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Challenges and Opportunities in The Encapsulation of Liquid and Semi-Solid Formulations into Capsules for Oral Administration

Ewart T. Cole, Dominique Cadé, Hassan Benameur

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Abstract

The encapsulation of liquids and semi-solids provides solutions for convenient delivery through improved oral absorption of poorly water-soluble drugs. In addition, low dose (content uniformity), highly potent (containment), low melting point drugs, those with a critical stability profile and those for which a delayed release is required are candidates for liquid or semi-solid formulations. Both hard and soft capsules can be considered and in each case the capsule wall may comprise gelatin or some other suitable polymer such as hypromellose. The choice of a hard or soft capsule will depend primarily on the components of the formulation which provides the best absorption characteristics as well as on the physical characteristics, such as the viscosity of the formulation and the temperature at which the product needs to be filled. Numerous excipients are available for formulation of lipid-based systems and their compatibilities with hard gelatin capsules have been tested. The availability of new enhanced manufacturing equipment has brought new opportunities for liquid-filled hard capsules. Filling and sealing technologies for hard capsules, provides the formulator with the flexibility of developing formulations in-house from small scale, as required for Phase I studies, up to production.

Keywords

Gelatin capsules, Hypromellose, Liquid filling, Formulation characteristics, Licaps™, Drug Delivery System.

Authors

Ewart T. Cole[a], Dominique Cadé[b], Hassan Benameur[b]
[a]Capsugel Division of Pfizer, CH-4114 Hofstetten, Switzerland
[b]Capsugel Division of Pfizer, 10 Rue Timken, Colmar, France

1. Introduction

When active pharmaceutical ingredients (APIs) are classified according to the Biopharmaceutics Classification System [1] more than 35% of commonly prescribed drugs are considered to be poorly water-soluble [2]. Lipinski et al. [3] pointed out that leads obtained through high-throughput screening (HTS) tend to have higher molecular weights and greater lipophilicity than leads in the pre-HTS era. In such cases conventional formulation strategies are no longer adequate to achieve acceptable bioavailability. Although a number of alternative technologies are being developed, lipid-based formulations have shown promise in enhancing the oral bioavailability of lipophilic drugs [4]. Such formulations make use of excipients which are either liquid or semi-solid in nature and therefore the only solid oral dosage form that has good patient acceptability is the capsule.

Two types of capsule are commonly used and are classified according to the nature and flexibility of the capsule shell.

Soft capsules are single unit solid dosage forms comprising a liquid or semi-solid fill and are usually oblong or oval in shape. They are formed, filled and sealed in one operation using a rotary die process. The technology is currently available from a few specialist companies. Hard capsules are single unit dosage forms which are manufactured separately [5,6] and supplied empty for filling. They are always cylindrical in shape, consist of a cap and body and have domed ends.

Soft capsules have been used as unit dose containers for liquids for many years whereas hard capsules have conventionally been used for delivery of solids in the form of powders and pellets. Over the last 25 years, new equipment has become available for filling and sealing liquids and semi-solids into hard shell capsules thereby providing a viable option for filling such materials into hard capsules, as opposed to soft capsules. The manufacturing process and characteristics of soft capsules have been adequately reported [7–11] and will only be included in this manuscript where a comparison to liquid-filled hard capsules is required. This review will focus on the technology associated with the filling and sealing of liquids and semi-solids into hard capsules.

The liquid filling technology offers the opportunity for inclusion of APIs with characteristics other than poor water-solubility including compounds that are low dose or highly potent materials, have a low melting point or those with a critical stability profile. In addition the technology provides an opportunity to delivery molecules for which prolonged release is required.

2. Relevant characteristics of an API for liquid-filled capsules

2.1. Poor water-solubility

The main characteristic of NMEs for which the liquid fill technology is applicable are those classified according to the BCS as low solubility and high permeability compounds. The cardiac glycoside digoxin is poorly water-soluble and when formulated as a tablet it is critically important to control the particle size of the API to avoid variable bioavailability. Ghirardi et al. [12] reported that the bioavailability of digoxin increased significantly when formulated and administered as a liquid in a soft capsule and that dose adjustments were necessary when patients were switched from tablets to liquid-filled capsules [13]. Soft capsules were the only option available at that time and it was not until the early 1980's that equipment was developed to facilitate filling of hard capsules with liquids [14–16]. Lahr [17] made use of these advances in filling equipment technologies and developed a semi-solid formulation for nifedipine and the hard gelatin capsule was shown to be bioequivalent to nifedipine oral liquid and soft gelatin capsules [18].

Yessksel et al. [19] performed an *in vivo* comparison of hard gelatin capsules filled with pure piroxicam API or a formulation using polyglycolized glyceride Gelucire 44/14 and Labrasol. The area under the plasma concentration versus time curve (AUC) and rate of absorption from the semi-solid formulation were higher than that following administration of pure API. The use of a capsule filled with a semi-solid formulation may be advantageous in treating acute painful conditions where a rapid analgesic effect is desired.

Schamp et al. [20] demonstrated that a semi-solid formulation of a BCS Class II drug in hard gelatin capsules resulted in better dissolution, stability and bioavailability than a formulation manufactured using lactose powder

blend. The semi-solid formulation comprised a mixture of Gelucire 44/14 and 2-vinylpyrrolidone which was incorporated as a solubilizing agent. Besides the solubilizing properties of this formulation an additional benefit is that the API is retained in solution following release in the gastrointestinal tract (GIT).

A similar conclusion was drawn by Joshi et al. [21] in studies in which a hard gelatin capsule containing a micronized poorly soluble API blended with lactose and microcrystalline cellulose was compared to a hard gelatin capsules filled with a solid dispersion of the API in PEG 3350 and polysorbate 80. A significant improvement in the bioavailability of the API was observed in dogs following administration of the solid dispersion. The improvement in bioavailability was attributed to the inclusion of polysorbate 80 which ensured the complete release of API in a finely dispersed form and which was likely to facilitate solubilization by bile acids in the GIT.

The *in vitro* dissolution rate of flubiprofen, a BCS Class II compound was significantly improved when the API was delivered from a mixture of Gelucire 44/14 and Labrasol [22]. The crystalline nature of the drug was altered in the semi-solid dispersion compared to the drug alone, flubiprofen being present as a fine dispersion with a particle size of 194 to 278 nm. Dissolution of the API was enhanced in water and in media between pH values of 1.2 and 7.2.

The formulation of self-emulsifying Drug Delivery Systems (SEDDS) has been reviewed by Pouton [23] and the essential properties of a poorly soluble drug for which SEDDS technology can be useful in improving bioavailability have been reviewed by Benameur [24].

2.2. Low dose/high potency

Drugs in this category present two main challenges for the manufacture of solid dosage forms including issues of content uniformity and the containment of potent drug entities during processing. Compounds in this category include hormones and cytotoxic APIs.

2.2.1. Content uniformity

It has been reported [25,26] that the pumps on capsule-filling machines used for dispensing liquids are capable of achieving weight variations of <1%. Consequently for a low dose API in solution excellent content uniformity would be achieved. A formulation which incorporated 20 µg of a model drug, triamterene, was shown to have a content uniformity of 1.8% for liquid-filled capsules compared to 3.1% for powder filled capsules [27].

2.2.2. Containment

A semi-solid formulation of phenacetin (3 mg dose) was used to demonstrate the potential for containment of API during filling of capsules [28]. Swab tests on the surfaces of various parts of the filling machine after completion of a filling operation revealed that no API was present on any of the capsule-filling machine bushings, which would not be achievable when powders are filled. The lower detectable limit of the analytical method was 0.25 µg. This result indicates that the incorporation of potent drugs into liquid fill materials has the potential to drastically reduce the danger of exposure of operators to dust particles.

2.3. Low melting point

During any tableting or capsule-filling operation heat is generated by friction. Consequently any API with a low melting point may stick to tooling surfaces or change parts thereby introducing potential processing or stability issues. Similarly, if an API is liquid at room temperature a large amount of excipient is required to convert the API into a free flowing powder which can result in the production of an excessively large dosage form that will be difficult to administer. Commercially available products which fall into this category include fish oils, vitamins A and E and phospholipids.

2.4. Critical stability profile

In certain cases the stability of a drug is adversely affected by the environmental conditions, particularly exposure to high humidities. The stabilizing effect, on an unstable API, following the production of systems of fusible excipients was investigated [29] and applied to vancomycin formulations [30]. Vancomycin hydrochloride is freely water-soluble and hygroscopic and if not packaged appropriately absorbs large amounts of moisture with subsequent instability. When first marketed a unit dose of vancomycin was filled into glass vials for reconstitution immediately prior to use. The incorporation of vancomycin into a polyethylene glycol (PEG) matrix protected the drug from moisture and when filled into hard gelatin capsules produced a stable and convenient dosage form. The capsule formulation produced systemic levels of the antibiotic similar to those obtained following administration of a solution of the API [31].

2.5. Short half-life

The rate of release of APIs from hard capsules filled with semi-solids can be controlled by selecting excipients with different hydrophilic–lipophilic balance values (HLB). The Gelucire range of excipients are characterised by their melting point and HLB values. For example Gelucire 44/14 has a melting point of 44 °C and an HLB value of 14. The *in vitro* release rate of salicylic acid from a system of mixed Gelucire products was found to be directly proportional to the HLB value of the composition of the fill material [32]. The release rate of ketoprofen, a BCS Class I drug, from hard gelatin capsules was sustained *in vivo* by use of a slowly hydrating erodible highly ethoxylated wax formulation [33]. Drug absorption was found to be dependent on physiological variables such as gastric emptying and intestinal transit as assessed by gamma scintigraphy.

Vial-Bernasconi et al. [34] reported that erosion controlled release formulations manufactured using Gelucire are particularly suitable for short half-life poorly soluble compounds such as indomethacin. The *in vivo* study was not sufficiently powered to show true bioequivalence to a pellet formulation but a simulation on 24 volunteers revealed that the two products would have been found to be bioequivalent. Furthermore, sustained release hard gelatin capsules with thermosetting fill materials are versatile and easy to produce and provide a useful alternative to tablet dosage forms.

The ACE inhibitor captopril has a short half-life of approximately 2 h and peak concentrations in plasma occur within an hour following administration.

A captopril fill formulation in hard gelatin capsules using an oily semi-solid matrix comprising soyabean oil and glyceryl monostearate has been developed [35–37]. In dogs inhibition of ACE activity was maintained over a period of 10 h with the oily semi-solid matrix as compared to only 1–2 h following administration of a tablet formulation. Furthermore, it was determined in a human study that the oily semi-solid matrix capsule administered twice daily was able to provide antihypertensive activity comparable to that achieved following administration of tablet three times a day for the same total daily dose.

Using a variety of hydrophilic and lipophilic excipients, polyethylene glycols as channelling agents and Gelucires a delayed release form of oxyprenolol hydrochloride was developed [38]. Comparing the release kinetics with the commercial preparation in the polymer matrix form of the drug, it was found that Gelucires were the most appropriate excipients for the preparation of semi-solid matrices and that drug release can be improved depending on the quantity and type of channelling agent used.

From the various characteristics of drugs which could benefit from being formulated as liquid or semi-solids in capsules there are a number of pharmaceutical products that are commercially available and the details for some of these are listed in Table 1, together with the physical characteristics of the API included in the formulation and the manufacturer of the dosage form.

3. Comparison of hard to soft capsules

The most frequently used polymer for the production of hard capsules is gelatin. Additional components of the capsule shell include water, which acts as a placticizer, colouring agents and/or opacifiers. If an alternate to gelatin is required, hard capsules may be manufactured from

Table 1.

Some products marketed as liquid-filled hard gelatin capsules.

API characteristics	API	Trade name/ company
Poorly soluble	Nifedipine	Aprical®/Rentschler
	Ibuprofen	Solufen®/SMB
	Piroxicam	Solicam®/SMB
	Fenofibrate	Fenogal®/SMB
	Danthron	Co-Danthramer®/ Napp
	Cyclosporin A	Gengraf®/Abbott
Low melting point	Oils of avocado and soya	Piascledine®/ Pharmascience
	Ethosuximide	Suxilep®/Jenapharm
	Peppermint oil	Colpermin®/Tillotts
	Saw palmetto	Permixon®/Pierre Fabre
	Essential phospholipids	Lipostabil®/Aventis
Critical stability	Vancomycin hydrochloride	Vancocin®/Lilly
Short half-life requiring frequent dosing	Captopril	Captoril®/Sankyo

hydroxypropyl methylcellulose (HPMC) [6]. Differences have been shown in the *in vitro* dissolution rate between gelatin and HPMC capsules [39]. However, the bioavailability of ibuprofen, a BCS Class II drug, delivered from the two capsule types was not statistically different when AUC and C_{max} values were compared. Recent advances made in the HPMC capsule technology have resulted in the achievement of similar *in vitro* dissolution rates to gelatin capsules.

The composition of the shell material for hard gelatin capsules for powder or liquid filling is identical, as are the capsule sizes. Which ever method is used to seal the capsules the zone between the cap and body of the capsule must be kept clean and free of fill material for an effective sealed capsule to be produced.

Soft shells are generally thicker than those of hard capsules and are most commonly manufactured from gelatin and in which, in contrast to hard capsules, a plasticizer, usually glycerin or sorbitol is used in addition to water, a colouring agent and/or an opacifier. Alternative shell materials to gelatin that are either commercially available or in development, include a combination of iota carrageenan and hydroxypropyl starch, a specific potato starch and polyvinyl alcohol and the advantages and disadvantages of alternative materials to gelatin have been discussed [9].

The presence of a plasticizer in the soft gelatin shell can give a relatively high permeability to oxygen and it has been reported [40] that at relative humidities of between 31 and 80%, the log of the oxygen permeability coefficient decreases linearly with decreasing glycerin content. Therefore it is likely that the oxygen permeability of a sealed hard gelatin capsule will be lower than that of a soft capsule. An assessment of the smell of highly odorous products which were transferred from commercially available soft capsules into hard capsules and sealed effectively demonstrated this to be the case [26]. In practice soft gelatin capsules can perform well as oxygen barriers by modification of the type and level of placticizer used. The primary function of the plasticizer in a soft capsule shell is to maintain the flexibility of the shell wall. The plasticizers are, however, hygroscopic and absorb moisture when exposed and it has been shown that the sorption of water by soft gelatin shells containing different plasticizers is considerably higher than is the case with hard gelatin capsules [41]. The commonly used plasticizers for soft gelatin shells also have the ability to solubilize water-soluble APIs. Armstrong et al. [42] have shown that such a water-soluble API can migrate into the shell of a soft capsule which can result in instability of the API and incomplete release of drug. For drugs of poor water-solubility this is much less likely to occur.

As previously mentioned, hard capsules are manufactured in a separate operation and supplied empty to the pharmaceutical company for in-house product development and manufacture. In contrast, soft capsules are formed, filled and sealed in one operation and therefore, as the process is fairly specialized, this is usually carried out by a limited number of contract manufacturers. Consequently, once it has been established that an API requires a liquid/semi-solid formulation approach the development activities must necessarily be contracted out. However, many companies prefer to keep these activities in-house for reasons of confidentiality and also because the API is usually in short supply in the early stages of product development.

4. Excipients and their suitability for formulation of hard gelatin capsule fill materials

The development of a solubilized oral formulation for a liquid-filled hard gelatin capsule is often driven by the need to increase or improve the reproducibility of the oral bioavailability of a poorly water-soluble drug. A good example of such an approach is exemplified by the research work undertaken with the immunosuppressant, cyclosporin A [43].

Numerous excipients are available for investigation, many of which have not been previously considered for use in capsule fill materials and these have been reviewed by Strickley [44]. In addition to biopharmaceutical considerations of a formulation the chemical and physical stability of the final dosage form are also important to consider. The following section of this manuscript will examine an approach to determining the suitability of excipients for fill material formulations for hard gelatin capsules that will produce a safe, effective, physically and chemical stable dosage form.

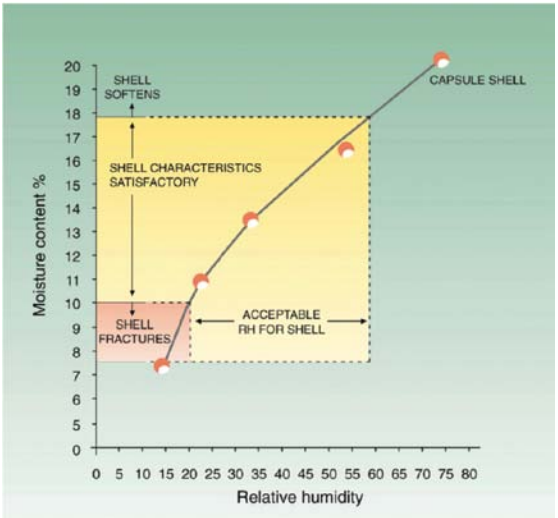

Fig. 1. Equilibrium moisture content of empty gelatin capsules shells stored at different relative humidities for 2 weeks at 20°C (Adapted from Ref. [45]). Reproduced with permission of Marcel Dekker Inc. via Copyright Clearance Center.

4.1. Moisture effects

The relationship between relative humidity, gelatin moisture content and capsule properties has been reported [45] and is depicted in Fig. 1. In addition, capsule brittleness as a function of relative humidity has also been evaluated [46].

Chang et al. [47] have described a sorption–desorption moisture transfer (SDMT) model and suggest that it can be used as a tool to guide a formulation scientist to select the optimal initial moisture contents for an empty capsule shell and the formulation that are necessary to avoid the incidence of brittle capsule problems. Another approach that has been reported [48] makes use of textural analysis at the experimental stage of formulation design and permits the identification of formulations that are compatible with gelatin capsules.

Table 2.

General Guide lines for filling liquids/semi-solid fill materials into hard gelatin capsules.

Parameter	Recommendation
Temperature of fill material	Max. ~70°C
Viscosity at the temperature of dosing	0.01–1Pa s
Dosing characteristics	Clean break from dosing nozzle Absence of “stringing”

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Any formulation approach must, therefore, consider the potential interaction between the fill material and the capsule wall. To illustrate this point the moisture content of a range of different molecular weight PEGs at a relative humidity of 55% has been shown to vary between 18.8% for PEG 200 and <1% for the solid PEGs [49,50]. Liquid PEGs can thus only be used in low concentrations for filling hard gelatin capsules.

A method for determining the potential interaction between a gelatin shell and a fill material has been described [51]. Capsules are filled with potential excipients and are stored under different relative humidity conditions between 2.5% and 65% for up to 2 weeks and the mechanical properties of the capsule and the weight change determined. Excipients that result in a weight change within the limit of ±2% can be recommended, and those found to be incompatible on this basis may be considered for use at a lower concentration, provided that the final formulation is subjected to the testing procedure described.

4.2. Dissolution

Gelatin comprises of a mixture of amino acids derived from collagen and the presence of certain functional groups, in particular aldehydes, have the potential to cross-link gelatin thereby altering the solubility of the polymer and producing a delay in dissolution [52]. A decrease in the dissolution rate of etodolac from hard capsules that

Table 3.

Lipophilic liquid vehicles compatible with hard gelatin capsules.

Refined specialty oils	Medium chain triglycerides and related esters
Arachis oil	Caprylic/capric triglycerides (Akomed E, Akomed R, Miglyol 810, Captex 355)
Castor oil	Medium chain triglyceride (Labrafac CC)
Cottonseed oil	Propylene glycol diester of caprylic/capric acid (Labrafac PG)
Maize (corn) oil	Propylene glycol monolaurate (Lauroglycol FCC)
Olive oil	Fractionated coconut oil (Miglyol 812)
Sesame oil	Caprylic/capric/diglyceryl succinate (Miglyol 829)
Soybean oil	Medium chain diesters of propylene glycols (Miglyol 840)
Sunflower oil	Partial ester of diglycerides with natural fatty acids (Softisan 645)

Quality may vary between different suppliers and also from batch to batch and should be routinely checked and the thermal history of excipients during manufacture should be recorded.

were exposed to conditions of high relative humidity and temperature during storage has been reported [53] but these conditions were found to have no significant effect on the *in vivo* performance of the dosage forms.

The dissolution testing of gelatin capsules has been the focus of interest of an FDA/Industry Working Group during which methods were developed to stress hard and soft gelatin capsules [54,55]. With the aid of gamma scintigraphy [56] researchers were able to show that cross-linked hard capsules exhibit the same gastric opening time as fresh capsules. In a further study [57] it was demonstrated that hard and soft cross-linked capsules were bioequivalent to unstressed capsules. The findings of the latter study have resulted in a modified USP monograph for dissolution testing of gelatin capsules that permits the use of enzymes in dissolution media when pellicle formation is deemed to cause a delay in dissolution of an API.

Table 4.

Semi-solid lipophilic vehicles and viscosity modifying substances compatible with hard gelatin capsules

Hydrogenated specialty oils	
– Arachis oil	Groundnut 36
– Castor oil	Cutina HR
– Cottonseed oil	Sterotex
– Palm oil	Softisan 154
– Soybean oil	Akosol 407
Aerosil	
Cetosteryl alcohol	
Cetyl alcohol	
Semi-synthetic glycerides based on hydrogenated vegetable oils (Gelucires 33/01, 39/01, 43/01)	
Glyceryl behenate (Compritol 888 ATO)	
Glyceryl palmitostearate (Precirol ATO 5)	
Hydrogenated coco-glycerides (Softisans 100, 142)	
Caprylic/capric/stearic triglycerid (Softisan 378)	
Bis-diglyceryl/caprylate/caprate/stearate/adipate (Softisan 649)	
Stearic acid	
Steryl alcohol	

Quality may vary between different suppliers and also from batch to batch and should be routinely checked and the thermal history of excipients during manufacture should be recorded.

Some of the excipients used in the formulation of the liquid fill for capsules may have, or generate on storage, low levels of aldehydes. A technique to monitor incompatibilities between gelatin shells and the fill materials has been described [51]. Of particular importance when using hot melt fills is the effect of the temperature, and the time held at temperature, on the potential for formation of aldehydes. The rate of cooling of a batch may also influence the structural characteristics of certain excipients which in turn may modify the release characteristics of an API from semi-solid matrices [58].

4.3. Physical Characteristics of Fill Formulations

Fill formulations for hard gelatin capsules may be Newtonian liquids, such as oils, thixotropic or shear thinning gels or semi-solid matrix products that are filled at elevated temperatures and in which the API is either dissolved or suspended as a fine dispersion. A model system in which lactose was dispersed in poloxamers of different viscosities revealed that the limiting concentration of the dispersed phase decreased as particle size decreased and as the molecular weight of the poloxamer increased [59]. Satisfactory filling characteristics were achieved with poloxamer F68 up to a concentration of 35% w/w when the mean particle size of lactose was 22.6 µm and 27.5% w/w when the mean particle size was 15.3 µm.

In principle any formulation composition found to be compatible with gelatin can be used provided that the viscosity of the fill material conforms to the requirements of the filling process. The uniformity of capsule fill weights was shown to decrease as the viscosity of thermosoftened fill materials increased [60,61]. In addition, fill formulations should not show stringing and should allow for a clean break from the dosing nozzle. The general guidelines for fill materials are listed in Table 2. Final modifications to the flow characteristics of the formulation may need to be made after trials on the specific machine and dispensing pump which will be used for filling the capsules.

4.4. Compatibility Screening Tests

The previously described tests have been performed on a range of excipients that can be filled into hard gelatin capsules and in which single excipients were tested. This level of fill represents the worst case scenario as usually a fill formulation for a specific API is comprised of a mixture of excipients. If an excipient is found to be

Table 5.

Solubilizing agents, surfactants, emulsifying agents and absorption enhancers compatible with hard gelatin capsules.

Propylene glycol monocaprylate (Capryol 90)
Polyglycolized glycerides (Gelucire 44/14, 50/13)
Polyoxyl-40 hydrogenated castor oil (Cremophor RH 40)
Glycerol monostearate/di-triglycerides + glycerin (Imwitor 191)
Glyceryl monocaprylate (Imwitor 308[a])
Glyceryl cocoate/citrate/lactate (Imwitor 380)
Glyceryl mono-di-caprylate/caprate (Imwitor 742)
Isosteryl diglyceryl succinate (Imwitor 780 K)
Glyceryl cocoate (Imwitor 928)
Glyceryl caprylate (Imwitor 988)
Oleoyl macrogol-8 glycerides (Labrafil M 1944 CS)
Linoleoyl macrogolglycerides (Labrafil M 2125 CS)
PEG-8 caprylic/capric glycerides (Labrasol)
Lauric acid
Propylene glycol laurate (Lauroglycol 90)
Oleic acid
PEG MW >4000
Polyglycerol dioleate (Plurol Oleique CC 497)
Polyoxyethylene-polyoxypropylene copolymer (Poloxamer 124, 188)
Partial glycerides of hydroxylated unsaturated fatty acids (Softigen 701)
PEG-6 caprylic/capric glycerides (Softigen 767)
Polyoxyethylene glyceryl trioleate (Tagat TO)
Polyoxyethylene(20)sorbitan monooleate (Tween 80)

[a] Glycerin content <5%.

Quality may vary between different suppliers and also from batch to batch and should be routinely checked and the thermal history of excipients during manufacture should be recorded.

incompatible with a capsule shell the need for that material, its concentration in a formulation and the compatibility of the final formulation must be evaluated prior to excluding the component from a formulation.

Compatible excipients have been categorized into three groups and are summarized in Tables 3, 4 and 5. The broad categories are lipophilic liquid vehicles, semi-solid lipophilic vehicles and viscosity modifiers for lipophilic liquid vehicles and solubilizing agents, surfactants, emulsifying agents and absorption enhancers.

Table 6.

Major capsule-filling machines for liquid filling of hard gelatin capsules up to production scale.

Machine type	Filling action	Approximate filling rate (capsules/h)
Robert Bosch GmbH		
GKF 1400 L	Intermittent motion	60,000
GKF 701 L		36,000
Harro Hoefliger GmbH		
KFM III-C	Intermittent motion	25,000
IMA Zanasi Division		
Zanasi 6/12	All intermittent motion	6,000-12,000
Zanasi 25/40		25,000-40,000
Zanasi Lab 8/16		8,000-16,000
Zanasi Plus 32E/48E/ 70E/85E		32,000–85,000
MG2		
MG Compact	All continuous motion	6,000-96,000
MG Futura		6,000-96,000
Planeta 100		100,000
Qualicaps		
F-5	All continuous motion	4,000
F-40		30,000
F-80		60,000
F-120		90,000
F-150		120,000
Schaefer Technologies Inc.		
LF-10	Semi-automatic	10,000-25,000
Bonapace		
IN-CAP	Intermittent motion	3,000

5 Equipment for filling and sending liquids into hard gelatin capsules

5.1 Capsule Filling

The equipment that is necessary to enable automatic filling of hard gelatin capsules with either hot or cold liquid is available in a range of filling rates, from laboratory to production scale. The liquid to be filled is usually dispensed by volume and the machines all meet the requirements reported by Cole [62] to allow for the industrial manufacture of liquid-filled capsules. The machines that are available are manufactured by companies that supply the industry with conventional capsule-filling equipment and are listed in Table 6.

A capsule-filling machine for dosing hard capsules with high viscosity pastes and which operates by extrusion of a cylinder of material directly into a capsule body has been described [63] and analternate system for filling highly

Fig. 2. The CFS 1200 capsule liquid filling and sealing machine.

viscous materials has been developed [64] and operates by filling hot mixtures under high pressure by means of time controlled pneumatic valves and which has been used in a production environment for many years.

A unique machine (CFS 1200™) that has been developed by Capsugel for development and small scale clinical batch manufacture not only fills material into hard capsules but also seals the capsules. The machine is capable of filling up to 1,200 capsules/h with hot melt or thixotropic fills and is depicted in Fig.2.

Table 7.

Stages during the sealing of liquid-filled hard gelatin capsules.

Stage	Process
1. Moisturizing	50:50 water/ethanol mixture sprayed onto join and capillary action draws liquid into the space between body and cap.
	Excess fluid removed by suction.
	Melting point of gelatin lowered by presence of water.
2. Warming	Application of gentle heat of approx. 45°C-50°C completes the melting over a period of about one min and the two gelatin layers are fused together to form a complete 360° seal.
3. Setting	Gelatin setting process is completed while the product returns to room temperature.
	This process is best carried out on trays.

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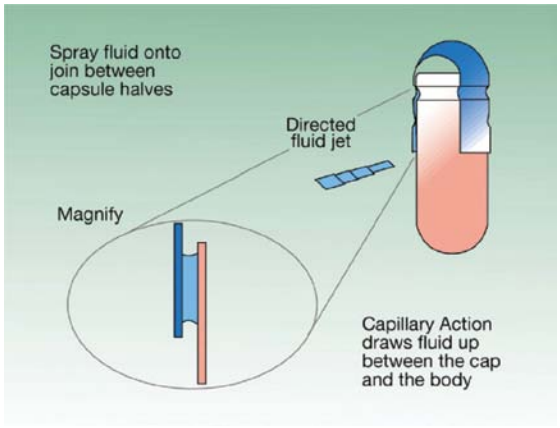

Fig. 3. Illustration of spraying process to moisturize the space between cap and body of the capsule. Reproduced with permission of Marcel Dekker Inc. via Copyright Clearance Center.

During the early stages of drug development API is often in short supply and there are many competing needs for experimental material. Therefore the ability to produce small uniform and representative batches of formulated drug is of the utmost importance. Whether the NME is poorly soluble, highly toxic, of low melting point or has a critical stability profile, equipment is commercially available which provides the industry with the option to keep its development activities in-house.

5.2. Capsule Sealing

Whereas soft gelatin capsules are formed, filled and sealed in one operation, hard gelatin capsules containing liquids or semisolids are filled and sealed sequentially. Different methods have been developed for sealing hard gelatin capsules [65]. The two commonly used industrial methods for sealing of capsules are banding, in which a gelatin band is applied to the overlap between the cap and body of the capsule, and sealing, in which a hydroalcoholic solution is applied to the overlap and the two technologies have been compared [62]. Both methods are industrially feasible and are described in the General Information section of the USP on capsules [66]. The banding of hard gelatin capsules has also been described by Bowtle [67] and Rowley [50].

The LEMS capsule sealing process, first described by Wittwer [65] and subsequently by Cadé et al. [26] uses the principle of lowering the melting point of gelatin by the application of moisture to the area between the capsule shell body and capsule cap and the stages of the process are summarized in Table 7 and depicted in Fig. 3.

The commercially available machine (LEMS™ 60) for sealing capsules, which is manufactured by Capsugel, has a sealing capacity of 60,000 capsules/h and is thus compatible with the filling machines shown in Table 6.

The Licaps™ Drug Delivery System comprises bulk liquid preparation tanks, filling machine, conveyor belt, LEMS™ sealing machine and inspection system. In the case of hot melt fills the capsules can be cooled if necessary prior to sealing, by applying a cooling system to the conveyor belt. The complete manufacturing set-up is shown in Fig. 4.

6. Conclusions

To achieve absorption of a poorly water-soluble drug from the GIT requires an innovative formulation approach. Encapsulation of formulations as liquids or semi-solids provides opportunities for delivering such drugs with reproducible absorption and acceptable bioavailability. Low dose or highly potent API, low melting point API and those with a critical stability profile are ideal candidates for encapsulation as liquids or semi-solids in to either soft or hard capsules. Additional opportunities offered by the hard capsule include the option of using laboratory scale equipment in-house to manufacture small batches for stability and clinical trial purposes in the early stages of drug development during which API supply is usually limited. The filling and sealing of liquids and semi-solids in to hard capsules has a significant advantage over soft capsule manufacture: on the one hand there is no need for a time consuming gel mass preparation because empty hard capsules are ready for use; on the other hand the time taken from capsule filling to packaging of the filled sealed capsules only takes from 6 to 12 h. Soft capsule manufacture due to gel mass preparation and the time consuming drying process may last from 2 to 5 days. During soft capsule forming, the gelatin films contain a significant amount of water and there is a high potential for water to migrate into the fill and for components of the fill to migrate into the soft capsule shell. Hard gelatin capsules have a controlled and significantly lower moisture level which may be lowered further to limit possible water exchange with the fill. However, as with any process, the filling of liquids and semisolids into capsules also presents challenges to the formulation scientist. The stability of an API in a liquid dosage form, as opposed to a solid dosage form is, in itself, a challenge, as is matching the formulation with the characteristics of the capsule shell and the dosing system of the capsule-filling machine. In cases where gelatin as a capsule material is not suitable, alternative polymers for capsule production are available.

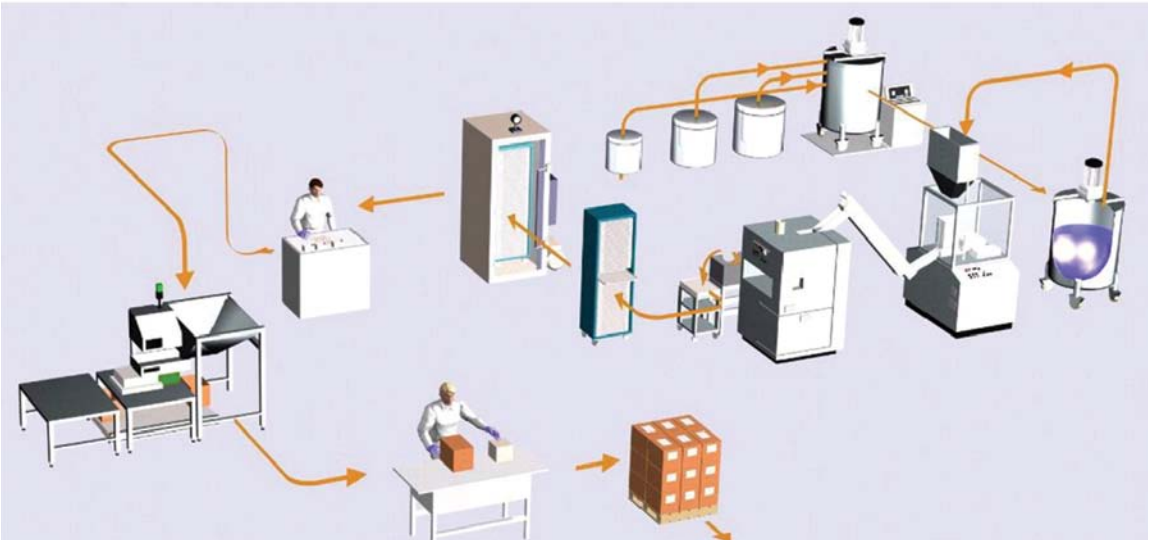

Fig. 4. Manufacturing set-up for the Licaps™ Drug Delivery System.

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