Table VI: Desirable Flow Parameters for Capsule Blends.[9]

	Very poor flow	Recommended Range	Very good flow
Flow parameter	Level powder bed not maintained Poor filling of cavities on tamping disc machines High fill weight variability	—	Water effect seen on tamping disc machines. Stable plug may not be formed on dosator machines
Compressibility Index	>35%	15–25% 5–35% may be suitable for dosator nozzle machines	<15%
Angle of repose	>30°	25–30°	<25°
Flow function coefficient (from ring shear testing)	<4	4–10	>10

GI tract. Lipids such as carnauba wax or beeswax have also been used to create the barrier coat.[51]

In the *Pulsincap* device, a nondisintegrating capsule body is closed with an insoluble plug which separates the capsule contents from the external medium. The plug swells on contact with the medium and, after a controlled lag time, is extruded from the shell thereby releasing the capsule contents. A range of polymers can be used to form this plug[53] as follows:

- Insoluble but permeable and swellable polymers e.g. polymethacrylates such as *Eudragit*.
- Erodible compressed polymers e.g. hypromellose, polyvinyl alcohol, polyvinyl acetate, polyethylene oxide.
- Congealed, melted polymers e.g. saturated polyglycolated glycerides, glyceryl monooleate.
- Enzymatically controlled erodible polymers e.g. pectin.

Drug delivery devices such as these can also be tailored to synchronize drug release with the circadian rhythms shown by many physiological functions (e.g. hormone secretion, gastric emptying and gastrointestinal blood transfusion) or the pathophysiology of several disease conditions (e.g. bronchial asthma, myocardial infarction, ulcer and hypertension).[51]

Excipients for Capsule Formulation

Despite the enduring popularity of the compressed tablet, there are several circumstances where a capsule may be more appropriate:

- It is necessary to mask the taste of an unpalatable drug.
- The formulation is not sufficiently compactible to form a robust tablet.
- The stability of the API or the excipients is adversely affected by the compaction process.
- The dosage form must be easy to swallow (important for specific patient groups).
- To prevent the patient from subdividing tablets.

In addition, a capsule shell presents a versatile canvas for product recognition and dose strength differentiation through the use of colored shells and/or printing.

The excipients used to formulate capsules are generally similar to those used for tablets. A survey conducted in 1994 found that various grades of lactose were the most commonly used excipient in capsule formulations registered in both the US and Europe; next in popularity were microcrystalline cellulose in the US but chiefly starch in Europe.[54] A coprocessed mixture of corn starch and pregelatinised starch has been designed for successful capsule production. It has good flow properties and a reduced level of very fine particles to minimize dust; it also yields capsules with good disintegration regardless of pH.[4]

The majority of modern capsule filling machines used within the pharmaceutical industry fall into one of two categories based on their mode of action: tamp-filling machines or dosator nozzle machines. In both cases, good flow is essential to ensure consistent plug production and filling.[9] However, powders designed for capsule filling using a dosator machine must also possess sufficient cohesivity to form a robust arch within the dosator nozzle as the powder plug is transferred to and dropped into the capsule shell.[9]

Glidants, such as colloidal silicon dioxide or talc, are commonly added to capsule formulations to improve flow and reduce the sticking propensity.[9]

Powders with very good flow are by definition not cohesive and may not form a plug of sufficient robustness to remain intact during the filling process; this is particularly important for dosator machines, where the formed powder plug must remain within the dosator tube without losing any powder as it moves to the filling station. In tamp-filling machines, powders with very good flow may also exhibit the 'water effect' in which the powder is displaced sideways rather than downwards by the descent of the pins into the powder bed.[9] Capsule blends should therefore be formulated to fall within a range of flow values, as described in Table VI.

As with tablet development, issues related to flow or plug formation may be resolved by selecting a more appropriate excipient grade. It is also important to remember that apparently equivalent material from different manufacturers may not behave in a similar fashion on a capsule machine.[55] Particle size has a large effect on capsule filling as shown in Table VII.

A hard gelatin capsule shell contains 13–16% moisture as a plasticizer and for this reason hygroscopic materials should not be considered for capsule filling as they will draw water from the shell, causing it to become brittle.

Cross Linking of Gelatin Capsule Shells

The gelatin forming a capsule shell is susceptible to a phenomenon known as crosslinking, which hinders dissolution by the formation of an insoluble, swellable hydrogel around the powder fill. Crosslinking can be induced by storage at elevated humidities and temperatures. Crosslinking has also been correlated to the presence of a wide range of compounds; the most important of these are aldehydes, including formaldehyde, which unfortunately may be present as a reactive component in many common excipients used in capsule formulations;[56] *see also* Reactive Components in Pharmaceutical Excipients. Where it is unavoidable to exclude the presence of a material known to be implicated in gelatin crosslinking, an alternative to gelatin capsules exists in the form of capsule shells made from other polymers such as hypromellose (HPMC). These capsules contain less water than their gelatin counterparts (approximately 5%) so are preferable where filling particularly hygroscopic materials; in addition, the water present in HPMC shells does not act as a plasticizer, so changes will not have the deleterious effects on capsule robustness to which gelatin capsules are prone.

General Conclusions

The range of excipients available to the formulator that may be used for the preparation of oral solid dosage forms is highly diverse. However, as a general rule, excipients are only selected if they aid