$D$ rather than $P$ is expected to be the quantity relevant to the relative rates and equilibria of partitioning for a series of agents under physiological conditions, and this point has been re-emphasized in the context of narcotics and narcotic antagonists (Kaufman et al 1975). It follows therefore that the *pharmacologically effective* partition coefficient of atenolol is about half that of sotalol.

In conclusion, under physiological conditions i.e. pH 7·4 and 37·0 °C, atenolol has an *effective partition coefficient*, i.e. distribution coefficient, which is about half that of sotalol. On the basis that the distribution coefficient is the determinant of tissue distribution in-vivo, atenolol may be regarded as the most hydrophilic of the clinically available β-blockers.

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# The evaluation of an automatic system for filling liquids into hard gelatin capsules

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A system is described in which an intermittent motion powder filling capsule machine is modified to fill liquids into hard gelatin capsules suitable for pilot scale or small production batches. The system is shown to be suitable for filling materials covering a wide range of viscosities and to give excellent fill weight uniformity which is largely independent of operating conditions. The process is clean and trouble-free.

The advantages of filling hot melt or thixotropic liquids into hard gelatin capsule shells in which they solidify to form a stable solid plug, have been well documented in recent years. These include low content uniformity variation, reduced dust generation giving rise to reduced cross contamination hazards, controlled dissolution rate using solid solution or slow release systems, the ability to process low melting point or liquid drugs and the possibility of in-house formulation development and manufacture (Walker et al 1980a, b; Cuiné & Francois 1981).

Equipment is available to manufacture very small batches of liquid filled capsules by hand and at the other extreme very large batches can be processed using purpose-built liquid fill capsule machines. There is currently no machine available for the manufacture of pilot scale and small production batches. We therefore describe the modification and evaluation of a Zanasi LZ64 (ACM Machinery Ltd.) automatic, intermittent motion powder filling machine to enable the manufacture of 4400 liquid filled capsules per hour.

*Equipment.* The modifications to the capsule filling machine comprise a series of elements now described; (the sequence of operation is described and the system is illustrated schematically in Fig. 1).

*Liquid filling system.* The powder hopper and dosator tubes are replaced by a heated stainless steel reservoir and liquid metering pump (Hibar Model HBD-1A, Höfliger, West Germany). The pneumatically operated pump can deliver volumes of 0·05 to 1·5 ml of liquid at a rate of up to 150 doses per minute with infinitely variable dose and temperature control over the range ambient to 100 °C. The reservoir and dosing nozzle are maintained above ambient temperature by heating tape (Hot Foil Ltd. U.K.) and a heating block respectively and thermostatic control is achieved by thermistors (R.S. Components Ltd.).

*Capsule detection.* A system was developed to disable the pump in the absence of a capsule shell at the filling

Table 1. Fill weight uniformity using the liquid fill system.

| Trial | Duration min | Total Wt* (mg) mean | range | c.v. % | Fill wt mean mg |
|---|---|---|---|---|---|
| I | 100 | 328 | 318–338 | 0·71 | 254 |
| II | 120 | 324 | 317–339 | 0·76 | 250 |

* Size 1 capsule shells, mean weight 74 mg c.v. 3·2%.

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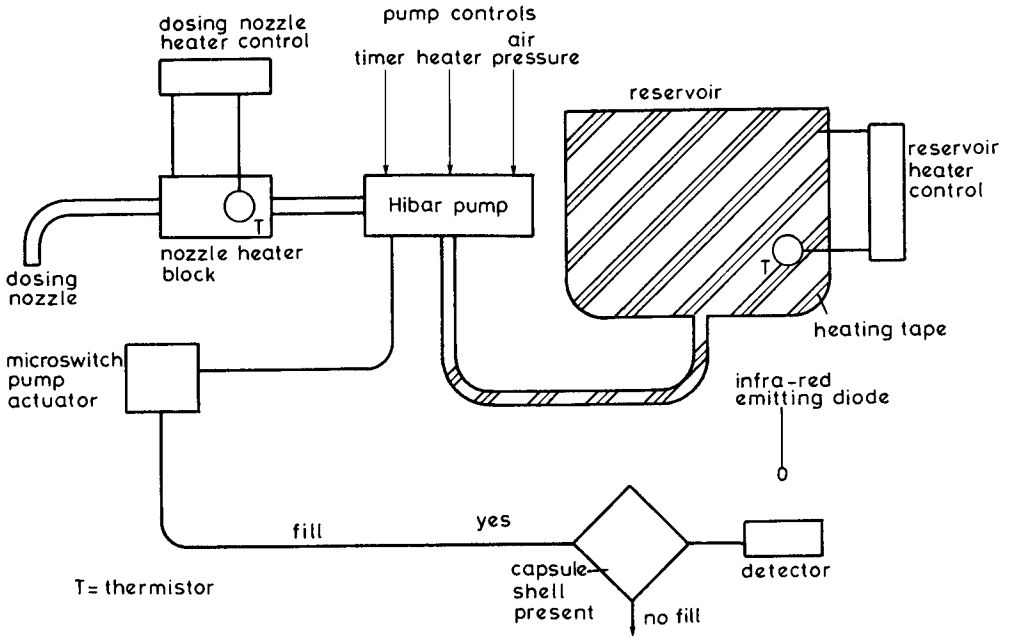


FIG. 1. Schematic diagram of liquid filling pump and control systems.

station to prevent liquid contaminating the turn-table. This consists of two elements: a detector system and a delay circuit to allow filling to continue when the capsule shell feed resumes. The powder dosator tube was replaced by a rod at whose tip is mounted a light emitting diode (R.S. Components Ltd.) and a sensor is mounted beneath the Zanasi turn-table. If a capsule shell is missing a signal is relayed to the pump which prevents the next filling operation, provided normal capsule shell feed is resumed dosing recommences automatically.

*Synchronization of dosing.* In the powder filling mode synchronization of filling with the presence of an open stationary capsule shell is achieved mechanically. In the liquid filling mode, synchronization is achieved by a microswitch mounted on the capsule ejection rod platform which triggers the dosing pump at the stationary phase of the cycle.

*System evaluation*

The modified Zanasi filling system was evaluated under the following conditions: fill rate 4400 capsules $h^{-1}$; reservoir temperature 60 °C; pump temperature 60 °C; dosing nozzle temperature 70 °C; air pressure to pump 2 atm; duration of dosing 0·5 s; filling material 1 : 8 w/w polyethylene glycol 400 : 3000; target fill weight 250 mg.

Two filling trials of 100 and 120 min duration were conducted, samples were taken at 10 min intervals throughout the run and the weight uniformity of 20 capsules determined. Fill weight uniformity is illustrated in Table 1.

The filling trials were trouble-free and demonstrate that the system can be used for prolonged development trials. Fill weight variation is excellent and compares favourably with that achieved by powder filling methods. No fill weight adjustments were necessary throughout the runs, which confirms the stability of the dosator system and also illustrates the advantages of volumetric dosing of liquids. In contrast, volumetric powder dosing in all solid dose form manufacture can suffer from bulk density variation of the feed material.

Table 2. Fill weight variation at various operating conditions, mean weight mg and (% c.v.).

| Reservoir Temp °C | | | Hibar pump Air press (Atm) | | | Dosing nozzle Temp °C | | |
|---|---|---|---|---|---|---|---|---|
| 55 | 253 | (0·4) | 1 | 247 | (0·2) | 60 | 252 | (0·4) |
| 60 | 252 | (0·7)* | 2 | 251 | (0·2)* | 70 | 252 | (0·7) |
| 70 | 253 | (0·5) | 3 | 250 | (0·3) | 80 | 253 | (0·6) |
| 75 | 252 | (0·3) | 4 | 251 | (0·3) | 90 | 253 | (0·6) |
| | | | Temp °C | | | | | |
| | | | 50 | 254 | (0·8) | | | |
| | | | 60 | 252 | (0·7)* | | | |
| | | | 70 | 252 | (0·6) | | | |
| | | | 80 | 252 | (0·7) | | | |
| | | | 90 | 252 | (0·3) | | | |

* Constant conditions selected for subsequent evaluations.

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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# 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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