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Hard gelatin capsules today – and tomorrow

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The capsule is one of the oldest dosage forms in pharmaceutical history, known to the ancient Egyptians. [1] The earliest European reference is contained in a travel account of 1730 which mentions the pharmacist de Pauli from Vienna, who produced oval-shaped capsules in the hope of covering up the unpleasant taste of the pure turpentine he prescribed for people suffering from gout. [2]

A further 100 years were to pass before the first gelatin capsule appeared. The first patent for such a product was granted in 1834 to the pharmacist Joseph Gérard Auguste Dublanc and the pharmacy student François Achille Barnabé Mothès. [3] Mothès, who ended his collaboration with Dublanc in 1837 [4], continued to work on improving the gelatin capsule and to take out patents for the manufacture and use of capsules.

Mothès' invention was so successful that, by the following year, capsules were being produced in many different parts of the world. [5] Eventually, this resulted in several more patents for gelatin capsules being taken out by others, not least to circumvent those held by Mothès.

The Frenchman Jules César Lehuby was successful in this strategy and, in 1846, was granted a patent for his 'medicine coverings', which formed the basis of his future inventions.[6] He was also the first to suggest two-piece capsules, which he produced by dipping silver-coated metal pins into a gelatin solution and then drying them.

Despite the great interest in Lehuby's patent, which describes the principle of hard-gelatin capsule manufacturing that is still used today, technical difficulties in manufacturing the separate fitted sections – the body and the cap – stopped further development of this dosage form for another century.

It was in 1931 that Arthur Colton, on behalf of Parke, Davis & Co., succeeded in designing a machine which simultaneously manufactured both bodies and caps and fitted them together to form a hard gelatin capsule. [7] It is amazing to realise that a machine originally built in 1931 still represents the basic design of today's machinery. Only minor modifications have been made to it since that time, in the interests of improved product quality and greater technical efficiency.

Hard gelatin capsules – a growing market

Hard gelatin capsules are a modern dosage form for medicinal use, stemming from the increased emphasis on pharmacokinetics found in drug development today. This has considerably expanded the range of possible formulations utilising hard gelatin capsules as a simple dosage form for oral drug delivery. Nowadays, modern capsule-filling machines can produce up to

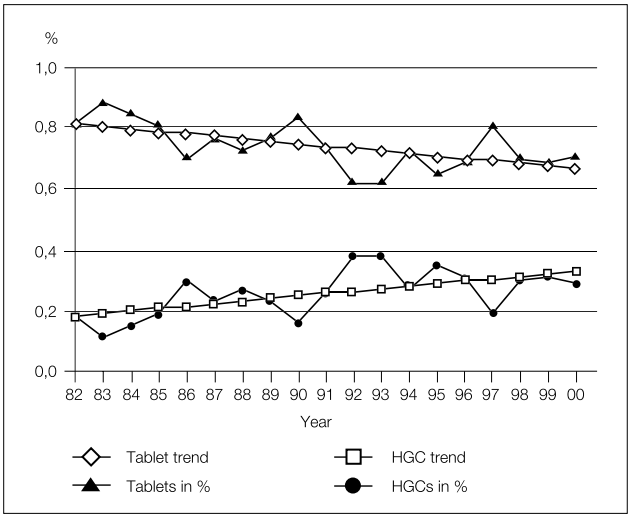

Figure 1: Comparison of new chemical entities formulated as hard gelatin capsules and tablets since 1982.

200,000 capsules an hour and are also capable of filling a number of different substances in a single process run.

These developments probably account for the fact that use of the hard gelatin capsule has grown steadily over the years. Between 1970 and 1975, capsules showed sales growth rates ranging from 8% to 21% in the four largest European markets. [8]

And it is a continuing trend. The hard gelatin capsule is increasingly being chosen for new medicines in solid oral dosage form. In 1982, only 17.5% of newly-licensed products were presented as hard gelatin capsules. By 1996 the figure had already reached 34% (Figure 1).

Hard gelatin capsules as a dosage form

In the development of new medicines, there are several problems to be solved. As well as the formulation, and its important stability and release-characteristics,control and reproducibility of the production process are other factors to be taken into account and, increasingly, research costs and development timeframes have also to be considered.

When it comes to a decision at the end of phase II, which dosage form will be developed for the market, high production costs of hard gelatin capsule products are generally assumed. This assumption is valid if the production costs are limited to the comparison of the excipient costs only. When taking into account the total manufacturing costs, which include the hidden costs coming from process equipment, GMP space required, total production time, in-process-controls, analytical, cleaning and validation work the comparison easily turns out in favor of the capsule formulation [9].

More. As the development costs for new medicines continue to rise, it is becoming imperative to obtain international registration for the formulation. Ensuring that all new entities conform to the various pharmacopoeias and regulatory requirements is yet another task for the formulation scientist. Companies are aiming at achieving – reproducibly – a consistency of product quality acceptable on a worldwide scale.

As will be pointed out in the following chapters, the simplicity of hard gelatin capsule formulation and manufacturing as well as the versatility of this dosage form substantially supports these requirements.

Pharmacopoeial monographs

When talking about hard gelatin capsules, powder and granular fillings are what spring to mind. These products still account for most hard gelatin capsules on the market, which is why the monograph on capsules in the German Pharmacopoeia DAB 10 (1996) describes the fillings for hard gelatin capsules as 'normally in solid form (powder or granules)'.

In fact, historically, the first hard gelatin capsules were actually developed for liquid medicines. Thanks to the gelatin capsule, it was possible to formulate a new dosage form for liquid balsam copaivae, which had been used during the Napoleonic wars as a cure for vascular diseases. This was of great importance, as the substance causes severe nausea if taken as an oral solution. [10]

Now, the German monograph on capsules urgently needs revision in the light of the increasing number of new-wave hard gelatin products coming onto the market which include fillings in sustained release pellets and – as per the tradition – in liquid and semi-solid form.

The European Pharmacopoeia (Eur. Ph.) describes capsules as follows: 'Capsules are solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active ingredient. They are intended for oral administration.'

Also included in its monograph is a description of hard capsules: 'Hard capsules have shells consisting of two cylindrical sections, one end of which is rounded and closed, the other open. The active ingredient or ingredients, usually in solid form (powder or granules) are filled into one of the sections which is then closed by slipping the other section over it. The security of the closure may be strengthened by suitable means.'

A similar general description of the capsule can also be found in the US Pharmacopeia (USP 24). It defines capsules as solid dosage forms in which the active ingredients are sealed in a hard or soft container or shell. In contrast to the European monograph, the USP also mentions starch and other substances used in the production of the shell.

Shapes of hard gelatin capsules

The general descriptions given in pharmacopoeias hardly do justice to the variety of shapes on offer today. These have been developed over the last few years as a result of increased demand and requirements,

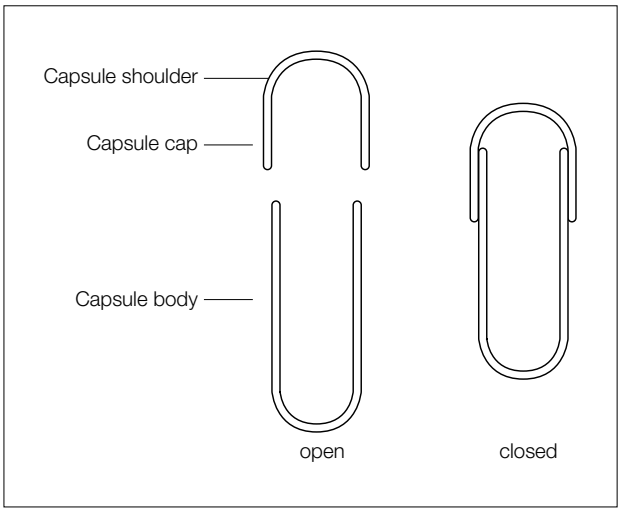

Figure 2: Standard hard gelatin capsule.

aided by the introduction of fully-automatic filling machines. In a single operation, automatic capsule-filling machines line up and rectify the hard gelatin capsules, separate body and cap, fill the body, join cap and body together (for closing), and eject the filled capsule.

Where capsule design is concerned, its main features are its two fitted sections, body and cap. In the beginning capsules had smooth edges (Figure 2), which could slide freely against each other.

During manufacture, pressure frequently builds up within the capsules as a result of the speed of the closing process and of mechanical strain during production and packaging, and this often results in capsules of varying length, and a risk of the capsules bursting after filling. Two encircling grooves were introduced, one placed around the body just below the rim, the other around the cap just under the top to interlock when body and cap are pressed together (Figure 3), ensuring firm closure and equal lengths.

However, this does not in itself resolve the problem with the only lightly fitted together cap and body that tend to fall apart during transport or in the filling machines. This problem needed the invention of notches on the cap just below the rim, which allow temporary closure of the sections. The capsule is held securely closed during transportation but can easily be opened by the filling machine (Figure 3).

As the capacity of filling machines increased, priority turned to improving hard gelatin capsules in terms of their safe and speedy closure following filling. Body and cap are designed to fit only if the two parts are precisely in line; the slightest sideways movement of the capsule halves during the closing process results in splitting or denting. This problem was solved with the invention of a tapered rim on the body section of the capsule (Figure 4).

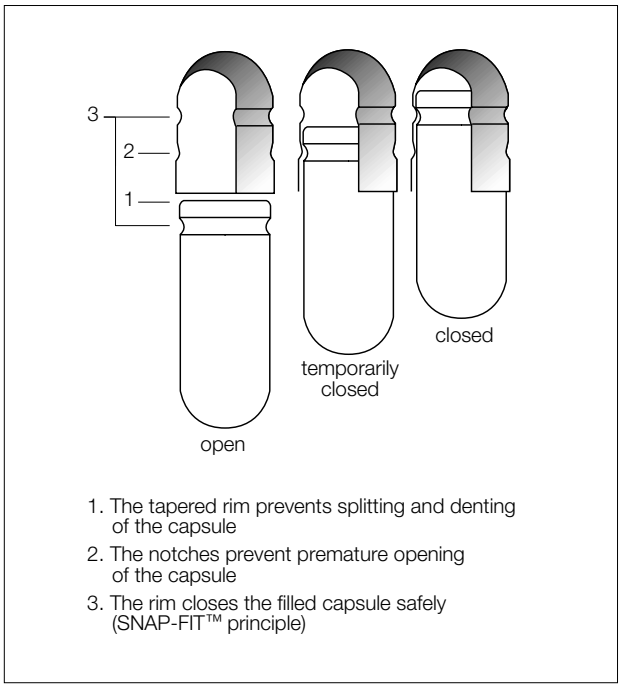

Figure 3: Recent hard gelatin capsule with features (notches or dimples) for pre-closing; closing features (e.g. SNAP-FIT™) and tapered rim (e.g. CONI-SNAP™).

During the closing process, the cap's position can be adjusted to a certain extent by means of the tapered rim, so enabling the capsule halves to fit properly. The approach reduces the number of defects due to splitting or denting by an average of 88%. [11]

To prevent pressure build-up in the capsule owing to the speed of the closing process, the airvent closure has come onto the scene. This allows for the escape of air between body and cap. The principle of all air-vent closures on the market is to reduce the air space left between body and cap after filling. Examples such as SNAP-FIT™ work by flattening the body rim.

Another recent demand has been for capsules that can hold liquid or semi-solid substances (LICAPS™). LICAPS™ is a gelatin capsule exclusively designed to optimize liquid filling by a special body design and the missing air-vent to prevent leakage before sealing

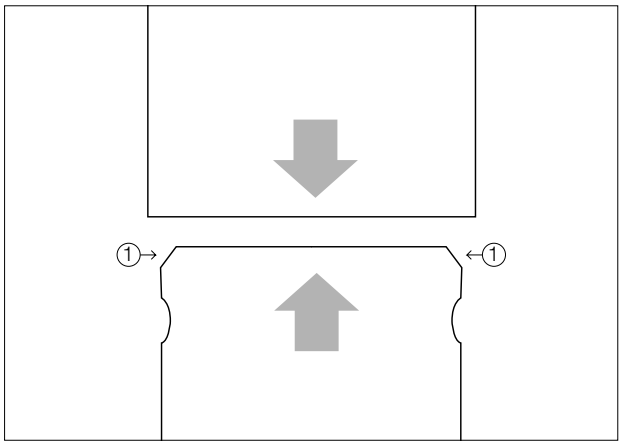

Figure 4: Design of the tapered rim ① of the capsule body (e.g. CONI-SNAP™).

(Figure 5). Moreover, the six dimples maximize the area for sealing of the two-piece hard gelatin capsule by a hydroalcoholic fusion process described later in this article (see LEMS™).

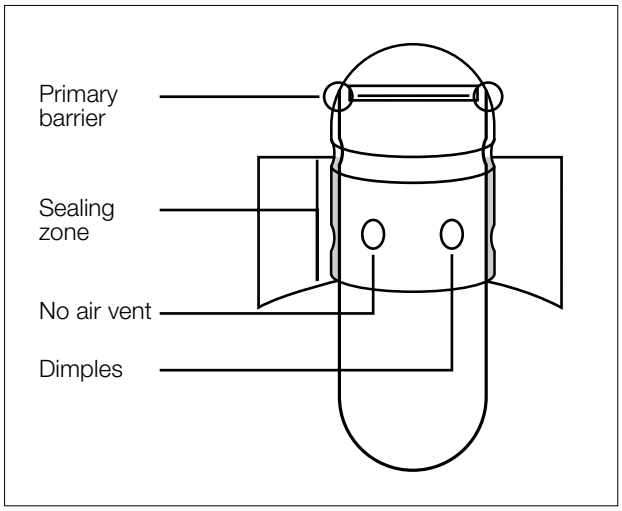

Figure 5: Features of the LICAPS™.

Especially for blinding purposes of clinical trials, hard gelatin capsules that are virtually impossible to re-open after filling are required. There is available the DBcaps™ capsule with a cap covering most of the body so that only the rounded end of the body is visible, which impedes opening (Figure 6).

DB caps™ are hard gelatin capsules whose size, colour and shape meet the worldwide requirements

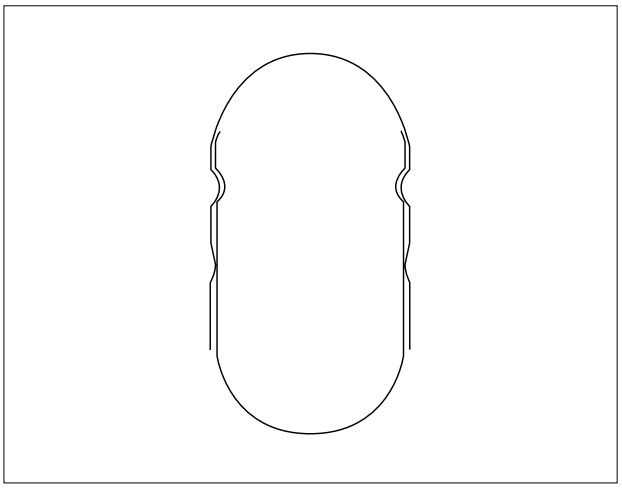

Figure 6: Hard gelatin capsule with the cap that covers most of the body (e.g. DB caps™).

of double-blind clinical trials. They are available in three different sizes and cater for single doses or formulations up to a diameter of 9 mm. Different neutral colours recognized for blinding are available, which are internationally accepted for medicinal use.

The capsules cannot be reopened once they have been closed. This ensures that the administration of placebo, test drug and reference preparations, or of sustained-release doses is consistently accurate and can not be identified by the doctor or patient. Capsules for double-blind trials are also available in small quantities and hospital pharmacists are therefore in the position to provide individual test medications.

Table 1 lists the capsule sizes on the market and their respective filling capacities.

Capsule size	Capsule volume in ml	Capacity in mg powder density 0.6	0.8	1.0	1.2 g/ml
000	1.37	822	1096	1370	1644
00el	1.02	612	816	1020	1224
00	0.91	546	728	910	1092
0el	078	468	624	780	936
0	0.68	408	544	680	816
1	0.50	300	400	500	600
2	0.37	222	296	370	444
3	0.30	180	240	300	360
4	0.21	126	168	210	252
5	0.10	78	104	130	156

Table 1: Examples for hard gelatin capsule dimensions and filling capacities.

Even more recent developments are capsules specifically designed for preclinical research (PC caps™).

PC caps™ are capsules for preclinical and animal trials. They could be described as size 9 capsules. The dimensions of the closed capsule are 7.18 mm in length and 2.06 mm in diameter, with a volume of 0.2 ml. They are especially suitable for administering an exact quantity of substances to rodents. They help to avoid a number of stress factors such as unpleasant taste, irritation of the mucous membranes and regurgitation, so reducing the overall strain on the animal during the experiment.

Hard gelatin capsules with powder filling

The production process

Immediate-release capsules with a simple powder filling are the best-known type of hard gelatin capsules. They require only a few manufacturing process steps. Usually, it is easy to mix the active substance with excipients and to fill the mix into the capsules.

Depending on the process a light pre-compression, to form a so-called 'plug', might also be necessary. The force used for pre-compression is normally between 20N and 30N, far below the usual pressure for tablets of 3 x 10^4N [12]. In comparison with conventional tablet production, capsule production does not require expensive and time-consuming operations like repeated mixing and sieving, or granulation and compression (Table 2).

In contrast, other types of oral dosage forms might also require a considerable number of excipients as well as additional processing steps. This results in higher costs, partly due to the cost of excipients, but also to increased analysis and validation costs, which can add as much as 15% to the overall cost of production. [13]

Tablets	Capsules
1. Weighing	1. Weighing
2. Preparing ingredients	2. Preparing ingredients
3. Mixing	3. Mixing
4. Granulating	4. Filling into capsules
5. Drying	5. Packing
6. Sieving	
7. Addition of lubricants/ mixing/sieving, as necessary	
8. Compression	
9. Packing	

Table 2: Production process operations in the manufacture of tablets and capsules.

Use of excipients

One of the major initiatives of the pharmaceutical industry to reduce production costs in the past decade was dedicated to the reduction of the raw materials and its stocks. The average number of excipients in tablet, sugar coated tablet and hard gelatin capsule formulations are shown in Table 3. Hard gelatin capsules usually require between one and four excipients, while some five to eight are needed in tablet formulation. Sugar coated tablets require at least nine excipients, since a special formulation is used for the coating [14]. Moreover, the addition of any excipient carries the potential risk for promoting degradation of the drug molecule by an interaction with its functional groups or residues [15].

Number of excipients	Capsules	Tablets	Sugar coated tablets
1-4	18	3	-
5-8	5	15	-
9 or more	-	5	6

Table 3: Number of excipients needed for the manufacture of capsule, tablet and sugar coated tablet products.

Considering that more and more tablets are similarly undergoing a costly coating process, the number of excipients and operations involved in their production may actually be greater. It can therefore be assumed that, in a large number of cases, production costs for hard gelatin capsules are the same as – or even less than – those for tabletting. Yet the misconception remains that hard gelatin capsules are an expensive form of medication.

As well as diluents and lubricants, other excipients used in the manufacture of hard gelatin capsules include colloidal silicon dioxide for improved flow characteristics and reduced adhesion of the substance to metal parts in the filling machine, and disintegrants and wetting agents to facilitate release.

Some excipients might have several functions. Talcum, for instance, serves as a lubricant in concentrations below 5%. At higher concentrations, it is mainly considered a filler. [16] And besides being an

excellent filler, microcrystalline cellulose also serves as a disintegrant. [17]

In addition, the functions of excipients in hard gelatin capsules can be different from their functions in tablets. Starch, which is commonly added to tablets as a disintegrant owing to its macerating properties of 5% to 10%, might be used as a filler in hard gelatin capsules because the macerating properties are not strong enough to really disintegrate the lightly compressed substances in hard gelatin capsules. [16]

Diluents

→ Improved plug formation and compression

- Mannitol
- Microcrystalline cellulose
- Lactose
- Starch 1500
- Corn starch

Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Glyceryl monostearate
- Stearic acid

Glidants

→ Improved powder flow properties

- Aerosil
- Talcum

Disintegrants

→ To ensure disintegration of powder mixture

- Croscaramellose
- Corn starch
- Crospovidone
- Starch 1500
- Sodium glycyl starch
- Alginic acid

Wetting agents

→ Improved water penetration into powder mixture

- Sodium lauryl sulphate
- Tween 80

Table 4: Excipients used in formulations of immediate-release hard gelatin capsules.

The characteristics of many excipients depend on storage conditions (temperature or humidity, for instance). Excipients that show hysteresis in their sorption-isotherms – as, for example, gelatin, starch or microcrystalline cellulose – might show different levels of absorbed water on their surfaces even when subject to the same humidity in the controlled conditions of the production room, due to individual storage conditions. It is therefore advisable to dry these excipients before use. [17]

The stability of many compounds is pH dependent. Acetylsalicylic acid for example is a compound that is most stable at a pH 2.4. In a dry formulation acetylsalicylic acid is in contact with the surface of the particles of all the other excipients. As the humidity in the environment will always lead to absorption of moisture on the surface, the particles will be surrounded by a mono-layer of a saturated solution. To optimize product stability, the excipients need to be selected according to their surface acidity in the dry state (pH eq) rather than to add buffer agents [18-21].

The most common excipients used for the formulation of drugs in hard gelatin capsules, along with their functions, are listed in Table 4.

When formulating hard gelatin capsules for immediate- release, attention should be paid to establishing a reproducible product dissolution profile. In the fluid environment of the stomach, the shell of the capsule starts to soften and dissolve within one or two minutes, and comes apart at its weakest point, the capsule shoulder (see Figure 2).

Consequently, the uncompressed or only slightly compacted content comes into contact with water. If the capsule formulation is sufficiently hydrophilic or contains disintegrant or a wetting agent, water can penetrate the powder. The capsule disintegrates and its contents are released. Hard gelatin capsules are fully disintegrated within about 10 minutes. [22, 23]

To sum up, we would like to stress again that hard gelatin capsules are simple in their formulation and production and that their disintegration is both known and controllable. Hard gelatin capsules are actually easier and quicker to formulate and produce, whatever the batch size, compared with other solid oral dosage forms. Indeed, by using hard gelatin capsules it is possible to produce small or very small batch sizes on manual or semi-automatic filling machines.

This is of major advantage to the pharmaceutical industry when there is only a very limited quantity of active substance available for formulation and initial clinical testing. Dispensing pharmacies and clinics also gain by using hard gelatin capsules when they have to produce small quantities or when they have to prepare a single prescription as a solid oral dosage form.

Hard gelatin capsules are a means of providing patients with optimum therapy. They can be produced as individual medication for a single patient, to provide specific doses and combinations of substances, or to improve the patient's compliance. It is also possible to produce even complicated medications for clinical trial purposes.

Product requirements

One of the key advantages in formulating as immediate- release hard gelatin capsules is that it is a way of ensuring that each capsule contains the exact dose (Ph. Eur 2.9.6. Uniformity of content of single-dose preparations, and Ph. Eur 2.9.5. Uniformity of mass of single-dose preparations), and that this dose is released as quickly as possible to ensure bioavailability (Ph. Eur 2.9.1. Disintegration of tablets and capsules).

For optimum machine-filling performance, the powder must be of the right flow and density; the densities of the excipients and the drug should therefore be similar [24]. The flow is of special importance as problems can arise not only from poor flow properties but also from flow properties that are too efficient; for example, when a dosator, type of filling machine is used and the height of the powder bed varies. [25] In addition, the powder should show only minimal adhesive characteristics. [24]

High speed filling machines today mainly use two filling principles referred to as “dosator type” or “dosing disk or tamping type”. The dosator principle uses a dosing tube that dip in a powder bed that is normally two times higher than the final plug length. During the dipping and by the dosator piston movement, the powder is densified to form a cohesive plug. The dosing tube transfers the plug to the capsule body for ejection. The dosing disk principle is based on filling chambers that are bored into the dosing disk. Powder flows into the filling chambers followed by a slight compression by a tamping punch, which is repeated five times before the plug is ejected into the capsule body through the hole of the tamping disk.

To address the need of each company and their specific products, the capsule filling machine manufacturer

Machine	Dosing principle	Output caps / h	Products to be filled
Bosch *Further information : www.bosch.de*			
GKF 400	Dosing disk	24.000	Powder, pellets
GKF 700	Dosing disk	42.000	Powder, pellets, tablets, liquids
GKF 2000	Dosing disk	150.000	Powder, pellets, microtablets, tablets
Dott. Bonapace *Further information : www.dottbonapace.com*			
IN-CAP	Auger	3.000	Powder, pellets, tablets
Harro Höfliger *Further information : www.hoefliger.de*			
KFM III-C	Dosator or dosing disk	25.000	Powders, pellets, tablets, liquids
IMA *Further information : www.ima.it*			
ZANASI 6 / 12 : 25 / 40	Dosator	6.000 – 40.000	Powder, pellets, tablets, liquids
ZANASI Plus 8 / 16 / 32 / 48 / 70 / 85	Dosator	8.000 – 85.000	Powder, pellets, tablets, liquids
MATIC 60	Dosator	60.000	Powder, pellets
MATIC 90	Dosator	90.000	Powder, pellets
MATIC 120	Dosator	120.000	Powder, pellets
IMATIC 100	Dosator	100.000	Powder; pellets
IMATIC 150	Dosator	150.000	Powder, pellets
IMATIC 200	Dosator	200.000	Powder, pellets
IMPRESSA 130	Dosing disk	130.000	Powder
MG2 *Further information : www.mg2.it*			
SUPREMA	Dosator	48000	Powder, pellets
MG COMPACT	Dosator	6.000 – 96.000	Powder, pellets, tablets, capsules, liquids
MG FUTURA	Dosator	6.000 – 96.000	Powder, pellets, tablets, capsules, liquids
PLANETA 100	Dosator	100.000	Powder, pellets, tablets, liquids
G 37/N	Dosator	100.000	Powder, pellets, tablets
G 70	Dosator	70.000	Powder, pellets, tablets
G 100	Dosator	100.000	Powder, pellets, tablets
G 140	Dosator	140.000	Powder, pellets, tablets
G 250	Dosator	200.000	Powder, pellets, tablets
Romaco-Macofar *Further information : www.romaco.com*			
CD 5 and 20	Dosator	6.000 – 20.000	Powder, pellets, tablets
CD 40	Dosator	40.000	Powder, pellets, tablets
CD 60	Dosator	66.000	Powder, pellets, tablets

Table 5: Capsule filling machines on the market and it major features.

offer a wide range of full automatic capsule filling machines that range from 6.000 – 200.000 capsules an hour. Several of this machines are highly flexible and can fill different products in one cycle, which is especially interesting for drug delivery systems with different release profiles or drug products. The most common used capsule filling machines are listed in table 5.

To predict the required capsule size as well as to estimate and adjust powder flow and compressibility if requested, the Carr's Index is used [26].

$$\text{Carr's Index} = \frac{\text{Tapped density - bulk density}}{\text{Bulk density}} \times 100$$

A Carr's index of < 15 % is referred to as a very good flow, while 16-26 % are good, 27 – 35 are fairly good and > 35 % the flow properties are considered as poor.

Research by Heda demonstrated that there is no significant difference in the formulation requirements for a dosator or a dosing disk filling principle. However, the optimum Carr's index for a dosator type was calculated with 25 – 35 %, while the optimum Carr's index of a dosing disk type is between 18 – 30 %. [27].

Decisions on the type and quantity of excipients such as diluents, disintegrants, lubricants and wetting agents are therefore of major importance in the formulation process. But, above all, the formulation depends on the required quantity of an active and its physico-chemical properties.

Now, to aid in this process, Capsugel has developed a computer-based Expert System for the formulation of immediate-release hard gelatin capsules. This work has been carried out in conjunction with more than 30 pharmaceutical companies, as well as the Universities of London (Europe), Kyoto (Japan), and Maryland (USA) and some 50 other experts.

At the heart of the system lie three databases. The first comprises data on products that are available on the market. The second contains data from publications and from the experience of the experts involved, while the third is based around the results of experiments and mathematical and statistical calculations on the effect of single excipients on formulations, carried out by the participating university of London. [28]

There now follows a briefing on the most important parameters and their effects on formulations of hard gelatin capsules.

Important parameters for the formulation of hard gelatin capsules with powder formulation

Compatibility with gelatin

When starting to formulate a medicine in hard gelatin capsule form, the first thing to study is its compatibility with the gelatin shell. Incompatibilities are known to occur; for instance, with certain substances that contain reactive aldehydes. The aldehydes can react with the gelatin by forming crosslinks.

A recent review has shown that cross-linking is not inevitable, but depends on several mechanisms. [29] The main contributory factors are storage stress (high temperatures, high humidity, excessive light exposure) and the presence of aldehydes (for example, formaldehyde).

In the case of reactivity of the gelatin, which consists of a mixture of water-soluble proteins, lysine residues are mainly responsible for cross-linking, either within a gelatin strand (intra-strand cross-linking) or between separate strands (interstrand cross-linking).

It is sometimes possible to reverse the type of chemical reaction involved, but this will depend on the pH level or the presence of enzymes. It has been shown, for example, that reducing the release rate in in vitro dissolution tests bears no relationship to the in vivo dissolution rate and the consequent bioavailability of substances. [30, 31] However, adding the enzymes pepsin and pancreatin to the dissolution medium prevents the inhibitory factors from taking effect. [32] This result has led to the assumption that inhibited dissolution is due to the test conditions.

The USP 24 propose therefore that pepsin (for acid media) and pancreatin (for alkaline media) can be added in dissolution tests aimed at establishing the likely in vivo dissolution properties (Two Tier Dissolution Test). Only in cases where the enzymes have been added and the test still shows poor dissolution should a negative effect due to cross-linking be assumed.

A further incompatibility can be caused by the water content of the gelatin shell. If a substance is highly hygroscopic, it might absorb water from the capsule shell. This process can lead to brittleness of the shell, which might break under mechanical strain. If the drug substance in the capsule is sensitive to humidity the water content of the shell, which is normally between 13% and 16%, can lead to the degradation of the drug substances.

Doses

The dose of the drug active that is to be formulated is the main parameter for a suitable formulation. For low doses in the milligramme range, homogeneity of the substance within the powder has to be maintained. For doses in excess of 100 mg or in the smallest suitable capsule size, the properties of the active are of key importance, as the quantities of excipients are minimal.

High concentrations of drug active usually lead to difficulties during the filling process, proportional to the concentration of the active in the formulation. Problems at this stage can be prevented by a properly thought-through choice of diluents and adequate quantities of lubricants. [33]

Doses over 600 mg in powder form are virtually impossible to put into capsules of acceptable size. It has, though, been possible to produce such doses in hard gelatin capsule form by increasing the density of the formulation; for instance, by granulation. Granulation usually leads to an improvement of parameters such as product flow. It is also possible to improve the dissolution rate of substances by granulation, due to increased dispersion of the drug active in the granules.

Shape of particles

To achieve the specification for content uniformity on filling machines, it is vital to have an adequate powder flow. Poor powder flow is characterised by the formation of a central cavity ('rat-holing') when flowing out of a cylinder, while the powder at the edge remains static. [34]

Product flow is mainly defined by the shape of the particles as well as by inter-particulate cohesion and surface films (sorption water). The fluidity of anisometric particles such as needle-shaped, plateshaped or prismatic particles is peculiar, insofar as it not only follows the primary direction but also a secondary direction according to the orientation of the particles. [35] This is the reason why anisometric particles result in significant differences in the bulk and tap density. The mechanical vibration is strong enough to allow the particles to gain a higher grade of order.

Isometric – for example, round – particles are already in highly compact order, forming the most dense shape. [36] So, for hard gelatin capsules the drug substances and excipients should preferably be of isometric shapes. In the case of anisometric particles, grinding or granulation should be considered.

Solubility

Solubility of the drug active and the excipients is the major contributory factor in disintegration and dissolution. The more water-soluble the formulation, the quicker it disintegrates and releases the substance. In the case of substances which are poorly soluble in water, disintegration and release depend heavily on disintegrants and diluents. [33]

Particle size

The particle size of the drug active is critically important to the homogeneity and fluidity of the powder. By decreasing the particle size the electrostatic charge increases. While leaving the filling funnel, this may lead to the formation of agglomerates, which hinder the flow during the filling process. [37]

For the filling of hard gelatin capsules, experience suggests a minimum particle size of 10µm. If the particle size is more than 60µm, the fluidity of the powder starts to deteriorate, which leads to unwanted deviations of the filling weights. [33] The size of particles should ideally measure between 10µm and 150µm. Excipients should be chosen in relation to the particle size of the drug active.

Hygroscopic compounds

Hygroscopic compounds can have a negative influence on the formulation of hard gelatin capsules, in a number of ways. Firstly, hygroscopic compounds can absorb water out of the shell, which normally has a water content of 13% to 16 %. This can subsequently lead to brittleness and drying-out of the shell.

Secondly, the absorption of moisture during production can lead to the build-up of a sorption film that affects the fluidity of the powder mix filling. Ideally, hygroscopic compounds should be combined with the diluent mannitol, as mannitol is relatively inert where water absorption is concerned. [38]

Adhesion

The tendency towards adhesion of many drug actives or excipients might lead to difficulties during capsule filling, as particles stick to the surfaces of the filling machine. The consequence is that the fill substance breaks up, which leads to unacceptable fill variations. If the actives or excipients have a tendency to adhere, it is advisable to add a glidant or a combination of a glidant and lubricant such as Aerosil™/magnesium stearate or talcum/stearic acid.

Wetting properties

The wetting properties of the filling are of critical importance to the release of the substance. The release of hydrophobic substances can be enhanced by the addition of lactose as a diluent, or of a wetting agent such as sodium lauryl sulphate. Magnesium stearate has the opposite effect. It reduces the wetting properties and can significantly slow-down disintegration and dissolution. [39, 40]

When using hydrophobic drug substances, especially if they are high-dose and form the major part of the formulation, an appropriate disintegrant should be added. The strong disintegrants include sodium croscaramellose and crospovidone, but moderate disintegrants such as sodium glycol starch or corn starch may often be sufficient.

Moisture sensitivity of the drug substance

It is important to have precise knowledge about the moisture sensitivity of the drug active in the hard gelatin capsule, as there might be implications for the compound's stability. A sensitive drug active might be damaged by the water contained in the capsule shell. As with hygroscopic substances, the addition of mannitol can prevent damage to the substance caused by the humidity of the shell or the environment. [38]

Lactose anhydrous is also suggested as a suitable diluent to prevent degradation of moisture sensitive drugs. However lactose anhydrous will pick up considerable amount of water to convert to the hydrated form when exposed to increasing humidity and temperature, while the lactose hydrous remains unchanged. During the transition state of the lactose anhydrous to lactose hydrous, an increasing water interaction with a moisture sensitive drug was observed and subsequently more drug degradation compared to the lactose hydrous formulation occurred [41].

Lubrication

Lubrication fulfill different functions within a formulation. It has to prevent the powder adhering to the metal surfaces of the machine like dosing tube, dosing disk and punches as well as to optimize the powder flow and compressibility characteristics. Beside the lubricating effect the commonly used lubricants have hydrophobic properties that reduce the dissolution significantly when used in excess. Overlubrication not only result in a decreased dissolution but may also negatively impact the content uniformity, powder density and plug formation [42].

It should also be noted that the time required to mix the lubricant with the formulation has a significant influence on the release profile even if the concentration remains unchanged. When mixing nitrofurantoin, lactose and magnesium stearate, for example, a considerable reduction in the solubility of nitrofurantoin can be seen, related to the length of mixing time. [43]

The addition of lubricants should therefore be restricted to the minimum. Some diluents like Starch 1500 are “self-lubricating” and not necessarily need additional lubrication when used at high portion of

Oral Dosage Form Design Element	Desirable Attribute	Rationale
Size	Lower limit: 6mm Upper limit: 25mm Practical range: 12 – 22mm	• Must be large enough to pick up and handle easily; particularly if used by elders. • Upper size limit is impacted more by mental evaluation vs. a true physiological limit
Appearance	Lustrous and precise	• Luster provides perception of lubriciousness • Precision provides perception of quality and efficacy
Shape	Narrow oblong shape, with no sharp corners	• Reduced perception of getting stuck in esophagus
Color	Light colors, mono- or bi-chromatic but noticeable	• Deep, dark colors not generally favored • Noticeable colors, particularly two-tone color combinations, can reduce potential for medication errors
Surface Texture	Smooth and flexible	• Enhances perception of swallowability
Taste	None	• Taste of medicines are not viewed as desirable
Odor	None	• Odor of medicines are not viewed as desirable

Table 6: Summary of oral dosage form design considerations.

the formulation. Magnesium stearate, which is used in 80 % of the formulation as a lubricant [44] provides sufficient lubrication at a concentration 0.5 – 1 % when filled on a dosator type of filling machine and even half of this concentration, when filled on a dosing disk type filling machine [27].

Choice of hard gelatin capsule

The choice of an appropriate hard gelatin capsule is mainly based on the capsule size (Table 1). The determining factors are the minimum amounts of drug active and excipients required. It is possible to achieve a smaller capsule size by increasing the density of the formulation through granulation or compression, or to arrive at a larger size by increasing the amount of excipients.

The key elements of solid oral dosage form design that determines the ease of swallowing by patient and consumers are size, shape, surface area and surface structure. Comparing the perception of tablets and capsules Overgaard et al. found that 66 % of the patients chose capsules, 18 % coated tablets and only 4 % uncoated tablets as easy to swallow [45]. Another important finding of this study was the result that the patients swallowing multiple medications a day preferred coloured dosage forms as a way to distinguish these medications.

Table 6 summarizes the desirable attributes of a solid oral dosage form. It is obvious that capsules (soft and hard capsules) are lustrous and precise in appearance, have a narrow oblong shape, are smooth and flexible in texture and mask taste or odor, which predominates them as a preferred dosage form.

A further important aspect is choosing the appropriate colour or colour combination for the capsule. Colour associations can affect people emotionally and psychologically. Orange and red are stimulating, while blue shades come across as calming. So it is hardly surprising that several studies have been carried out on the effect on patients of the colour of a medicinal treatment. [46-48] One of the most important papers on this topic was published by Lüscher [49], who studied a number of different colours and their associated characteristics and created a colour scale for individual medical indications.

Besides such psychological effects on patients, colours also help enormously in making medicines distinctive and easy to recognise. As the number of medications increases, colours help patients with their treatment regime, and medical staff with giving out the correct medication. Product recognition can be made still easier by printing the brand name directly on the capsule.

A study on the treatment of anxiety states, comparing compliance with either tablets or hard gelatin capsules, is also relevant to this context. Although the results were not significant they showed that, on a treatment regime of three times a day, compliance was better with hard gelatin capsules. Capsules were taken on average 2.92 times a day, compared with the 2.61 for tablets. [50]

Hard gelatin capsules for multiple-units

Multiple-units are single dosage forms that disintegrate into several parts after ingestion. Hard gelatin capsules are particularly suitable for their development and manufacture. Multiple-units might consist of a single pellet, or homogeneous granules, or a combination of several pellets and granules with various substances and different release characteristics.

It is even possible to include a number of dosage forms – such as tablets, pellets, capsules, powders and granules – within a single formulation. In this way, incompatibilities and interaction between the different drug substances in combination products can be prevented.

There are now machines which allow multiple-units hard gelatin capsules to be filled with different types of pellets and/or formulations via several filling stations within a single process. Hard gelatin capsules with multiple-units therefore offer a highly flexible solution for specific treatment requirements.

Multiple-units currently tend to be developed as controlled-release pellets by using an appropriate film coating. Two groups of polymers are commonly used for the coating: derivatives of acrylic acid such as Eudragit™, and cellulose derivatives such as ethyl cellulose (Aquacoat™, Surelease™). [51]

The biopharmaceutical properties of multiple-units also show advantages over single-unit formulations. [52]

Gastrointestinal (GI) transit time is of major importance to a medicine's effectiveness, especially if controlled release is required. This will mainly be for drug substances which are unstable in the acid conditions of the stomach or which are only absorbed within a defined part of the intestinal tract.

Digenis studied the properties of multiple-units dosage forms compared with single-unit tablets, using the radioactive tracer polystyrene triethylene

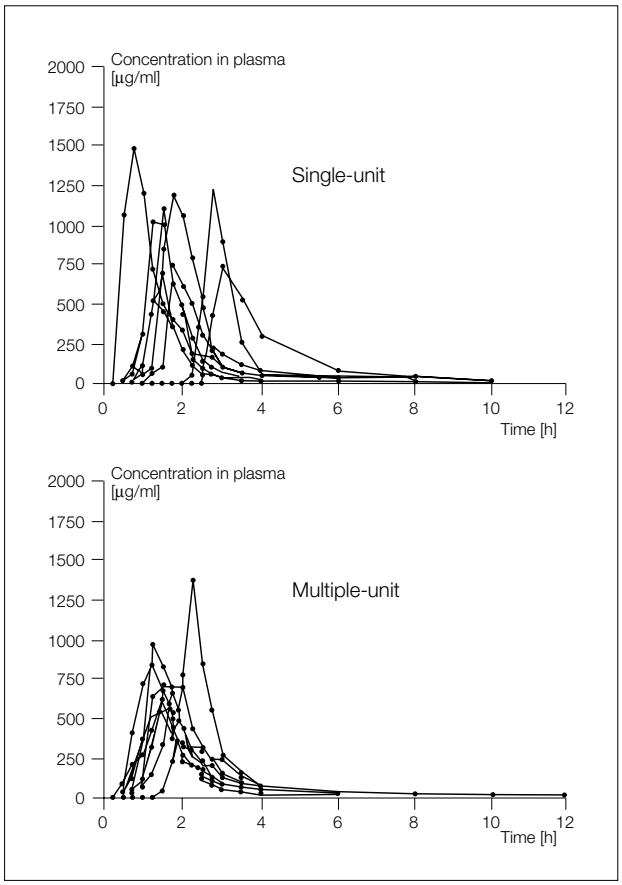

Figure 7: Concentrations of Diclofenac in blood plasma after administration of controlled-release pellets. [55]

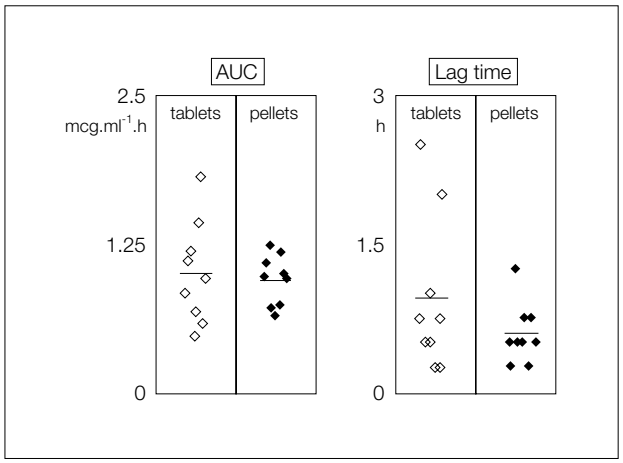

Figure 8: Inter-individual variation of AUC and lag time after administration of gastric fluid-resistant single-unit and multiple-unit formulations. [55]

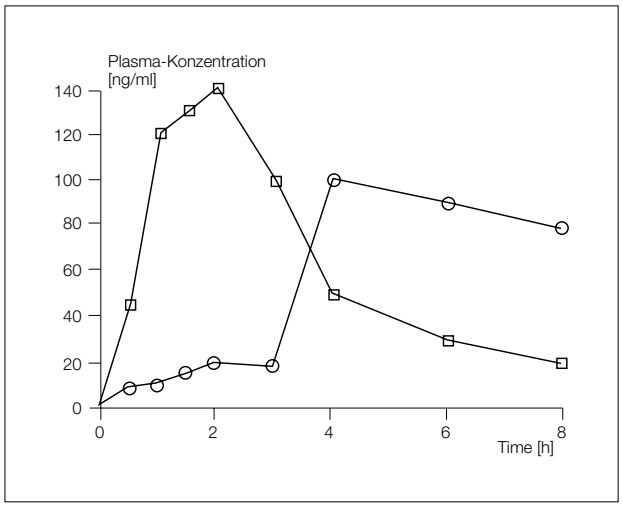

Figure 9: Plasma concentrations after administration of glibenclamid as a single oral dosage form to the same person on two successive days [55]

tetramine. [53] Under fasted conditions, undissolved particles of between 0.6 and 3 mm were able to pass the closed pylorus and showed a mono-exponential emptying from the stomach between 45 and 80 minutes later. After a light breakfast that allowed the particles to disperse extensively within the stomach, particles of 3.1 mm in diameter left the stomach gradually within 180 minutes. However, after food, single units stayed in the stomach for 60 to 570 minutes. [54]

These highly significant inter-individual differences between single and multiple-units have also been extensively demonstrated by Krämer and Blume [55] with the drug substance Diclofenac (Figures 7 and 8).

Intra-individual differences are also more significant for single units than for multiple-units. The example in Figure 9 of the plasma concentration levels of glibenclamid following administration to the same volunteer on two successive days strikingly demonstrates the variation of intra-individual transit time [55].

That differences in GI transit times can have serious implications for the efficacy of a formulation has been shown with the example of erythromycin. [53] Following administration of a 250 mg multiple-units dose, the plasma concentrations of all subjects were above the minimum inhibitory concentration (MIC), under both fasted and non-fasted conditions. The same dose, administered as enteric coated single-unit tablets after food, produced plasma concentrations below the antibiotic's MIC in 50% of cases.

Increased control of GI transit time also avoids the formulation remaining too long in the stomach. Enteric-

	Mio units 1996	%	Mio units 2001	%	CAGR * %
Tablets	1 030	81	1 140	79.5	2
Hard Gelatin capsules	165	13.5	220	16	6
Soft gelatin capsules	65	5.5	60	4.5	0
Total	1 225	100	1 420	100	3

Table 7: Market share (%) of different oral dosage forms (IMS)
** Compounded Growth Rate per Year.*

coated dosage forms that, according to the pharmacopoeia, need only be tested for two hours in vitro at pH 1, can actually lead to several undesirable effects; as Feely has shown in his experiments, a lag time in the stomach of 570 minutes. This can result in premature release with the consequence of destruction of the drug active, as well as irritation of the stomach mucosa. [54]

The lag time in the stomach can also affect the properties of the coating and the release parameters in the upper intestinal tract (pH>5.5). In turn, this can increase or decrease the release time and the bioavailability of the substance. [53]

To conclude, the choice of drug form is the main contributory factor in successful treatment, especially with enteric-coated and sustained-release preparations, where the release time is directly dependent on the GI transit time. Hospital pharmacists should pay close attention to this in advising medical staff on the choice of medication, as patients in a hospital often show a reduced GI transit time, due to concomitant disease and confinement to bed. This is particularly the case for people who have diabetes mellitus and, to an even greater extent, with those who have diabetic gastroenteropathy. [56-58]

It is no surprise, then, that controlled-release pellets have become ever-more important in the development of new formulations over recent years. From 1992 onwards, the figures for the use of controlled-release as compared with rapid-release capsules clearly demonstrate this upward trend (Table 7).

Hard gelatin capsules with liquid or semi-solid fillings

The introduction of high throughput screening and combinatorial chemistry in the early nineties changed the drug discovery process from an empirical discovery process to a real screening process [59]. Advances in biotechnology in terms of genomics and proteomics led to the identification of new therapeutical targets and the possibility to express these relevant targets eg receptor suptypes for the screening process. For a high throughput screening dimethyl sulfoxide (DMSO) rather than any aqueous media is used as a stock solution to achieve the required drug concentration in the µM range [59]. As a result about 40 % of the lead compounds entering into the clinical phase today have a poor aqueous solubility.

Poor aqueous solubility of the drug is known to be a major factor that lead to a variable and poor bioavail-

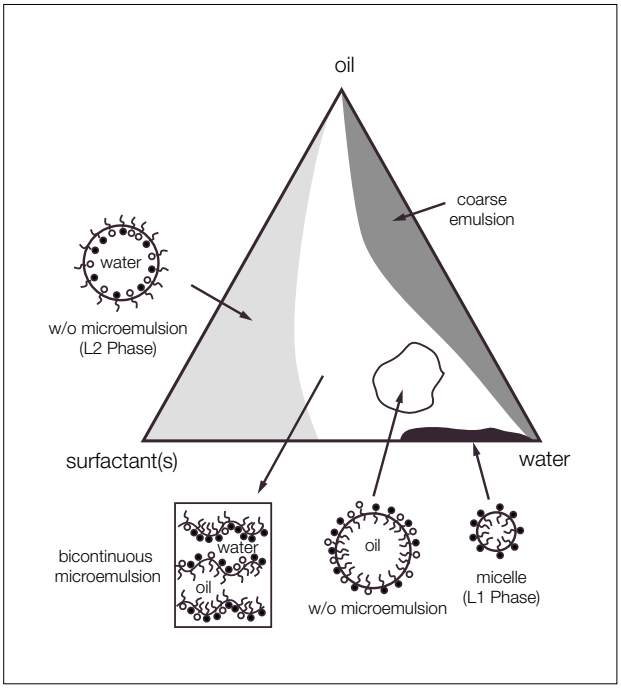

Figure 10: A hypothetical pseudo-ternary phase diagram of an oil/surfactant/water system with emphasis on microemulsion and emulsion phases. Within the phase diagram, existence fields are shown where conventional micelles (L1 phase), reverse micelles or w/o microemulsions (L2 phase) and o/w microemulsions are formed, along with the bicontinuous microemulsion and coarse emulsion phases. Outside the phase diagram, surfactant microstructures in various phases are schematically indicated. [60]

Formulation	C_{max} (µg/ml)	t_{max} (h)	AUC (µg h ml^{-1})	% relative bioavailability
Self-emulsified solution (SEDDS)	5.57	2.50	29.77	389.0
Drug solution in PEG 400 (control)	1.44	2.00	7.64	100.0
Capsule form. of wet-milled spray dried powder	0.78	3.00	2.69	35.3
Tablet form. of micronized drug	0.58	2.00	1.32	17.2

Table 8: Pharmacokinetic parameters of Ro 15-0778 from different formulations in non-fasted dogs. [62]

successfully developed to optimize the bioavailability with regard to an increased systemic drug availability, a reduced inter- and intrapatient variability and the reduction of food effects.

The basic concept of lipid drug delivery systems is to dissolve the compound in a lipophilic vehicle to deliver the drug in solution to the side of absorption. The drug delivery to the side of absorption can be enhanced by the addition of surfactants to form an o/w emulsion, which may also protect the drug from presystemic metabolism or precipitating out in the GI tract. These self-emulsifying drug delivery systems (SEDDS) are isotropic preconcentrates of 3 - 5 components (solvent, surfactant, cosurfactent) that form spontaneously a fine o/w emulsions in aqueous environment under gentle agitation. With a droplet size of < 100 nm microemulsions form thermodynamically stable clear solutions. The optimal product composition can easily be identified from phase diagrams as shown on a hypothetical pseudo-ternary phase diagram (Figure 10) [60].

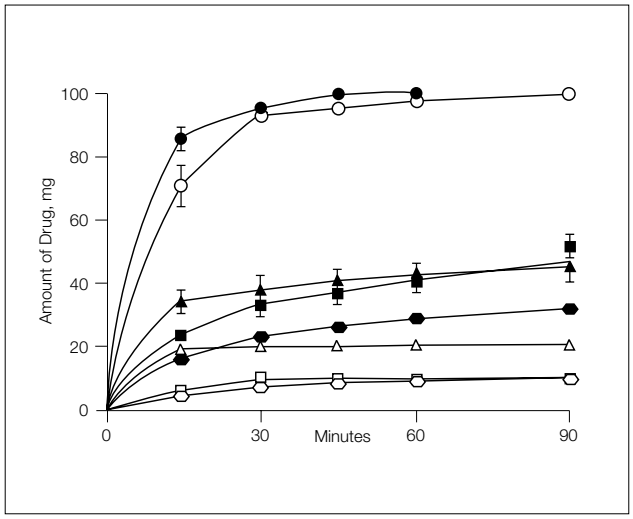

Figure 11: Effect of vehicle on the dissolution in simulated gastric fluid (closed symbols) and the dispersion on water (open symbols) of the encapsulated solid solution of REV-5901 (drug 100 mg, vehicle 550 mg) at 50 rpm and 37° C. Key: dissolution of capsules containing PEG 1000 (▲), PEG 1450 (■), PEG 8000 (⬣), and Gelucire 44/14 (●); dispersion in water of capsules containing PEG 1000 (▵), PEG 1450 (□), PEG 8000 (⬭) and Gelucire 44/14 (○). Each data point represents the average ± SD of three determinations. [61]

Gelucire™ (Gattefossé) provides an interesting range of semi-solid excipients for such formulation. Each contains a defined mixture of mono-, di- and tri- glycerides of mono- or dicarboxylic acid ester of polyethylene glycol. The various Gelucire™ products differ in their melting point and HLB (Hydrophilic-Lipophilic-Balance), which is also the basis of their brand name. Gelucire™ 44/14, for instance, has a melting point of 44°C (111.2°F) and an HLB of 14. It corresponds to the monograph Lauryl macrogolglycerides, while Gelucire™ 50/13 corresponds to the monograph Stearyl macrogolglycerides in the European Pharmacopoeia.

Gelucire 44/14 have been compared with polyethylene glycols (PEG) of different chain length for in vitro and in vivo performance of the poorly water soluble drug REV-5901 (aqueous solubility: 0.002 mg/ml). In vitro Gelucire 44/14 dissolves a dose of 100 mg within 45 min while the drug dissolution in PEG 1000 was only 40 mg after 90 min (Figure 11). The initial dog study confirmed that the improved in vitro dissolution of the Gelucire 44/14 formulation could increase the bioavailability of the drug by two fold [61].

The lipophilic naphthalene derivative RO 15-0778, with a water solubility of < 0.01 mg/ml and a peanut oil solubility of 95 mg/ml has been Investigated using a SEDDS formulation of polyglycolized glycerides In a peanut oil/Neobee M5 mixture compared to a drug solution In PEG 400, a wet milled spray dried and a micronized drug formulation. While the PEG 400 solution showed the fastest in vitro dissolution the in vivo bioavailability in dogs was 4 times superior to the PEG 400 solution (Table 8) [62].

Self-emulsifying drug delivery systems have also demonstrated their potential in peptide delivery. Cyclosporin A, a highly lipophilic cyclic peptide with a molecular weight of 1200, which is absorbed slowly and concentration dependent by passive diffusion. It

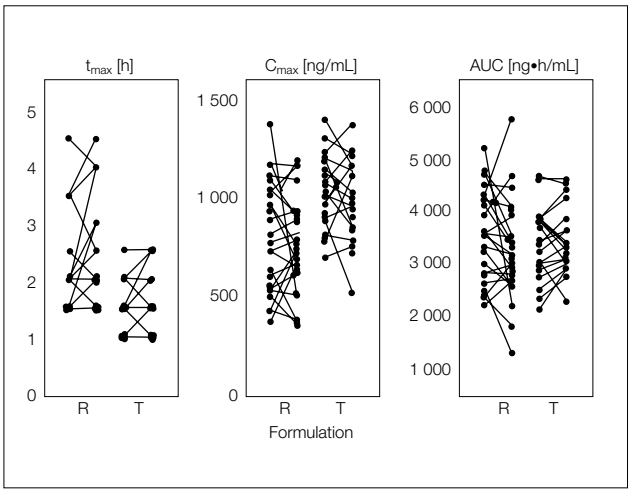

Figure 12: Intraindividual comparison of the primary pharmacokinetic characteristics of Cyclosporin following replicated oral administration of 300 mg reference (R) formulation and 180 mg test (T) formulation to 24 healthy volunteers. [65]

is substrate to pre-systemic metabolism and has an absolute bioavailability of 10 – 60%. Moreover, Cyclosporin A has very narrow therapeutical window and different blood concentration are targeted for each organ transplantation (eg. 250 – 350 µg/L for liver transplant and 80 – 120 µg/L for kidney transplant [63].

The first market formulation of Cyclosporin (Sandimmun™) was composed of corn oil, dehydrated ethanol and polyglycolzed glycerides (Labrafil M 1944) that form a coarse emulsion. Even if the achieved bioavailability was acceptable, the major issue remains the inter- and intrasubject variability of the formulation. The high inter- and intrasubject variability of 20 – 60 % was caused by the digestion before releasing the drug, which led to a significant food effect and bile salt dependent absorption [64].

The second formulation generation of Cyclosporin A (Neoral™) is a composition of a hydrophilic solvent (propylene glycol), a hydrophobic solvent (mono-, di- and triglycerides of corn oil and a surfactant (polyoxyl-40 hydrogenated castor oil), which forms a microemulsion with a droplet size of < 100 nm in gastric fluid [63]. As reviewed by Friman & Bäckman several clinical studies confirmed that the Neoral formulation significantly increase the absorption (decreased t_{max}), the C_{max} and AUC, which led to a dose reduction [63]. Figure 12 also shows that the inter- and intrasubject variability, which is critical to maintain the drug concentration in the therapeutical range, was substantially improved [65].

To develop a once-daily formulation of Cyclosporin A Kim et al investigated the possibility of enteric coating the microemulsion. A SEDDS was developed based on medium chain triglycerides as a solvent and a surfactant mixture of Cremophor RH 40, mono- and diglycerides and Poloxamer 124. The formulation forms a microemulsion with a droplet size of 18-33 nm that was bioequivalent to the Neoral formulation in dogs. This microemulsion droplets were enteric coated with Eudragit L 100 to remain undissolved for 2 h in pH 1.2 and to dissolve rapidly at pH 6.8. As shown in Figure 13 the in vivo results of a dog study comparing 100 mg of uncoated Cyclosporin with a formulation of 100 mg uncoated and 100 mg as coated microemulsion droplets demonstrate the maintenance of the required therapeutical blood concentration over 24 h [66].

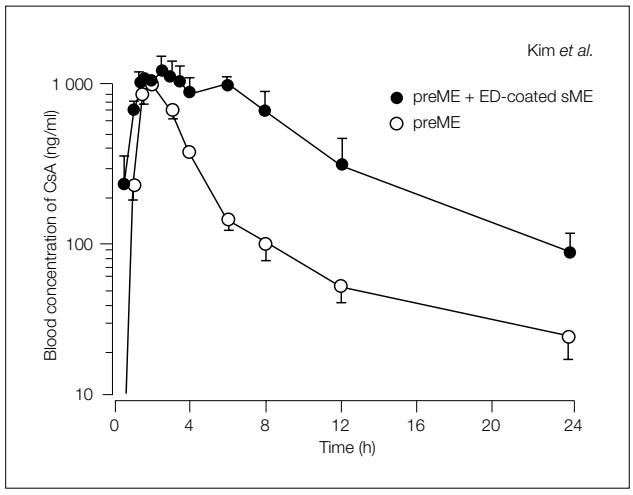

Figure 13: Oral absorption profiles of Cyclosporin A after oral administration of immediate release micro-emulsion (100 mg Cyclosporin) alone and together with Eudragit coated micro-emulsion (100 mg Cyclosporin) (overnight-fasted dogs). [66]

Other examples to use lipid based drug delivery systems to formulated as a once-daily controlled-release dosage form by using Gelucire™ is Captopril. [67] The patent states that a combination of Gelucire™ 50/13 and Gelucire™ 53/10 is the best formulation, and assumes that the chemical stability of Captopril in the gastrointestinal system is enhanced and that interference with food is reduced.

Another semi-solid once-daily formulation was described by Seta et al. He discovered that Captopril in suspension in an oily semi-solid matrix of ascorbic acid, soyabean oil and glyceryl monostearate in hard

gelatin capsules was superior to standard Captopril tablets (25 mg, Sankyo, Japan) in terms of the duration of the plasma concentration and the AUC (Area Under Curve) [68]. Seta ascribed this to a longer GI transit time, adhesion of the oily matrix to the mucosa and protection of the drug active against degradation by food particles [69].

A sustained-release formulation of Captopril in hard gelatin capsules has now reached the market in Japan (Captoril-R™, Sankyo).

From a pharmaceutical point of view, there are several other advantages in formulating liquid and semisolid fillings as hard gelatin capsules [70]. Drug actives with certain characteristics — a low melting point, low dose, critical stability — present problems which make development in solid oral dosage form difficult, but which can be circumvented by formulation as liquid or semi-solid fillings in hard gelatin capsules.

Drug substances with a low melting point might liquify or becoming 'sticky' at room temperature. If so, up to 50% excipients have to be added to maintain flow properties that enable manufacture in filling machines. At high doses, this might lead to quantities which are no longer suitable for formulation as a single dosage form.

A low melting point may also impair the compression process in the production of tablets, as the heat resulting from compression can cause the substance to melt. One example is the product Piascledine ™ 300, available in France, which has recently been reformulated from a tablet to a hard gelatin capsule with liquid filling. The production processes for the two formulations are shown in Table 9.

Medicines intended for use in minimal dose are not easy to produce in a solid oral dosage form. Due to the highly potent nature of such drugs (cytotoxic agents, hormones, and so on), carry increased risks of cross-contamination and harmful exposure of staff to dust during production. For industrial production, as well as in hospital and community pharmacies, the dust-free liquid or semi-solid formulation is a valid alternative which protects against these risks.

In low-dose drugs, slight differences in the density of a powder mixture or minimal homogeneity of the mixture – perhaps as a result of agglomeration – might produce unacceptable variations in content uniformity. Such variations can be avoided by formulating the drug as a liquid or semi-solid. [71, 79]

Triamterene dosed at 20 µg in a PEG mixture as a semi-solid fill in capsules shows a standard variation of 1.8%, compared to 3.1% for powder-fill capsules. [72] The main reason for the improved standard deviation lies in the volumetric filling, which do not show the differences in density and homogenicity like powders. [73]

Tablets	Hard gelatin Capsules
Dissolution of substances in solvent	Dissolution of substances in semi-solid excipients
↓	↓
Mixing of solution and excipients	
↓	
Evaporation of solvent from mixture	
↓	
Mixing of powder and excipients	
↓	
Tablet compression	Filling of hard gelatin capsules

Table 9: Production process of Piascledine™ 300 as tablets and hard gelatin capsule.

Substance	Brand name*	Company	Region
Vancomycin	Vancocin®	Lilly	USA
Captopril	Captoril-R®	Sankyo	Japan
Ibuprofen	Solufen®	SMB, Ivax	Europe
Fenofibrate	Fenogal, CiL 200 mg®	Azupharm SMB	Europe
Peppermint oil	Colpermin®	Pharmacia Upjohn	Europe
Ethosuximid	Suxilep®	Jenapharm	Europe
Essential phospholipids	Lipostabil 300®	Aventis	Europe
Curcuma/ Cheledonium extr.	Cholagogum®	Aventis	Europe
Piroxicam	Solicam®	SMB	Europe
Nifedipin	Aprical®	Rentschler	Europe
Avocado/Soya extr.	Piascledine®	Pharmascience	Europe
Sabal extract	Permixon 160®	Pierre Fabre	Europe
Danthron	Co-Danthramer®	Napp	Europe
Isosorbide dinitrate	Isoday 40 mg®	Tillotts	Europe

* List of Brand names is not exhaustive

Table 10: Examples of liquid and semi-solid formulations in hard gelatin capsules.

A further group that profits from liquid or semisolid formulations comprises substances that are unstable when exposed to oxygen, light or humidity. For instance, after three months' storage at a temperature of 77°F (25°C), the hard gelatin capsule form of vitamin A in peanut oil, with the addition of tocopherol as antioxidant, shows the same stability as if stored in a closed glass bottle. [74] Although a certain amount of air is present in the capsule, due to the production process, this experiment shows that hard gelatin capsules are a reliable protection against oxidation, if the amount of antioxidant used is calculated to allow for the enclosed air.

The use of soft gelatin capsules as a solid oral dosage form for liquid and semi-solid formulation is already well known. Less well known is the fact that in recent years, several formulations of liquid or semisolids have been developed and manufactured in hard gelatin capsules. Table 10 shows the number of hard gelatin capsules with liquid or semisolid substances on the market.

The differences between soft and hard gelatin capsules lie in the composition of the shell and in the production process. Hard gelatin capsules consist of virtually pure gelatin with a sorption water content of 13% to 16%. Soft gelatin capsules normally have thicker shells and contain approximately 20% to 30% of plasticisers in the form of glycerol or sorbitol. Due to this high plasticiser content, the water content of soft gelatin capsules is approximately 30%.

There are virtually no differences between soft and hard gelatin capsules as far as the suitability of fillings is concerned, because compatibility of the formulation with gelatin is the main factor to consider. However, soft gelatin capsules have the limitation that they can only be filled with liquids or liquid suspensions. [74] It should further be noted that the plasticiser and the increased water content lead to higher oxygen permeability through the shell [76] and that the considerable exchange of humidity between hygroscopic substances, the shell and the environment can lead to problems in the formulation of a drug substance in a soft gelatin capsule [77]. On the other hand, the use of plasticiser make soft gelatin capsules suitable for filling with hygroscopic formulation like low molecular weight polyethylene glycols that may not always be compatible with hard gelatin capsules.

The main differences between the capsule types are apparent in the production process and storage requirements. Hard gelatin capsules require less stringent conditions during manufacture and storage than soft gelatin capsules.

The production of soft gelatin capsules has to be carried out under controlled conditions at 20% to 30% relative humidity at room temperature, while the processing of hard gelatin capsules can be carried out at 40% to 60% relative humidity at room temperature. [75] The maximum temperatures for the formulation to be filled into soft gelatin capsules is 104°F (40°C), while hard gelatin capsules can sustain temperatures up to 212°F (100°C) for a short period without deformation. [79]

A significant disadvantage of hard gelatin capsules is their tendency to leak at the join between body and cap. Until recently, this problem could only be helped by applying a gelatin film on the overlapping zone of cap and body, known as banding, a time-consuming and costly process. A new invention, where a solution of ethanol and water is sprayed between the overlap of body and cap, has been introduced in the market that significantly simplify the closure of hard gelatin capsules. [78].

This invention, which is referred to as 'sealing' in the USP 24 ‘capsules’ monograph, makes use of the low surface tension of the ethanol/water solution, which permits fast penetration of the solution into the overlap between body and cap. The ethanol/ water slightly dissolves the gelatin between the cap and body, which melts during the gentle heating to complete the fusion of the two gelatin layers . The gentle heating process implies a temperature of 40-60°C for less than a minute [78].

For large scale production the LEMS 30 (Liquid Encapsulation by MicroSpray) equipment is available. The LEMS 30™ is a stand alone sealing machine that

Figure 14: LEMS 30 machine for sealing two-piece capsules after filling and closing.

Figure 15: CFS 1000 semi industrial machine for filling liquid and semi solid formulation into two-piece capsule and sealing.

can seal 30.000 liquid filled capsules / h coming online from a filling machine or are fed from a bulk hopper. (Figure 14)

For development purposes, a fully automated, cGMP compliant liquid filling and sealing equipment have been introduced recently. The CFS 1000 (Capsule Filling and Sealing) operates at a maximum speed of 1000 capsules per hour for all capsule sizes from 00el - 4 with the ability to fill from 0.1 – 1.2 ml, which is sufficient for phase I and II clinical supply. With a minimum batch size of 15 ml, the equipment also addresses the need for the limited drug availability in early development. The use of the same filling and sealing principles than the high speed filling and sealing machines makes scaling up easy even for hot melts filled up to 70° C (Figure 15).

Maximum filling temperature:	70° C
Viscosity at filling temperature:	100 – 1000 cp
Particle size of suspensions:	10 – 20 µm

Table 11: Considerations for thermal and rheological characteristics of the formulation to be filled and sealed into two-piece capsules.

To develop a robust formulation that can be filled and sealed on high speed equipment some general guidance should be respected. The maximum filling temperature should not exceed 70°C to avoid heat damage of the capsules. For accurate dosing the viscosity at filling temperature should be between 100–1000 cp, moreover, if suspensions are filled the particle size recommended should be in the range of 10–20 µm (Table 11)

The rule that the active and the added excipients must be compatible with gelatin applies just as much to liquid and semi-solid fillings. Glycerol, propylene glycol and sorbitol, commonly used in formulations for soft gelatin capsules, are not suitable for hard gelatin capsules as they are too hygroscopic. Polyethylene glycols are only of limited suitability because their hygroscopic action increases with shorter strand length.

The hygroscopic action of the above excipients allows water to penetrate the capsule during storage, and the shell could become soft. Also, during storage in conditions where humidity is excluded, the water of the shell can be absorbed by the formulation, leading to capsule brittleness and breakage. The water uptake of glycerol and various polyethylene glycols in relation to humidity is shown in Table 12.

	40 r.h.	50 r.h.	60 r.h.	70 r.h.	80 r.h.
PEG 200	10,4	15,0	22,0	30,0	41,0
PEG 400	7,1	10,5	15,0	24,0	36,0
PEG 600	6,0	9,4	14,0	22,0	33,0
PEG 1000	2,7	5,8	10,5	21,0	33,0
PEG 2000	–	1,3	2,1	3,5	26,0
PEG 4000	–	–	1,4	2,5	8,0
Glycerol	15,0	22,0	29,0	38,0	51,0

Table 12: Water absorption (%) in relation to relative humidity.

Table 12 also shows that low molecular-weight polyethylene glycols (PEG 200 to PEG 3000) are not suitable for formulations in hard gelatin capsules. However, formulations for hard gelatin capsules which use mixtures containing PEG 200 as a drug solvent have been published.[79]

The commonly used excipients for liquid and semi-solid formulations in hard gelatin capsules are listed in Table 13.

The industrial production of liquid or semi-solid formulations in hard gelatin capsules will usually necessitate making a few, mainly technical, adjustments to the machinery. Today, most major machine manufacturers offer dedicated machines or will adapt existing equipment to meet the new filling requirements. Table 5 lists the filling machines currently on offer, and their capacities.

A note here about capsule packaging. Soft gelatin capsules can vary somewhat in their shape and size, and the size of blister pack chosen will need to allow for this by increasing the size of the alveols. Extra

A) Long chain triglycerides
- Maize (corn) oil
- Olive oil
- Soybean oil

B) Medium chain triglycerides
- Miglyol® 810*
- Miglyol® 812*

C) Solubilizing agents, surfactants, emulsifying agents absorption enhancers
- Cremophor® EL
- Gelucire® 44/14, 50/13
- Labrafil® M 1944 S, M 2125 CS
- PEG MW > 4000
- Softigen® 767
- Tween® 80

D) Co-solvents to be used in lower concentrations
At the 100% level the following excipients are incompatible with hard gelatin capsule shells. Mixtures with compatible excipients may allow these to be used in lower concentrations.
- PEG MW < 4000
- Propylene glycol
- Transcutol P
- Ethanol

* Property of the associated companies

Table 13: Examples of excipients for formulations of liquid and semi-solid fillings of hard gelatin capsules.

A note here about capsule packaging. Soft gelatin capsules can vary somewhat in their shape and size, and the size of blister pack chosen will need to allow for this by increasing the size of the alveols. Extra packaging material and, not least, the cost of waste disposal increase the overall costs of packaging. This can be avoided by using hard gelatin capsules, as they come in predefined and constant forms and sizes, even when they contain liquid or semi-solid fillings.

Summary

In recent years, interest in using hard gelatin capsules in developing and manufacturing medicines has increased considerably. This is most probably due to rapid advances in dosage forms for hard gelatin capsules. In tandem with this, the structural foundation of a new technology has been developed, and realised in the form of efficient process machinery.

The formulation of a rapid-release hard gelatin capsule can be largely deduced from the physicochemical properties of the drug active. Usually, only a limited number of excipients are necessary, and these are simply mixed with the active and directly filled into the capsules. The costly process of granulation and compression can mostly be avoided. The choice available in terms of capsule type, the range of sizes and the capsule's colour or combination of colours, as well as the possibility of printing directly onto the capsule, means that patient compliance, product recognition and product differentiation can be markedly improved.

A range of manual, semi-automatic and automatic filling machines is available for the manufacture of hard gelatin capsules. They enable the production of large, small, or even the minimal quantities that are often needed in community and hospital pharmacies. For multiple-units, hard gelatin capsules are the ideal solution. Multiple-units in hard gelatin capsules allow the combination of different products, even if they are incompatible with each other, or of substances with different release profiles.

The latest developments in the fields of formulation science and technology offer new opportunities for filling liquid and semi-solid formulations in hard gelatin capsules. Formulation in liquid dosage form enhances the bioavailability of several barely-soluble drug actives to achieve a solid oral dosage form. Also controlled-release characteristics can be developed using semi-solid formulation.

In-house production of hard gelatin capsules with liquid or semi-solid fillings is not a problem, as a rapid and easy sealing technology is now available and the capital outlay is reasonable. Further advantages are improved uniformity of content for low dose products, the avoidance of cross-contamination during production, and reduced packaging costs, due to the predefined dimensions of hard gelatin capsules.

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