)	131 ± 29 (14)	14 ± 3 (7)	67 ± 10 (14)
2·0	139 ± 71 (20)	2077 ± 360 (40)	14 ± 5 (7)	97 ± 10 (14)	10 ± 4 (7)	47 ± 5 (14)
4·0	70 ± 28 (14)	1136 ± 221 (28)	9 ± 5 (6)	92 ± 12 (14)	2·6 ± 0·6 (7)	27 ± 4 (14)
6·0	59 ± 19 (7)	609 ± 174 (13)	18 ± 6 (7)	79 ± 16 (14)	8·5 ± 2·5 (7)	32 ± 6 (14)

[a] Albino rabbits, Franklin Rabbitry, Greensboro, North Carolina.
[b] Normalized for a dose of 25 μl of (I) or 25 mg of (II).
[c] 2% sodium cromoglycate aqueous solution.
[d] 4% sodium cromoglycate dispersion in hypo-allergenic acetylated lanolin/paraffins base.
[e] Mean ± standard error of the mean (number of eyes).

between (I) and (II), formulation (II) after 4 h could be expected to provide significantly higher concentrations of sodium cromoglycate in the tear pool than formulation (I).

We have recently completed a third study that investigated the disposition of sodium cromoglycate in the tears and ocular tissues of the rabbit over 6 h (Shrewsbury, Swarbrick, Newton and Riggs, to be published). The experimental techniques used were similar to those described earlier (Lee et al 1983a). Several formulations were studied, including (I) and (II) as described above. The volume of formulation (I) used was 25 μl of a 2% solution while the weight of formulation (II) applied was 17·5 mg of a 4% dispersion. In the latter case, data were normalized to a dose of 25 mg to facilitate comparison with (I). Relevant results from this third study are presented in Table 1 and confirm our earlier suppositions concerning these two formulations. Thus these data show that for periods up to 4 h the concentrations of sodium cromoglycate in tears and the other ocular tissues studied are significantly higher from formulation (II) than from formulation (I). Indeed, these latest results clearly show that such differences persist for periods up to at least 6 h, the maximum time studied. For example, after 4 and 6 h, the concentration of sodium cromoglycate in the tear pool following application of (II) is 8 times and 5 times greater, respectively, than from (I). In the conjuctiva and cornea, the levels from (II) after 6 h are approximately twice those from (I). Table 1 shows that the concentration of sodium cromoglycate in tears, conjunctiva and cornea 6 h after the use of formulation (II) equals or exceeds the values arising from formulation (I) 1 h after instillation. These relative differences are calculated having taken into account the fact that formulation (I) contained 2% sodium cromoglycate while formulation (II) contained 4%. It is therefore evident that sodium cromoglycate is much better retained in the tear pool, conjunctiva and cornea of the rabbit eye when administered as a dispersion in a hypoallergenic acetylated lanolin/paraffins base than as a simple aqueous solution. Such relative differences could also be expected to exist in man.

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