

significantly smaller surface area than the equivalent quantity of pellets, thus, reducing the amount of coating required and improving its uniformity.

Semi-solid and liquid filling

Liquids can easily be dosed into capsules using volumetric pumps (Rowley 2004). The problem after filling is to stop leakage from the closed capsule. This can be done in one of two ways, either by formulation or by sealing the capsule. Semi-solid mixtures are formulations that are solid at ambient temperatures and can be liquefied for filling by either heating (thermosoftening mixtures) or by stirring (thixotropic mixtures). After filling, they cool and solidify or revert to their resting state in the capsule to form a solid plug. Both types of formulations are filled as liquids using volumetric pumps. These formulations are similar to those that are filled into soft gelatin capsules but differ in one important respect: they can have melting points higher than 35 °C, which is the maximum for soft capsules because this is the temperature used by the sealing rollers during their manufacture. Non-aqueous liquids, which are mobile at ambient temperatures, require the capsules to be sealed after filling. The industrially accepted method for this is to seal the cap and body together by applying a gelatin solution around the centre of the capsule after it has been filled. When this has been dried it forms a hermetic seal that prevents liquid leakage, contains odours inside the shell and significantly reduces oxygen permeation into the contents, protecting them from oxidation. An example of such equipment is the Qualicaps Hicap seal machine, which has outputs ranging from 40 000 to 100 000 per hour.

Formulation

All formulations for filling into capsules have to meet the same basic requirements:

1. They must be capable of being filled uniformly to give a stable product.
2. They must release their active contents in a form that is available for absorption by the patient.
3. They must comply with the requirements of the Pharmacopoeial and regulatory authorities, e.g. dissolution tests.

Table 33.4 Types of excipient used in powder-filled capsules

Diluents, which give plug-forming properties.
Lubricants, which reduce powder-to-metal adhesion.
Glidants, which improve powder flow.
Wetting agents, which improve water penetration.
Disintegrants, which produce disruption of the powder mass.
Stabilizers, which improve product stability.

In order to formulate rationally, it is necessary to take into account the mechanics of the filling machines and how each type of product is handled.

Powder formulation

The majority of products for filling into capsules are formulated as powders. These are typically mixtures of the active pharmaceutical ingredient together with a combination of different types of excipients (Jones 1995; Table 33.4). The ones selected depend upon several factors:

- the properties of the active drug: its dose, solubility, particle size and shape
- the filling machine to be used
- the size of capsule to be used.

The latter factor defines the free space inside the capsule that is available to the formulator (Jones 1998). The easier active compounds to formulate are low-dose potent ones, which in the final formulation occupy only a small percentage of the total volume (< 20%) and so the properties of the mixture will be governed by the excipients chosen. Those compounds with a high unit dose, e.g. 500 mg of an antibiotic, leave little free space within the capsule and the excipients chosen must exert their effect at low concentrations (< 5%) and the properties of the mixture will be governed by that of the active ingredient.

Formulation for filling properties

There are three main factors in powder formulation:

- good flow (using a free-flowing diluent and glidant)
- no adhesion (using a lubricant)
- cohesion (plug-forming diluent).

The factor that contributes most to the uniform filling of capsules is good powder flow, because all