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Liquid filled and sealed hard gelatin capsules

Ewart T. COLE

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It is generally accepted that many of today's NCE's are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form.

Until recently if liquid/semi-solid formulations were necessary the soft gelatin capsule was the only drug form available in which to encapsulate such poorly water soluble drug formulations.

This presentation will describe the use of hard gelatin capsules as an alternative for liquid/semi-solid formulations. A screening program has been developed from which a list of functional excipients which are compatible with the gelatin shell has been drawn up. Once compatibility has been established the capsules are filled and then sealed by spraying a small amount of a water/ethanol mixture at the cap and body interface followed by a gentle warming to fuse the two capsule parts together. The advantages offered by the LEMS™ (Liquid Encapsulation by Micro Spray) process over capsule banding will be discussed.

It is considered that this technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulations when only small quantities of drug substance is available. The process can be scaled-up and also kept in-house in a similar way to the operations of tabletting or powder/pellet filling of hard gelatin capsules.

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1. Introduction

The hard gelatin capsule has been conventionally used as a dosage form for Rx and OTC drugs and herbal products, which are formulated either as powder or pellets. Various categories of drugs, however, demand new and different ways of formulation and the market demands that these products are developed and launched in an ever decreasing time period.

This article will review how liquids filled into hard gelatin capsules can fulfill some of these demands and in particular will review the categories of drugs for which the liquid and semi-solid filled capsule is particularly relevant, examine the compatibility issues associated with excipients, compare the liquid filled and sealed hard gelatin capsule with soft gelatin capsules and also describe a new process for sealing hard gelatin capsules.

2. Drug categories

Figure 1 shows the different categories of drugs for which a conventional dry powder dosage form may be either unsuitable or impractical.

2.1. Poor bioavailability

Ghirardi et al. (1) reported in 1977 that the bioavailability of the poorly water soluble drug digoxin could be significantly enhanced when formulated as a liquid in a soft gelatin capsule, which at the time was the only available way to formulate a liquid unit dosage form. It was not until the early 80's when workers reported studies in which hard gelatin capsules can be filled with molten formulations of drug substances (2-7) that an alternative to soft gelatin capsules became a reality. One of the first commercial products to be developed as a liquid filled hard gelatin capsule was the poorly water soluble calcium antagonist nifedipine as described by Lahr (8). Bioequivalence with a drop solution and a soft gelatin capsule was achieved (9) and the product was marketed in Germany as Aprical®.

Since the early 80's the number of poorly water soluble drugs exiting from screening programs has increased sharply. Lipinski (10) recently reported that 35% of NCE's from the current Pfizer screening program are poorly soluble which agrees with the estimate given by Robinson (11).

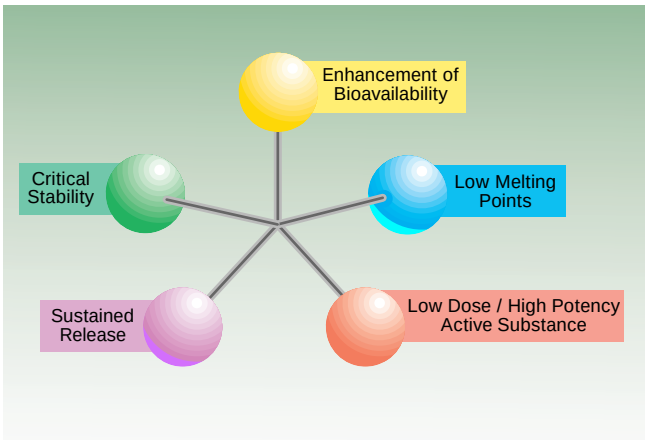

Figure 1: Reasons for formulating drugs as liquid or semi-solid dosage forms.

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Formulation of microemulsions is a technique, which has already been used (12, 13) to improve the bioavailability of poorly water soluble drugs and a continuation of this approach can be expected.

2.2. Low melting point

Materials which have low melting points or are liquid at room temperature present difficulties when formulating as dry powders, often requiring high concentrations of excipient to avoid processing problems.

The product Piascledine® 300, which was originally marketed in France as a tablet, is a good example of how a manufacturing process can be considerably simplified by filling as a hot melt into a hard gelatin capsule. The product contains a mixture of oils of avocado and soya for the treatment of skin disorders and the five step process to manufacture a tablet was reduced to a simple mixing and filling operation. Consumer acceptance was also enhanced due to the smaller size of the final dosage form.

Other actives with low melting points, which could benefit from this process include ibuprofen (14) and the oily vitamins.

2.3. Low dose / High potency

Drugs in this category present two main challenges; how to achieve acceptable content uniformity and how to control cross-contamination and worker protection.

2.3.1. Content uniformity

Duerr et al. (5) and Cadé et al. (15) have reported that the liquid filling operation is capable of achieving fill weight variations of < 1%. If a drug substance is in solution or is uniformly dispersed in a liquid vehicle then it follows that good drug content uniformity can also be achieved as has been reported by Walker et al. (3) for the model drug triamterene at a dose level of 25µg.

2.3.2. Cross-contamination

Companies manufacturing solid dosage forms of hormones and cytotoxic agents from powders are forced to install extremely elaborate systems to reduce contamination. Incorporation of the highly potent agent into a liquid for filling into a hard gelatin capsule can reduce the dangers when working with such drugs. A study carried out by Bowtle (16) using phenacetin as a model drug, demonstrated that in a swab test of the bushings on a capsule filling machine operating with liquids, no detectable level of phenacetin was found. Those familiar with capsule filling operations will realize that such clean conditions rarely exist when working with dry powders.

2.4. Critical stability

Sensitivity to moisture is an aspect of formulation which can be minimized by incorporating the drug into either a hydrophilic or lipophilic matrix. For example, the antibiotic vancomycin hydrochloride is highly hygroscopic and to achieve acceptable stability it needed to be formulated as a lyophilized powder for reconstitution. Bowtle et al. (17) successfully developed a hard gelatin capsule filled with a PEG 6000 matrix of the drug. This capsule formulation produced faecal, plasma and urine levels of the antibiotic that were similar to those obtained with the solution (18) and is marketed by Eli Lilly as Vancocin® HCL.

2.5. Sustained release

By choosing an appropriate excipient the release rate of an active can be modified. For example Gelucire, which is available as a semi-solid with a range of melting points and HLB values, can be mixed to obtain different drug release rates (19).

Seta et al. (20) compared the bioavailability of an oily semi-solid matrix of captopril in hard gelatin capsules with that of a tablet. They concluded that the oily semi-solid matrix of captopril containing soybean oil and glyceryl monostearate b.i.d. provided antihypertensive action that was comparable to the conventional tablet t.i.d., the total daily dose being equal. This product is marketed by Sankyo in Japan as Captoril®, and provides the patient with a more convenient dosage regime.

3. The empty hard gelatin capsule and comparison to soft gelatin capsules

The hard gelatin capsule for liquid filling is identical in composition to the capsule used for filling powders and comprises gelatin, water, colouring and opacifying agents. For an efficient sealing process, however, it is important that the fill material does not penetrate into the zone between the body and cap before the sealing operation.

Sizes and volumes of hard gelatin capsules for liquid filling (Licaps™ (1))

Size	Approx. volume ml	Approx. available volume (2) ml
00el	0.92	0.83
00	0.85	0.77
0	0.61	0.55
1	0.45	0.41
2	0.34	0.31

(1) Licaps™ is a registered trade mark of the Capsugel Division of Warner-Lambert Company.

(2) A complete filling of the capsule body is not possible because of the risk of spillage during the filling operation. This value assumes a filling level of 90% of the available volume.

Table 1.

A capsule with a special configuration has been designed to eliminate this problem and the range of capsule sizes available is given in *Table 1*.

In contrast to the hard gelatin capsule the soft gelatin capsule contains a plasticizer in addition to gelatin and water. Usually glycerol at a level of approx. 30% is used. As described by Bauer (21), the moisture uptake of soft gelatin capsules plasticized with glycerol is considerably higher than that for hard gelatin capsules. Another effect of the plasticizer has been reported by Armstrong et al. (22). They found that migration of a drug into the shell of a soft gelatin capsule can occur which may result in drug degradation and difficulties in assay.

One basic difference exists between the hard and soft gelatin encapsulation processes. In the hard gelatin capsule process, the capsule is pre-fabricated and supplied empty, whereas in the soft gelatin capsule process the encapsulation and filling take place simultaneously. The moisture content of the gelatin/plasticizer mass at this stage can be around 50%, the equilibrium moisture level only being reached after several days storage on trays. It is conceivable that this is the most critical period during which migration and degradation of moisture sensitive drugs, which are readily soluble in glycerol, can occur.

Hom et al. (23) reported that the oxygen transmission rate of a soft gelatin capsule film decreased with the level of glycerol in the film and also with the moisture content. As the hard gelatin capsule wall contains no plasticizer one may expect that the permeability of the hard gelatin capsule wall will be lower than that of a soft gelatin capsule. Cadé et al. (15) reported on the smell assessment of soft and hard gelatin capsules containing the highly odorous products fish oil, valerian and garlic oil. Their results agree with the conclusions of Hom et al. (23), in that the permeability of the gelatin shell without plasticizer was found to be lower than that of the soft gelatin capsule with plasticizer. This higher permeability could have consequences for oxygen sensitive drugs filled into soft gelatin capsules.

The soft gelatin encapsulation process is in the hands of a few contract manufacturers, and rarely, due to the complexities of the process, do pharmaceutical companies get involved in this operation. This means, that from an early stage of development, once it has been established that a unit liquid/semi-solid dosage form is necessary, all development activities must be contracted out. Many companies would prefer to keep these activities inhouse for reasons of confidentiality, control over the development process, availability of drug substance at the early stages of development and not least control over costs.

The aspects of hard and soft gelatin capsules are summarized in *Table 2*.

4. Suitability of fill materials

As the tendency for poorly water soluble drugs to enter the pipeline increases so does the challenge to find innovative ways of developing bioavailable and stable dosage forms.

Excipient suppliers, encouraged by the potential opportunities in this field, are developing new materials comprising mixtures of functional excipients. An example is the introduction of SMEDDS (Self Emulsifying Drug Delivery System) by Gattefossé. Undoubtedly this approach was stimulated by the work performed by Sandoz, on the microemulsion formulation of cyclosporin A (12, 13).

Comparison of hard and soft gelatin capsules

Aspect	Hard gelatin capsule	Soft gelatin capsule
In house development and manufacture	Yes	Difficult
Ability to manufacture small batches	Yes	No
Scale-up	Simple and in-house	Requires large quantities of drug substance and must be outsourced
Temperature of fill	Max. ~ 70°C	Max. ~ 35°C
Plasticizer in shell	No	Yes
Risk of drug migration	Low	High for drugs soluble in plasticizer
Permeability of shell to oxygen	Low	High due to plasticizer Varies with moisture content
Sensitivity to heat and humidity	Low	High due to plasticizer
Limitation on excipients for formulation	High concentrations of hygroscopic excipients such as glycerol must be avoided	Hygroscopic excipients can be tolerated due to presence of plasticizer in shell
Capsule dimensions	Constant	May vary

Table 2.

The area of contact between the capsule shell and a liquid fill material is greater than is the case with a powder filled capsule. The potential for interactions must therefore be checked.

4.1. Moisture exchange fill-shell

A hard gelatin capsule contains 14-16% moisture, which acts as a plasticizer for gelatin. A hygroscopic material, when filled into the capsule, could extract moisture from the shell thereby inducing embrittlement.

The potential for this is checked by storing capsules filled with the product under various conditions of relative humidity from 2.5 to 65% and measuring the weight change as already described by Cadé and Madit (24).

The acceptance criteria have been set at a change in weight of plus or minus 2%.

4.2. Mechanical properties

The relationship between relative humidity during storage, gelatin moisture content and capsule properties was reported by Bond et al. (25) and is shown in *Figure 2*.

The change in capsule brittleness with relative humidity has also been studied by Kontny and Mulski (26). It follows that monitoring of the mechanical properties of capsules stored at various relative humidities is of critical importance in determining compatibility between the fill material and the capsule shell. The methodology to determine this is described by Cadé and Madit (24). Acceptance criteria proposed are that significant capsule brittleness should not be detected in capsules stored at 30% and 50% relative humidity for four weeks.

4.3. Dissolution stability indicator

The potential for interaction of an excipient or active with the capsule shell which can result in a change in dissolution behaviour has been described by Dey et al. (27) for capsules filled with powders. Dissolution of gelatin capsules was also the topic of an FDA/Industry Working Group and a modified dissolution testing procedure allowing the use of enzymes has been accepted when a delay in dissolution is a result of pellicle formation (28). No relevance to the in vivo behaviour of the capsules was established (29, 30).

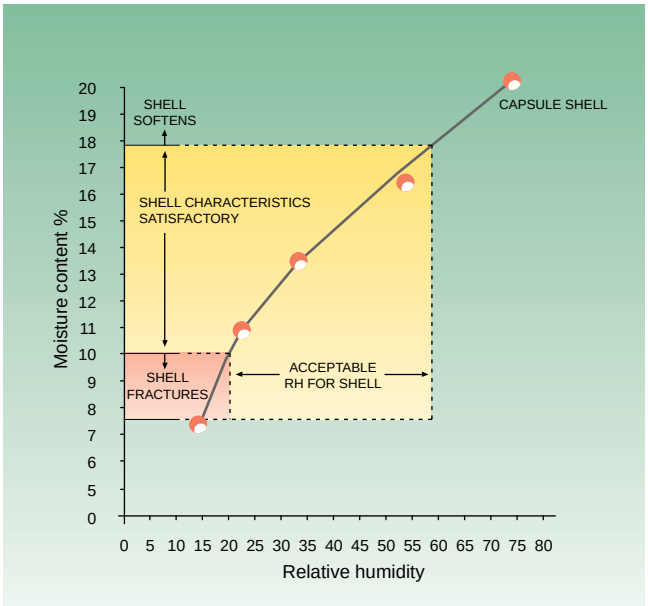

Figure 2: Equilibrium moisture content of empty gelatin capsule shells stored at various relative humidities for two weeks at 20°C.

Certain excipients used in the formulation of liquid filled capsules may have, or may generate during storage, low levels of aldehydes, which can potentially react with gelatin. As a means to evaluate potential interactions with the gelatin shell, capsules are filled with the test material and stored in closed HDPE bottles at 40°/75% RH for periods of up to six months. After the appropriate time has elapsed the capsules are emptied and cleaned. Acetaminophen is used as a dissolution reference material and is filled into the capsules which have been stored and the dissolution rate determined using the USP method 2. Comparison of the acetaminophen dissolution profiles from the stored and from a reference capsule gives an indication of a potential interaction between the fill material and the capsule shell.

Particularly in the case of hot melt fills the effect of melting temperature and time held at this temperature on the potential for formation of aldehydes needs to be investigated.

The rate of cooling can also have an influence on the structure of certain excipients which in turn may modify the drug release characteristics from the matrix itself (31).

4.4. Recommended Properties (Temperature And Viscosity) of Fill Materials

The important factors to bear in mind during a liquid filling operation are temperature and viscosity of fill material and in the case of a suspension the particle size of the suspended drug. Whereas in principle any excipient found to be compatible with the gelatin shell can be used, in practice in a manufacturing environment the viscosity of the fill material is important. If the viscosity is too low splashing of the bushings may occur which could contaminate the area of overlap between the capsule body and cap and prevent a good seal from being formed.

Absence of a clean break during dosing (“stringing”) can have the same effect.

The guidelines for problem free filling are given in *Table 3*.

4.5. Excipients compatible with hard gelatin capsules

The materials listed have been tested according to the procedures described above. Excipients which, from the aspect of compatibility, can considered to be suitable for formulation of drugs into hard gelatin capsules, are shown in *Tables 4, 5* and *6*. They have been classified into three arbitrary groups:

- Lipophilic liquid vehicles
- Semi-solid lipophilic vehicles/viscosity modifiers for lipophilic liquid vehicles
- Solubilizing agents, surfactants, emulsifying agents and adsorption enhancers

Excipients shown in *Table 7* are considered to be incompatible with hard gelatin capsules and should be avoided at high concentrations. They may, however, be used in mixed systems, in which case the critical concentration, above which compatibility could become an issue, must be determined experimentally.

It appears that the incompatibility of the medium chain monoglycerides may be due to the presence of quantities of glycerol remaining from the synthesis of these products. If the MCM’s are to be considered the glycerol level must be < 5%.

The compatibility screening of the final formulation including the drug substance must be monitored as part of the routine development process.

Recommended guidelines for dosing liquids/semi-solids into hard gelatin capsules	
Parameter	Recommendation
Temperature of fill material	Max. ~ 70°C
Viscosity at the temperature of dosing	0.1 - 1 Pa s
Visco properties	Clean break from dosing nozzle Absence of “stringing”
Particle size of suspended drug	< 50 µm

Table 3.

Lipophilic liquid vehicles	
Refined speciality oils	MCT's[1] and related esters
Arachis oil	Akomed E
Castor oil	Akomed R
Cottonseed oil	Captex 355
Maize (corn) oil	Labrafac CC
Olive oil	Labrafac PG
Sesame oil	Lauroglycol FCC
Soybean oil	Miglyol 810
Sunflower oil	Miglyol 812
	Miglyol 829
	Miglyol 840
	Softisan 645

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

(1) Medium chain triglycerides.

Table 4: Excipients compatible with hard gelatin capsule shells.

Semi-solid lipophilic vehicles / Viscosity modifiers for lipophilic liquid vehicles
Hydrogenated speciality 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
Gelucires 33/01, 39/01, 43/01
Glyceryl behenate (Compritol 888 ATO)
Glyceryl palmitostearate (Precirol ATO 5)
Softisans 100, 142, 378, 649
Steryl alcohol

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

Table 5: Excipients compatible with hard gelatin capsule shells.

Solubilizing agents, surfactants, emulsifying agents adsorption enhancers
Capryol 90
Gelucire 44/14, 50/13
Cremophor RH 40
Imwitor 191, 308[1], 380, 742, 780 K, 928, 988
Labrafil M 1944 CS, M 2125 CS
Lauroglycol 90
PEG MW > 4000
Plurol Oleique CC 497
Poloxamer 124 and 188
Softigen 701, 767
Tagat TO
Tween 80

(1) Glycerin content < 5%

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

Table 6: Excipients compatible with hard gelatin capsule shells.

At the 100% level the following excipients are incompatible with hard gelatin capsule shells	
Ethanol	PEG's of MW < 4000
Glycerin	Pharmasolve
Glycofurol 75	Propylene glycol
MCM's	Span 80
– Akoline MCM, Capmul MCM, Imwitor 308[1]	Transcutol P

(1) Glycerin content > 5%

Mixtures with compatible excipients may allow these to be used in lower concentrations. Limit must be determined experimentally.

Table 7: Excipients for liquid/semi-solid formulations.

European automatic capsule-filling machines for liquid filling		
Machine type	Number of capsules/segment	Approximate filling rate (capsules/H)
Robert Bosch GmbH		
GKF 400 L	3	10,000
GKF 800 L	6	30,000
GKF 1500 L (2 pumps)	6	60,000
Harro Hoefliger GmbH		
KFM III-I	1	3,500
KFM III	3	10,000
IMA Zanasi Division		
Z 12	2	12,000
Z 48 Plus	6	36,000
Z 85 Plus	11	70,000
MG2		
Compact	Continuous motion	4,000 - 34,000
Futura	Continuous motion	4,000 - 70,000

Table 8.

5. Filling and sealing equipment

5.1. Capsule Filling Machines

Most of the modern European capsule filling machines can be modified to allow hard gelatin capsules to be filled with hot or cold liquids. The machine requirements to allow an industrial manufacture of liquid filled capsules are reported by Cole (32) and the models available are given in *Table 8*.

5.2. Equipment for sealing hard gelatin capsules

An essential part of a liquid filling operation is the ability to effectively seal the capsule. Various methods are available to seal hard gelatin capsules and these have been reviewed by Wittwer (33). The two most studied methods are banding using a gelatin band and sealing using a hydroalcoholic solution and both methods are described in the General Information section of the USP on capsules (34).

5.2.1. Hard gelatin capsule banding technology

The banding of hard gelatin capsules is a process which has been commonly used and was originally developed to prevent separation of powder filled capsules prior to the invention of capsule locking systems. The capsules are first rectified and then passed once or twice over a wheel that revolves in a gelatin bath. A quantity of gelatin is picked up by the serrated wheel and applied to the junction of the cap and body. The capsules remain in individual carriers for drying. It is generally accepted that the industrial banding operation is capital intensive and not user friendly.

Stages of the hard gelatin capsule sealing process	
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 completes the melting over a period of about one minute and the two gelatin layers are fused together to form a complete 360° seal.
3. Setting	Gelatin setting or hardening process is completed while the product returns to room temperature. This process is best carried out on trays.

Table 9.

Comparison of the hard gelatin capsule sealing and banding technologies		
Aspect	Capsule sealing using LEMS™	Capsule banding
Installation and start-up	Easy, Quick	Difficult, Time consuming
Machine operation	User friendly	User unfriendly
Initial capital costs	Low	High
Time for size change	~ 1 hour	~ 8 hours
Capsule rectification	No	Yes
Cleaning Time	2 - 3 hours	~ 12 hours
Sealed area	Large	Small area of band
Gelatin handling	No	Yes
Current maximum machine output	30,000 / hour	80,000 / hour
Solvent exhaust	Yes	No

Table 10.

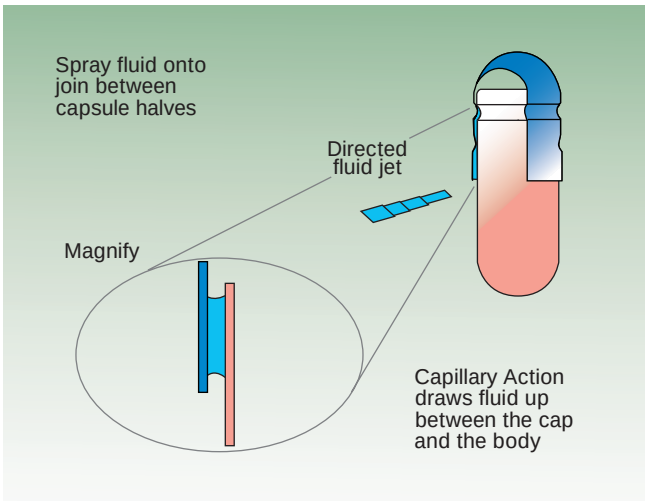

Figure 3: Illustration of spraying process to moisturize the space between cap and body of the capsule.

Figure 4: LEMS™ 30 machine for sealing hard gelatin capsules.

5.2.2. Hard gelatin capsule sealing technology by microspray

The capsule sealing process, which was first described by Wittwer (33) and subsequently by Cadé et al. (15), uses the principle of lowering of the melting point of gelatin by the application of moisture to the area between the capsule body and cap.

The first machine developed to seal capsules, described by Cadé et al. (15) involved dipping the capsules into a bath of liquid and drying in a fluidized bed chamber. During this process the capsules were subjected to considerable stress. In contrast to this, in the redesigned process every capsule is individually sprayed with a micro amount of sealing fluid at the body and cap junction as shown in *Figure 3*. Drying takes place by gently tumbling the capsules in a rotating drum. The various stages of the process are outlined in *Table 9*.

Control of the filled and sealed capsules is carried out as follows:

- Inspection on trays after 24 hours.
- Inspection after depression test at - 0.8 bar for 20 minutes.
- Inspection after 18 hours at 45°C after cooling to room temperature.

By incorporation of a dye tracer into the sealing fluid and observation of the liquid in the overlapping space it could be verified that the sealing liquid does not pass beyond the interlocking rings of a Licaps™ capsule.

The machine for industrially sealing hard gelatin capsules, shown in *Figure 4*, is commercially available and is marketed under the name LEMS™ 30[(1)] (Liquid Encapsulation by MicroSpray).

The machine is free standing and in practice is connected to the output of a capsule filling machine by means of a conveyor.

Numerous companies familiar with the hard gelatin capsule banding operation have evaluated the capsule sealing technology using LEMS™ and over a period of time a neutral comparison of the two processes has been possible. This comparison is shown in *Table 10*.

(1) LEMS™ is a registered trade mark of the Capsugel Division of Warner-Lambert Company.

6. Conclusion

The ability to be able to fill liquids and semi-solids into hard gelatin capsules has been an option for several years. The technology potentially provides the industry with an in-house process to develop drugs which are poorly water soluble, have low melting points, are highly potent or low dosed or have a critical stability issue, into bioavailable, stable and safe dosage forms.

One problem which has prevented wider acceptance of this technology was the fact that the capsules had to be banded using a process which is difficult to operate and capital intensive. Development of the LEMS™ technology provides a means to effectively seal hard gelatin capsules using a process which is easy to control.

Liquid filling and sealing of hard gelatin capsules thus becomes a much more feasible option. It provides the formulation scientist with an in-house option to rapidly develop products for clinical trials when drug substance is at a premium and also provides an easy route to scale-up and production.

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