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LIQUID FILLED AND SEALED HARD GELATIN CAPSULES [1]

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ABSTRACT

A method for sealing liquid filled hard gelatin capsules has been protection against oxidation, have very effective barrier properties against bad smelling products and have short disintegration times. These properties demonstrate that the liquid filled and sealed hard gelatin capsule offers a real alternative to the soft gelatin capsule.

INTRODUCTION

The development of the capsule originated from the desire to find an ideal oral dosage form for administering active substances which have an unpleasant taste or are difficult to swallow. Since approximately 1900, when the first industrial production was started by Parke-Davis & Co. in Detroit, it has traditionally been used as a container for powdered materials. However, as early as 1892 Pohl[2] described the hard gelatin capsule as being suitable for dispensing oils and Tschanter[3] in 1896, described a holder to keep the capsules upright while filling with such liquids. With the perfection of the rotary die process in the 1930's for producing soft gelatin capsules interest in using the hard gelatin capsule as a unit dosage form waned for dispensing liquids. Only in the late 1970's with the activities of Cuiné and others[4, 5, 6, 7] and Walker and

1. Marketed under the trade name LICAPS™

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others[8] was interest renewed in the liquid and paste filling of hard gelatin capsules. These activities concentrated on the formulation of the capsule contents into pastes having a consistency which was reported to be sufficient to withstand leakage from the unsealed capsule. The disadvantage of this method is the necessity to formulate the capsule contents into a paste with a melting point of 45° C or above. This can result in bioavailability and chemical stability problems.

A second approach was to seal the hard gelatin capsule after filling with a liquid or paste thereby eliminating the risk of leakage during storage at elevated temperatures. The various sealing methods described in the literature have been reviewed by Wittwer[9].

We at Capsugel have concentrated on developing a method to industrially seal oil filled hard gelatin capsules and this article describes the process and the properties of the product obtained.

SEALING PROCESS

Principle of Sealing

The sealing process developed by Capsugel has been protected by corresponding patent rights and operates by contacting the capsules with water containing selected water-miscible organic compounds. A water-ethanol mixture is used, thereby eliminating any problems concerning the legal and toxicological status of additives. The low surface tension and the resulting high capillary forces of this liquid allow its rapid penetration between the capsule body and cap. The area over which sealing takes place is shown in Fig. 1.

By the application of moderate heat the body and cap are melted together, thereby creating a sealed unit.

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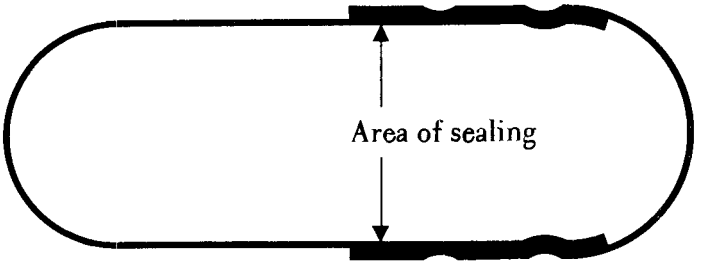

FIGURE 1

Diagram showing area of sealing of a liquid filled hard gelatin capsule.

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Sealing Method

The filled capsules are transferred directly from the filling machine into the contacting unit of the sealing machine, shown diagramatically in Fig. 2. The contacted capsules are transported into one of the fluidized bed chambers where the excess liquid from the surface of the capsules is removed at room temperature. After this phase, the temperature is increased to approximately 45° C to bring about the sealing of the cap and body. The two chambers operate in opposite cycles with one drying while the other is sealing. As soon as the sealing phase is completed, the capsules are discharged and the cycle repeats itself. The total processing time is 6 - 7 minutes.

The sealing machine[10], which is suitable for all capsule sizes without modification, has a theoretical capacity of up to 100.000 capsules per hour, depending on the capsule size.

After the capsules are discharged from the sealing machine it is recommended to spread them onto trays for inspection. As for normal powder filled capsules, packaging into blisters or bottles can be considered.

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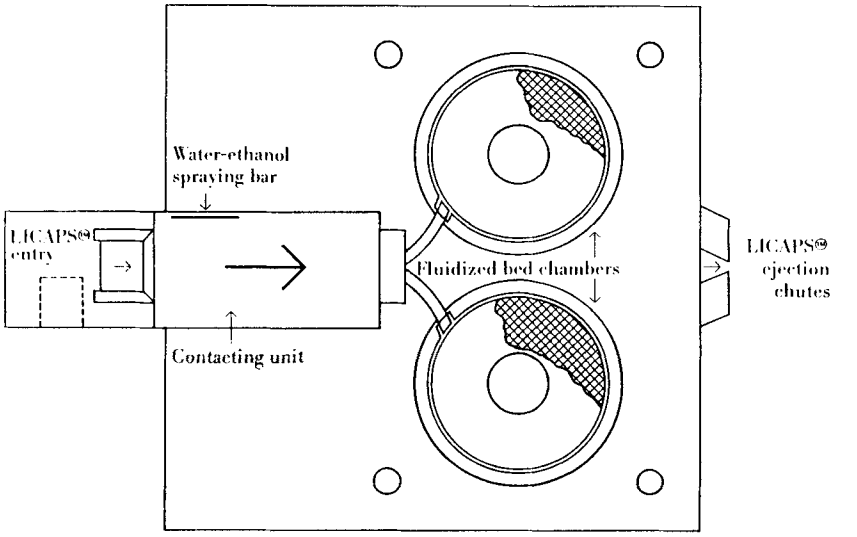

FIGURE 2

Plan view of sealing machine

FILL MATERIALS

Pure oily products with a viscosity preferably above approximately 100 cP can be filled and sealed without the necessity to add thickening agents. Thus products such as vitamin E, vitamin A and A+D oily solutions, garlic oil etc. can be filled and sealed into capsules without modification. This allows the maximum concentration and the minimum capsule size and also reduces the risk of stability problems. Suspensions of powdered drug substances in oils are also ideally suited and if necessary they may be thickened by the addition of suitable excipients (Table 1).

As generally known, highly hygroscopic excipients, such as glycerin, sorbitol, propylene glycol and polyethylene glycols of molecular weight below approximately 1000 should be avoided as they are not compatible with the capsule wall.

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Table 1: Examples of oily suspending agents and thickening agents which may be considered for filling into capsules.

Oils	Thickening Agents
Fixed oils	
Arachis oil	Hydrogenated arachis oil
Castor oil	Hydrogenated castor oil (Cutina HR)
Fractioned coconut oil	Stearic acid
(Miglyols, Neobee)	Steryl alcohol
Maize oil	Precirol
Soya oil	Magnesium Stearate
	Gelucire
	Lecithin
Paraffins	
Liquid Paraffin	
Light liquid paraffin	
Silicones	
Dimethicones	
Esters	
Isopropyl Myristate	
Isopropyl Palmitate	

The physical characteristics of the fill material should be such that it can be satisfactorily dosed by the filling machine between room temperature and approximately 70° C.

PHYSICAL PROPERTIES

Weight Uniformity

The weight uniformity of capsules filled using two commercially available filling machines was determined using the liquid products vitamin A, peanut oil and vitamin E. The results are given in Table 2.

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Table 2: Weight uniformity of liquid filled capsules
Sample size 30 capsules

Product	Vitamin A Palmitate	Peanut oil	Vitamin E
Machine	H + K GKF 400 L	ZANASI Z 5000-A3	ZANASI Z 5000-A3
Filling rate capsule/hour	11,000	30,000	30,000
Capsule size	2	1	1
Mean filled capsule weight (mg)	339	398	405
S rel % (Capsule + fill)	0.5	0.4	0.5

The mean weight of the empty size 1 capsules was 77 mg and the relative standard deviation was 2.2%.

Hence the relative standard deviation of the fill weight of peanut oil and vitamin E was 0.16% and 0.23% respectively. This is certainly equal to or better than the fill weight uniformity achievable with the soft gelatin capsule[11]. It thus follows that if a dispersion of a powdered drug substance in an oil is kept homogeneously stirred and free of air bubbles a satisfactory content uniformity of a low dosed product can be achieved, as described by Walker and others[8].

Protection against Oxidation

Vitamin A was used as a model substance to test the protective properties of the capsule against oxygen. The formulation used is given in Table 3.

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Table 3: Composition of vitamin A solution

	mg/capsule
Vitamin A Palmitate 1.7 m I.U./g [1]	32.0
stabilized with Tocopherol (ROCHE)	
dl-α-Tocopherol	7.2
Arachis oil peroxide-free	336.8
	376.0 mg

[1] Theoretical vitamin A content

The capsules were stored at 5° C, 25° C, 35° C and 45° C in HDPE bottles and analysed at intervals of 3, 6 and 12 months. The results are given in Table 4.

The same solution stored for 3 months in a tighty stoppered glass container at 25° C had a vitamin A retention of 97%. In view of the critical stability of vitamin A these results are fully satisfactory and demonstrate that little or no air entered the capsule. The sealed capsule is a good barrier against oxidation and thus an attractive form for encapsulation of sensitive products such as vitamins, essential oils and unsaturated fatty acids.

Barrier properties towards bad smelling products

Comparative tests between soft and hard gelatin capsules containing the bad smelling products valerian, fish oil and garlic oil were performed. The contents of the soft gelatin capsules were transferred into the hard gelatin capsule and the capsules sealed using the procedure described.

The capsules were submitted to a panel of experts of an internationally reputable perfume house and their assessment is given in Table 5.

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Table 4: Vitamin A content of capsules after storage

		Vit. A content I.U. ± 2%	% Retention
Initial		58,900	100
3 months	5° C	56,900	97
	25° C	57,000	97
	35° C	58,000	98
	45° C	52,700	89
6 months	5° C	55,800	95
	25° C	54,500	93
	35° C	54,100	92
	45° C	49,800	85
12 months	5° C	54,400	92
	25° C	54,800	93
	35° C	49,500	84
	45° C	46,800	79

Table 5: Smell assessment of soft and hard gelatin capsules

Contents of capsule	Smell assessment	
	Soft gelatin capsule	Hard gelatin capsule
Fish oil	Bad fishy smell	No smell
Valerian	Bad valerate smell	No smell
Garlic oil	Very strong garlic smell	No smell

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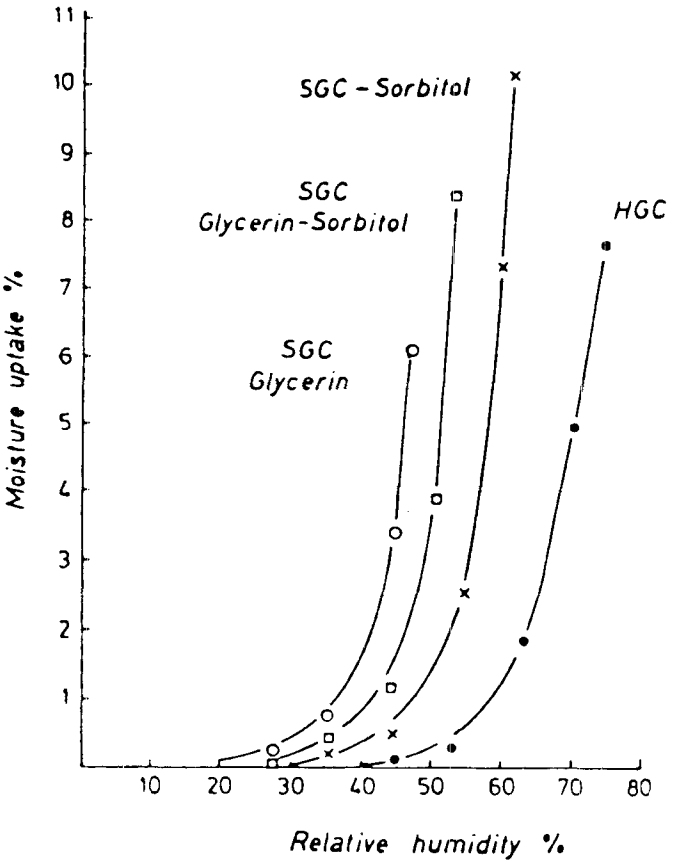

FIGURE 3

Sorption isotherms of gelatin capsules measured at room temperature. From Bauer[11].

The soft gelatin capsule shell always contains a plasticizer. Commonly used are glycerin, sorbitol or combinations of these up to a concentration of 30 - 35%. Although the moisture content of the soft gelatin shell after 3 - 8 days drying reaches 7 - 8%[11], the presence of a plasticizer results in a much more hygroscopic gelatin film then is the case for a hard gelatin capsule (Fig. 3).

Hom and others[12] have reported that the permeability to oxygen of a soft gelatin film is directly proportional to its moisture content and inversely

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Table 6: Disintegration time of soft and hard gelatin capsules

	Soft gelatin capsule Size 16 oblong Content: 1.0 g	Hard gelatin capsule Size 0 Content: 0.8 g
Time to opening	4 - 5 min	0.5 - 1 min
Disintegration time	9 - 10 min	4 - 5 min

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proportional to its thickness. Even though the thickness of a hard gelatin capsule wall is approximately four times smaller than that of a soft gelatin capsule wall, the volatile components of bad smelling products do not pass through the wall of a hard gelatin capsule. We suggest that the reason for the greater permeability of the soft gelatin shell is the decreased viscosity of the capsule wall due to the presence of plasticizer resulting in a greater mobility of gas molecules within the gelatin network.

Disintegration Time

The contents of a multivitamin soft gelatin capsule were transferred into hard gelatin capsules and the capsules sealed using the procedure described.

A comparative disintegration test was carried out using the method described in the European Pharmacopoeia. Discs were used in both cases. The results are shown in Table 6.

Both capsules met the European Pharmacopoeia specifications but the disintegration of the hard gelatin capsule was faster than the soft gelatin capsule. In view of the difference in thickness between the wall of soft and hard gelatin capsules this result is not surprising.

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CONCLUSIONS

The soft gelatin capsule has been to date the dosage form of choice for such products that are liquid in their normal form, are very hygroscopic or unstable, have a very low melting point or are very low dosed. The properties described demonstrate that the sealed hard gelatin capsule offers a real alternative to the soft gelatin capsule offering:

- excellent weight uniformity
- good protection against oxidation
- very effective barrier properties against bad smelling products
- shorter disintegration time.

In addition the following advantages are important for the pharmaceutical industry:

- in-house manufacturing possible
- real possibilities for product differentiation
- lower manufacturing costs
- local production where import of finished product is forbidden
- sealed hard gelatin capsules do not stick together
- reduced risk of microbial contamination due to the absence of hygroscopic plasticizers
- same blistering equipment for liquid and powder filled capsules.

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