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CHALLENGES AND OPPORTUNITY IN ENCAPSULATION OF LIQUID FILLED IN HARD GELATIN OVER SOFT GELATIN CAPSULES - AN INNOVATIVE TECHNOLOGY

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ABSTRACT

The encapsulation of liquids provide solutions for convenient delivery through improved oral absorption of poorly water-soluble drugs. In addition, low dose (content uniformity), highly potent (containment), low melting point drugs, those with a critical stability profile and those for which a delayed release is required are candidates for liquids. The choice of a hard or soft capsule will depend primarily on the components of the formulation which provide the best absorption characteristics as well as on the physical characteristics, such as the viscosity of the formulation and the temperature at which the product needs to be filled. Numerous excipients are available for formulation of lipid-based systems and their compatibilities with hard gelatin capsules have been tested. The availability of new enhanced manufacturing equipment has brought new opportunities for liquid-filled hard capsules. Filling and sealing technologies for hard capsules, provides the formulator with the flexibility of developing formulations in-house from small scale, as required for Phase I studies, up to production. **Liquid-fill hard capsule technology** is becoming increasingly accepted by the pharmaceutical industry and – while it can hardly be expected to replace more conventional dosage forms such as tablets and powder-filled capsules – it will become a mainstream alternative for those products with particular processing or clinical needs. Liquid filled hard gelatin capsule are well established as a solid dosage form for convenient administration of drugs orally in a liquid form in two piece HPMC capsule. This technology is more adopted for insoluble hydrophobic and potent drugs. And there are also many advantages in giving the drug in liquid form. Hence drug compounds are solubilised inside the hard gelatin capsules such that on subsequent dissolution of LFHGC in the gastro intestinal tract, the drug remains in solution, and contribute for good bioavailability of drugs.

INTRODUCTION

Liquid filled hard gelatin capsule are well established as a solid dosage form for convenient administration of drugs orally in a liquid form. Liquid filled capsule technology can be used for liquid and semisolid fills in two piece gelatin or HPMC capsule with or without banding. This range of liquid composition available to accommodate even the most challenging drug compounds in capsules has increased significantly in recent years. In particular it is possible to solubilize many drug compounds in a micro emulsion pre-concentrate inside the hard gelatin capsules such that on subsequent dispersion in the gastro intestinal tract, the drug remains in solution. 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 formulation when only small quantities of drug substance is available.

The Hard gelatin capsule has historically been used as a dosage form for pharmaceutical and Nutraceutical products that are formulated as powders or pellets. Liquid-fill hard gelatin capsule technology was established in the early 1980s as an alternative to soft gelatin capsules and offered a number of specific advantages such as lower moisture and gas transmission, use of high melting point excipients, plasticizer- and preservative-free, lower moisture content, ease of coating and choice of capsule composition (gelatin and hydroxypropyl methylcellulose, HPMC).

This technology is most suitable for: Insoluble compounds, highly potent compounds

After filling the hard gelatin capsules they are sealed by spraying small amount of Water \ethanol mixture at the cap and body interface followed by gentle warming to fuse the two capsules parts together. Materials which have low melting points or are liquids at room temperatures presents difficulty when formulated as dry powders and often requires high concentration of excipients to avoid processing problems.

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 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.

Fig 1 Shows the reasons for formulating actives in liquid dosage form.

A capsule is a shell or a container prepared from gelatin containing one or more medicinal and/or inert substances. The gelatin capsule shell may be soft or hard depending on their formulation. In the manufacture of pharmaceuticals, encapsulation refers to a range of techniques used to enclose medicines in a relatively stable shell known as a capsule, allowing them to be taken orally.

The two main types of capsules are:

- Hard-shelled capsules, which are normally used for dry, powdered ingredients or miniature pellets (also called beads that are made by the process of Extrusion and spheronization) - or mini tablets;
- Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Soft capsules have been used as unit dose containers for liquids for many years whereas hard capsules have conventionally been used for delivery of solids in the form of powders and pellets. Over the last 25 years, new equipment has become available for filling and sealing liquids and semisolids into hard shell capsules thereby providing a viable option for filling such materials into hard capsules, as opposed to soft capsules

. **HARD GELATIN CAPSULES:**

- The majority of capsule products are made of hard gelatin capsules. Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits snugly over the open end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colorless, and essentially tasteless.

- Gelatin is a product obtained by partial hydrolysis of collagen acquired from the skin, white connective tissue, and bones of animals. Gelatin is a protein which is soluble in warm (or hot) water, but insoluble in cold water. Gelatin capsules become dissolved in warm gastric fluid and release the contents.

  Normally, hard gelatin capsules contain 13–16% of moisture. If additional moisture is absorbed when stored in a high relative humidity environment, hard gelatin capsule shell may lose their rigid shape and become distorted. In an opposite environment of extreme dryness, capsules may become too brittle and may crumble during handling. Since moisture can be absorbed or released by the gelatin capsules, capsules containing moisture-sensitive drugs are usually packaged in containers. Gelatin for making hard shells is of bone origin and has 220–280 g bloom strength (the weight required to depress a standard plunger 4 mm into the gel).

Here are some of the formulation paramaters were compared between hard gelatin capsules and soft geltin capsules in Table1

Tab 1: ***Hard gelatin capsules*** *are preferred over* ***Soft gelatin capsules*** *due to following reasons*

FORMULATION PARAMETER	HARD GEL CAPS	SOFT GEL CAPS
Bio Availability	Good(For comparison with soft gel, further studies are to be conducted)	Good(For comparison with soft gel, further studies are to be conducted)
Stability	Good	Good
Weight variation	Minimum	High(6% to 8%)
Hot melts	Up to 70 degree centigrade	Up to 35 degree centigrade
Thru put time	Input of capsule & medicament into LF machine followed by band sealing & skin drying .10 hours time(for & inclusive of an eight hour shift production shift).	Soft gel encapsulation to drying process: 60 to 72 hours.

Dissolution time	Lesser dissolution time in comparison (Ibuprofen in HGC dissolves in less than 5 min)	
Combination filling	Liquids & pellets possible	Not possible
Shrinkage	No such issue	Non uniform during long period of drying process
Process	Simple	Operation, complex & messy
In house control	Yes	Out sourced
Gelatin wastage	Not applicable	40% in web
Environmental Issues	No such issue	Gelatin is buried directly or buried after incineration
Plasticizer	No	yes
Risk of drug migration	Low	High for drug 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
Capsule dimensions	Constant	May vary

Water Content - The soft gel shell has far higher water content than the hard capsule shell which is not acceptable for moisture sensitive products.

Plasticizers - Soft gels contain plasticizers (usually Glycerol or Sorbitol) which can migrate into the contents of the capsules or can aid migration of the filled material into the shell. The HPMC / Gelatine used in hard capsule shells contain no plasticizer.

Fill Vehicles - Thermo softening vehicles (melting at above 35 degrees C) are not acceptable for soft gel filling. Hard capsules can be filled at up to 75 degrees C offering a wider range of suitable excipients, particularly for controlled release formulations.

Microbial Growth- Soft gels are more susceptible to microbial growth due to higher moisture content.

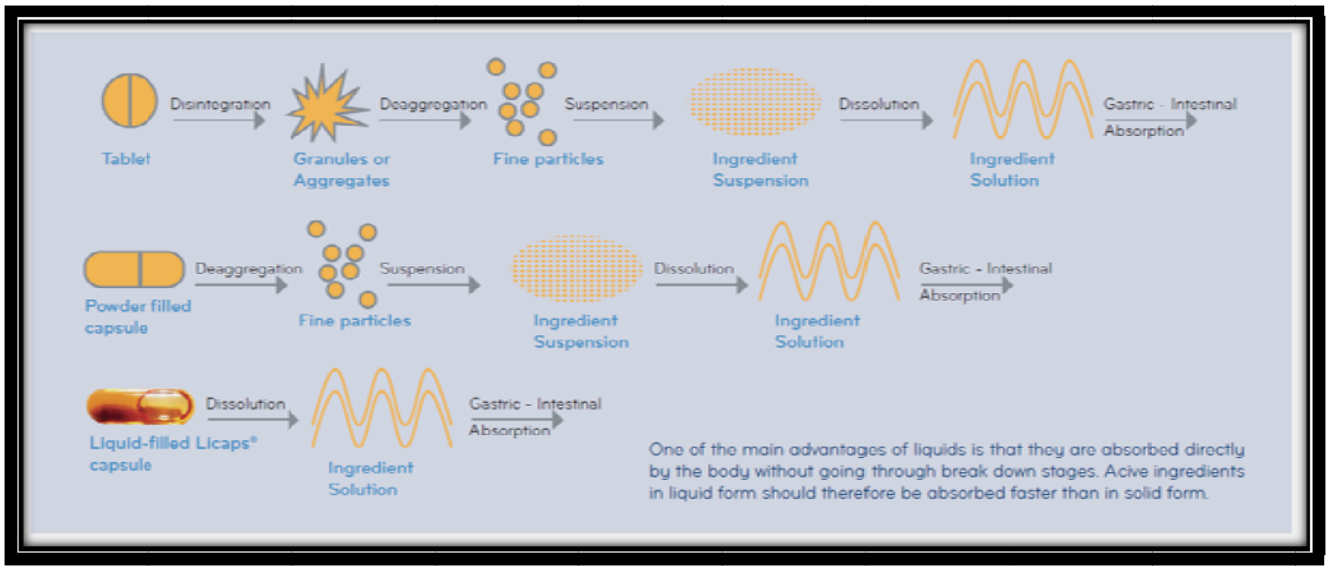
Shell permeability - Soft gels are more susceptible to moisture and gas transmission and can be an issue to oxidation sensitive products. This is caused mainly by the presence of plasticizers in soft gels which create channels in the shell that are larger than those found in hard capsules.

Coating- Hard capsules are generally regarded as being easier to coat (e.g. Enteric coating) than soft gels.

Intellectual property of shell - Liquid formulations may require a formulation of the shell itself. If this is contracted out to a soft gel manufacturer, intellectual property rights to the shell typically remain with the contract manufacturer, therefore limiting the possibility of changing manufacturers. This is not applicable for hard capsules which do not require reformulation of the shell.

Solvent - Soft Capsules are washed either with Benzene / Kerosene or any other organic solvent after filling operation which leaves traces of the solvent on the capsules which is not required for hard capsules.

LIQUID FORMULATION BENEFITS OVER TABLETS AND POWDER FILLED DOSAGE FORM



MODE OF SELECTION OF DRUGS :

1) Poor solubility drugs:

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. Lahr [10] made use of these advances in filling equipment technologies and developed a semi-solid formulation for nifedipine and the hard gelatin capsule was shown to be bioequivalent to nifedipine oral liquid and soft gelatin capsules [11].

Liquid and semi-solid filled hard capsule lipidic formulations are also ideally suited to compounds with low aqueous solubility, poor permeability and consequently low or variable bioavailability. Formulations which increase the solubility of the active or indeed present the drug as a solution can have a significant impact on the bioavailability of such drugs. Lipidic vehicles are generally well absorbed from the GI tract and in many cases this approach can significantly improve the oral bioavailability compared with administration of the solid drug substance. Yessksel et al. [12] performed an *in vivo* comparison of hard gelatin capsules filled with pure piroxicam API or a formulation using polyglycolized glyceride Gelucire 44/14 and Labrasol. The area under the plasma concentration versus time curve (AUC) and rate of absorption from the semi-solid formulation were higher than that following administration of pure API. The use of a capsule filled with a semi-solid formulation may be advantageous in treating painful conditions where analgesic effect is desired.

2) Low dose/high potency:

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

Content uniformity

It has been reported [13,14] that the pumps on capsule filling machines used for dispensing liquids are capable of achieving weight variations of <1%. Consequently for a low dose API in solution excellent content uniformity would be achieved. A formulation which incorporated 20 µg of a model drug, triamterene, was shown to have a content uniformity of 1.8% for liquid-filled capsules compared to 3.1% for powder filled capsules [15].

Containment: A semi-solid formulation of phenacetin (3 mg dose) was used to demonstrate the potential for containment of API during filling of capsules [16]. Swab tests on the surfaces of various parts of the filling machine after completion of a filling operation revealed that no API was

present on any of the capsule-filling machine bushings, which would not be achievable when powders are filled. The lower detectable limit of the analytical method was 0.25 µg. This result indicates that the incorporation of potent drugs into liquid fill materials has the potential to drastically reduce the danger of exposure of operators to dust particles.

3) 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 and the oily vitamins. During any tableting or capsule-filling operation heat is generated by friction. Consequently any API with a low melting point may stick to tooling surfaces or change parts thereby introducing potential processing or stability issues. Similarly, if an API is liquid at room temperature a large amount of excipient is required to convert the API into a free flowing powder which can result in the production of an excessively large dosage form that will be difficult to administer. Commercially available products which fall into this category include fish oils, vitamins A and E and phospholipids. Low-meltingpoint compounds are also suitable candidates for liquid filling. The low-meltingpoint drug can be dissolved in a single liquid vehicle and encapsulated. When these types of compounds are formulated as a powder for encapsulation Or compression into a tablet, they typically require high excipient loads to process reliably.(17)

4) Critical stability profile

In certain cases the stability of a drug is adversely affected by the environmental conditions, particularly exposure to high humidities. The stabilizing effect, on an unstable API, following the production of systems of fusible excipients was investigated and applied to vancomycin formulations [30]. Vancomycin hydrochloride is freely water-soluble and hygroscopic and if not packaged appropriately absorbs large amounts of moisture with subsequent instability. When first marketed a unit dose of vancomycin was filled into glass vials for reconstitution immediately prior to use. The incorporation of vancomycin into a polyethylene glycol (PEG) matrix protected the drug from moisture and when filled into hard gelatin capsules produced a stable and convenient dosage form. The capsule formulation produced systemic levels of the antibiotic similar to those obtained following administration of a solution of the API [18].

The chemical stability of oxygen-, moisture- and light-sensitive drugs can be significantly improved by using liquid or semi-solid capsule products. By dissolving the drug in non-aqueous vehicles which are compatible with capsules, this problem of instability can be reduced or eliminated. Similarly, the amount of moisture present in tablet- or powder-based formulations can be 10-100 times greater than in the oil- or lipid-based formulations used at Encap. This can have a significant impact in improving drug stability. Vancomycin is one product that was successfully developed as a liquid-fill capsule product in order to achieve acceptable stability. (19)

Comparison of Hard caps to Soft capsules:

The most frequently used polymer for the production of hard capsules is gelatin. Additional components of the capsule shell include water, which acts as a placticizer, colouring agents and/or opacifiers. If an alternate to gelatin is required, hard capsules may be manufactured from hydroxypropyl methylcellulose (HPMC). Differences have been shown in the *in vitro* dissolution rate between gelatin and HPMC capsules. However, the bioavailability of ibuprofen, a BCS Class II drug, delivered from the two capsule types was not statistically different when AUC and Cmax values were compared.

Recent advances made in the HPMC capsule technology have resulted in the achievement of similar *in vitro* dissolution rates to gelatin capsules. The composition of the shell material for hard gelatin capsules for powder or liquid filling is identical, as are the capsule sizes. Which ever method is used to seal the capsules the zone between the cap and body of the capsule must be kept clean and free of fill material for an effective sealed capsule to be produced.

Soft shells are generally thicker than those of hard capsules and are most commonly manufactured from gelatin and in which, in contrast to hard capsules, a plasticizer, usually glycerin or sorbitol is used in addition to water, a colouring agent and/or an opacifier. Alternative shell materials to gelatin that are either commercially available or in development, include a combination of iota carrageenan and hydroxypropyl starch, a specific potato starch and polyvinyl alcohol and the advantages and disadvantages of alternative materials to gelatin have been discussed. The presence of a plasticizer in the soft gelatin shell can give a relatively high permeability to oxygen and it has been reported that at relative humidities of between 31 and 80%, the log of the oxygen permeability coefficient decreases linearly with decreasing glycerin content. Therefore it is likely that the oxygen permeability of a sealed hard gelatin capsule will be lower than that of a soft capsule. An assessment of the smell of highly odorous products which were transferred from commercially available soft capsules into hard capsules and sealed effectively demonstrated this to be the case.

In practice soft gelatin capsules can perform well as oxygen barriers by modification of the type and level of plasticizer used. The primary function of the plasticizer in a soft capsule shell is to maintain the flexibility of the shell wall. The plasticizers are, however, hygroscopic and absorb moisture when exposed and it has been shown that the sorption of water by soft gelatin shells containing different plasticizers is considerably higher than is the case with hard gelatin capsules. The commonly used plasticizers for soft gelatin shells also have the ability to solubilize water-soluble APIs. It have shown that such a water-soluble API can migrate into the shell of a soft capsule which can result in instability of the API and incomplete release of drug. For drugs of poor water-solubility this is much less likely to occur.

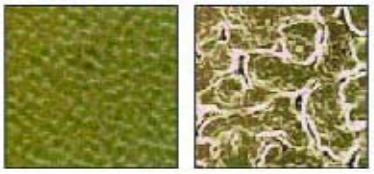
As previously mentioned, hard capsules are manufactured in a separate operation and supplied empty to the pharmaceutical company for in-house product development and manufacture. In contrast, soft capsules are formed, filled and sealed in one operation and therefore, as the process is fairly specialized,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

No discussion of filling hard gelatin capsules with liquids is complete without a comparison to soft gelatin capsules. There are significant differences between the dosage forms, and it's sometimes helpful to consider them complementary rather than competitive. Actually, the formulation often dictates the capsule type, but in cases where the formulation allows a choice between dosage forms, hard capsules have several advantages over softgels because they are less complex to manufacture.

Furthermore, soft gelatin may expose the fill material to more oxygen than a hard capsule would because the plasticizers in soft gelatin create channels that are larger than those in hard gelatin. See Figure 2. Greater exposure to air increases the potential for oxidizing (degrading) the fill material. In addition to an inherently lower oxidation potential, hard gelatin capsules can be filled in a nitrogen environment to further protect the contents. The smaller channels in hard gelatin capsules also mask the off tastes and odors associated with pharmaceutical formulations better than soft gels can.(18)

Soft gelatin (right) has larger channels than hard gelatin, as shown in these freeze etchings taken from a scanning electron microscope (1.6 x 10^{-6} magnification).

FIG:2



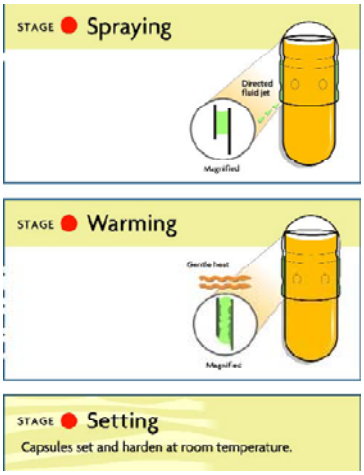
HARD GELATIN vs SOFT GELATIN

Manufacturing soft gels is also very different from filling hard gelatin capsules with liquids. Empty hard gelatin capsules are purchased separately and then filled. With soft gels, two ribbons of gelatin come together in a die to form the capsule, which is filled and sealed in one continuous process. Furthermore, the soft gel process cannot accept fill materials that exceed 35°C. And formulations containing large particles or fibrous materials are not good candidates for soft gels because they may prevent a secure seal when the two sides of the shell come together. Another potential drawback: Liquid formulations may require a formulation of the soft gel shell itself. If this is contracted out to a soft gel manufacturer, intellectual property rights to the shell typically remain with the contract manufacturer. That limits the possibility of changing to another contractor. In general, soft gel manufacture requires expensive equipment and is a labor-intensive process. For the development of soft gelatin capsules, contract manufacturers often require several kilograms of formulation, which can be challenging in the early development phase when large amounts of the drug substance are difficult to acquire. With hard gelatin capsules, small scale filling with only a few grams of formulation can be done in-house with lab-scale equipment. No lab-scale (bench top) equipment for soft gel production exists today (17).

A brief comparison of sealing methods:

Once closed, the capsule must be sealed to prevent leaks and tampering. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing [20]. See Figure 4. This fusion process begins with an application of less than 50 microliters of sealing solution to the cap-body interface. The solution penetrates the overlapping cap and body by capillary action, while a vacuum removes any excess sealing fluid from the capsule. Next, gentle application of warm (40° to 60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution. The entire process takes less than 1 minute and transforms the two-piece hard capsule into a leak-free dosage unit. Once sealed, the capsule meets tamper-evidence guidelines since it cannot be opened without visibly altering it.(17) see fig 3.

Fig:3, Capsule sealing using a hydro-alcohol solution



Another method entails banding the cap-body interface with a thin film of gelatin. Banding, however, involves several additional tasks compared with hydroalcoholic sealing. First, someone must prepare the gelatin bath, and its viscosity must be checked continuously. Operators must also address the risk of microbiological contamination associated with warm liquid gelatin. Furthermore, the gelatin band can cause physical defects in the capsule: Bubbles may form in the gelatin band or the capsules may take on a "banana" shape. The deformation usually occurs when the warm band of gelatin cools and the capsules are subjected to a long drying cycle.

The machine at left fills (LF 20)fills 20,000 capsules per hour and **t**he machine at right seals(BS 40) as many as 40,000 capsules per hour.

The photos above show liquid filling (LF 20) and band sealing equipment(BS-40). The GMP-compliant lab-scale filler-sealer fills and seals as many as 40,000 per hour. It is well suited to conducting R&D and making early clinical trial supplies. It can handle thixotropic and hot-melt fill materials and has proven itself in both the pharmaceutical and the dietary-supplement markets.

As per pharmaceutical industry aspects, maintaining an liquid filled hard gelatin capsules manufacturing unit is more benefictionary.

40% saving in operating cost and more than 65% savings in capital cost.

Commercial comparison

ASPECT	SOFT GEL	LIQUID IN HARD CAPSULE
Space Requirement	10,000 SFT	1000 SFT
Power Consumption	70 kwh	20 kwh
Man power	6 people	1 people
Gelatin wastage	Up to 40 % of web size	No such issue
Process cycle	3 to 4 days from gelatin preparation to blister packing	Same day.
A.C, ducting, electrification & utilities etc	Investment Greater in soft gel, because of larger constructed area & the process is complex	Less investment as the process is simple
Storage	3 day production to be stored	No such issue

CONCLUSION

Liquid formulations filled into two-piece hard capsules have attracted substantial interest in the pharmaceutical industry over the last decade. Today's challenges in product development due to the poor aqueous solubility and high potency of the new molecular entities are being addressed by several development groups that are focused on liquid formulations. With today's equipment, filling and sealing these formulations into two-piece hard gelatin capsules can be done easily in-house. The processes have also been proven to be commercially viable for in-house manufacturing. Several pharmaceutical products currently under development are expected to reach the market within the coming years, increasing the number of commercial products using a liquid-filled and sealed capsule. 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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