USE OF HARD CAPSULES AS CONTAINER IN LIPID BASED FORMULATIONS. CAPSULE FILLING TECHNOLOGY
INTRODUCTION

Pharmaceutical drug discovery and development has undergone astounding change in the last few decades. These have been fueled by advances in many areas, especially cell and molecular biology, recombinant DNA technology, genomics, proteomics, biochemical and chemical informatics, as well as laboratory equipment and automation. At the same time, new and more efficient manufacturing technologies and processes have enabled purer and more potent drugs to be produced.

These facts have led to an increase in the complexity of the drugs structure developed (figure 1) and its physic chemical properties.

The oral absorption of a drug is fundamentally dependent on that drug's aqueous solubility and gastrointestinal permeability. Extensive research into these fundamental parameters has led to the Biopharmaceutics Classification Systems (BCS) that categorizes drugs into four groups, Class 1-Class 4 (Figure 2). The BCS classifies compounds based on the critical components related to oral absorption. Centrally embracing permeability and solubility, the objective of the BCS is to allow prediction of in vivo pharmacokinetic performance of drug products from in vitro measurements of permeability and solubility.

Nowadays the easy molecules are already discovered, only 5 % of the drugs under development belong to the category I (high bioavailability), 70 % belong to Class 2, this fact means that the bioavailability of these drugs is low and it is necessary to increase solubility in order to improve its bioavailability.

However, this is not a limiting factor and it is possible for R&D scientists to improve the solubility and permeability by various means of formulation modification. One of these technologies is the use of lipid based formulations (1-5).

<table>
<thead>
<tr>
<th>CLASS 2</th>
<th>CLASS 3</th>
<th>CLASS 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles</td>
<td>Permeability enhancing excipients</td>
<td>Solubility and permeability enhancing excipients</td>
</tr>
<tr>
<td>Select more soluble polymorphs</td>
<td>Efflux inhibitors</td>
<td>Pro-drugs</td>
</tr>
<tr>
<td>Liquid filled capsules</td>
<td>Pro-drugs</td>
<td>Gastroretention</td>
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<td>Solid dispersions and solutions</td>
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<td>Addition of surfactant</td>
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Approaches to increase API solubility (From Ref 6)
LIPID BASED FORMULATIONS

Fundamentals
The principle behind lipid based formulation is not complicated. Drug must be dissolved in a mixture of solvents. This mixture may consist of: Triglycerides, mixed glycerides, cosolvents (i.e. PEG, Propylene glycol), water insoluble surfactants (i.e. Tween 80), water soluble surfactants (i.e. Cremophor EH 40), solubility enhancer (Acconon MC 8/2) and additives (i.e. α tocopherol).

The key for the formulator is getting the mixture that dissolves the drug, increases the drug bioavailability and is compatible with container (capsule).

To complete the process a suitable capsule and a filling machine to fill the liquid formulation is necessary.

Advantages
Apart from the bioavailability increase, lipid based formulations reduce the food effect. This effect on drug absorption leads to a serious concern about the sub-therapeutic plasma drug concentration when co-administered without food, this is a serious problem for drugs with a narrow therapeutic index, where increased bioavailability may lead to serious untoward effects.

ELEMENTS OF LIQUID- FILLING TECHNOLOGY

Capsules
A container must be used to accommodate the liquid. There are mainly two possibilities: Hard capsules and soft capsules. Hard capsules offer the following advantages versus soft capsules:

- Capsule wall thickness. Hard capsules contain 3 times less material than soft capsules. As result of this, hard capsules will disintegrate faster due to the capsule wall thinner than the walls of soft capsules.
- Plasticizer: Hard gelatin capsules do not require plasticizer. They consist of gelatin and water. Soft gelatin capsules require addition of glycerin or sorbitol for softening purposes.
- Stability: Hard capsules are stable in hot climates while soft capsules tend to stick together and become gluey.
- Migration: Hard capsules yield less drug migration into the shell and less diffusion of odors.
- Dimensions: Hard capsules have constant external dimensions (easier blistering/packaging), soft capsules vary according to filling weight and vary throughout a batch.
- Heat resistant: Hard capsules allow filling of thermo-stable substances up to 80ºC. In soft capsules filling temperature is limited to about 35ºC (there is some new development in soft capsules technology where this limitation seems to be reduced).
- The important point formulators shall consider while using hydrophilic carrier is compatibility with hard shells since the shell does not contain plasticizer unlike softgel capsules.

There are two options available: Gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules. It is out of scope of this paper making a deep analysis of these products, but summarizing it can be said that the main differences between these capsules are the moisture content, HPMC has lower moisture content, and the mechanical properties. HPMC capsules are more elastic and gelatin becomes brittle at low relative humidity.

Suppliers offer two alternatives in HPMC capsules: With gelling agent and without gelling agent. Some studies suggest that the lack of gelling agent in shell appear to have a detrimental effect on compatibility of the liquid solvents, resulting in splits and cracks observed immediately after banding (9-11).
Just summarizing the main advantage of hard HPMC capsules vs soft gelatin capsules is the lower moisture content. They remain stable when exposed to heat or humidity and related to the nature some people do not like taking gelatin capsule because of their religious affiliation that do not permit them to consume part of animals.

The geometry of capsules for liquid filling must be different that the geometry of capsules used for oral solid dosage forms. In liquid filling the capsules are filled and, after a time, the capsules are sealed and dried. Because of this, capsules must be designed suitably for accommodating liquid. The design has been modified in capsules used for liquid encapsulation to avoid bubbles formation on sealing and to also prevent a “banana effect” in capsules post-band sealing.

Flofit technology (ACG) offers a capsule with a special design that avoids these problems.

Sealing
Sealing two piece hard capsules serves two basic purposes: It creates a leak-proof closure to contain oil, pastes, and other liquids and non-solids and enables manufacturers to comply with the regulatory requirement for OTC (over the counter) capsule products sold in the USA (FDA’s compliance Policy Guide 400.500).

There are two main procedures in the industry: Application of a gelatin or HPMC solution on the gap between cap and body junction (adhesion of band to external shell surface) or micro spraying aqueous Ethanol between the cap and body gap (fusion of inner cap and outer body surface).

The first mechanism shows advantages in terms of visible sealing, leak detection, tamper evident property and product suitability for subsequent coating.

Fluidocap S40 and S70 (ACG) with outputs of 70000 capsules per hour are a good example of this filling and sealing technology. (12-13).

Filling machines
Two – piece capsules can be filled easily with liquid formulations at all the required levels of demand. Experimental batches can be filled manually using a hypodermic syringe. This process is useful for preliminary investigations into capsule shell integrity and compatibility with excipients, as well as in-vitro and in-vivo dissolution and pharmacokinetic studies at initial development phase. There are semi-automatic and automatic filling machines available for all scales of output from bench to commercial production. There are minimal challenges to scale-up to a production scale because increase in output is achieved by using multiples of dosing pumps.

The right filling machine should fulfill these requirements:
• Machine should be able to maintain the product at a constant temperature up to 80ºC
• Machine should be able to maintain a homogeneous suspension in the product hopper and filling block.
• Machine should be able to fill accurate doses of volumes ranging from 0.1 to 1.0 ml
• Machine should be able to eject a filled capsule body when the cap is missing
• Machine should be able to control specific dosing when cap and body is not separated.
• Machine should be able to fill dosage with wide range of viscosity value
• Machine should have a compatible Band sealing machine for 100% sealing of capsules (14-16).
This technology is used by many pharma companies for drugs which are under development, for example Astra Zeneca is using hard HPMC capsules for developing AZ6244 (selumetinib). This drug is being developed for the treatment of various types of cancer. Oramed Inc, is developing oral insulin with liquid filled capsules and recently (April 2017), a patent has been granted by European patent office.

Chiasma is developing Octreotide, growth hormone inhibitor used to treat acromegaly, the formulation is based on Chiasma’s transient permeability enhancer system which combines excipients to form an oily suspension of solid hydrophilic particles in a hydrophobic medium, which protects the active and allows it to permeate through the gut wall.

Present and Future

The technology is not new and there are a lot of products by many manufacturers are available in the market using this concept. In table 1 are shown some of them.

<table>
<thead>
<tr>
<th>Active</th>
<th>Brand</th>
<th>Dosage Form</th>
<th>License holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danthron</td>
<td>Co Danthroner</td>
<td>Hard Capsule</td>
<td>Napp</td>
</tr>
<tr>
<td>Captopril</td>
<td>Captopril R</td>
<td>Hard Capsule</td>
<td>Sankyo</td>
</tr>
<tr>
<td>Pepperment oil</td>
<td>Colpermint</td>
<td>Hard Capsule</td>
<td>Jansen</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Claravis</td>
<td>Hard Capsule</td>
<td>Teva</td>
</tr>
<tr>
<td>Mebeverine</td>
<td>Mebeverine</td>
<td>Hard Capsule</td>
<td>Teva</td>
</tr>
<tr>
<td>Dutasteride/Tamsulosin</td>
<td>Combodart</td>
<td>Hard/Soft Capsule</td>
<td>GSK</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Neoral</td>
<td>Soft capsule</td>
<td>Novartis</td>
</tr>
<tr>
<td>Ritonivir</td>
<td>Norvir</td>
<td>Soft capsule</td>
<td>Actavis</td>
</tr>
</tbody>
</table>
Some researching works in this area are innovative and challenging. University of Innsbruck is developing systems to increase the bioavailability of drugs changing the zeta potential of the formulation “in situ” (Flip-Flop system) (figure 6).

There are two main areas where this technology is expected to grow strongly in the future: Highly potent APIs (HPAPIs) and semi-solid formulations:

- **HPAPIs.** Liquid formulations in hard shell capsules are becoming a preferred option for HPAPIs because of advantages such as improved safety and lower risk of potential exposure and product cross contamination. Although they form a relatively small portion of the API market, HPAPIs are thought to be one of the fastest growing segments in the pharmaceutical industry. The global HPAPI market is expected to hit 25.86 billion$ by 2022 with oncology being the primary driver for this increasing demand.

- **Semi-solid formulations.** They are mixtures at liquid state in the filling process solidifying in the hard capsule to form a non-porous crystalline plug, or solid dispersion. These formulations can be used not only to improve dissolution of active substances with low aqueous solubility but also to sustained release from relatively simple formulations (17-20).

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