Evaluating Development and Production Costs: Tablets versus Capsules

by Graham Cole
In the face of increasing research costs and mounting pressures to get products to market in shorter times, the dosage form for a new chemical entity (NCE) may play an important role in defining the financial success of a new drug. In this article, an evaluation of the relative costs in the development and production of film-coated tablets compared with a dry-filled hard shell gelatin capsule is given.

The pharmaceutical industry is currently faced with escalating research costs in the development of new products. The recent spate of mergers is an attempt to maximize research efforts and provide companies with a critical mass that ensures new discoveries are frequently brought to market and therefore, generate a cash flow. This will ensure sufficient capital to produce the next generation of compounds, provide a benefit to shareholders and give therapeutic relief to patients.

This rationalization process is also extending to primary and secondary manufacturing. Primary produces the active ingredient, such as paracetamol and methyldopa, and secondary the dosage form, such as the tablet, capsule or injection. Companies are now rationalizing manufacturing to concentrate products at specific sites that give economies of scale, longer campaign runs and a reduction in down-time between product changeovers.

Bringing a mainstream drug to market can cost in excess of US$300 million. This involves research, development, manufacturing, distribution, marketing and sales. The time cycle from discovery to launch takes many years but in any case will probably not be less than four years for a new chemical entity (NCE). Any reduction in this time frame improves the company’s profitability and generates income. This has been likened to a relay team with each member handing the baton to the next runner and disclaiming any responsibility if he or she drops it. The speed to market can only be dramatically reduced and able to provide a sustainable competitive advantage if the time element is integrated into all functions and binds them together in a common purpose. For NCEs, many companies conduct the early studies for safety, toxicity and blood levels using capsules. This is because of the very small amounts of available NCE and the ease of preparing the dosage form without loss of material. Only when larger quantities of the NCE become available is a tablet formulated. The product design process must take into account the demands of regulatory approval (manufacturing licences, validation), variation in demand and flexibility of operation.

Capsule or tablet?

The choice of whether to present a drug as a tablet or a capsule is usually based on factors other than bioavailability. Comparison of capsule formulations with solutions and suspensions shows that they may fail to deliver the whole of their drug content to the body or delay the release of the drug. However, tablets do not perform as well as solutions either, so it is by no means certain whether tablets or capsules give better release.
Tablets have been stated to be generally worse, but that this generalization is not exact is evident from some reports of tablets with greater bioavailability than capsules. Sometimes the reason for the difference cannot be found because the products are commercially available and no formulation details are given. Tannenbaum found that a commercial capsule containing triamterene and hydrochlorothiazide was absorbed less effectively than an experimentally formulated tablet. However, found that a capsule formulation of the same two drugs was bioequivalent to an aqueous solution, suggesting that the capsule formulation of the earlier study was probably not optimized. Commercial capsules and tablets of pivampicillin were absorbed to the same extent but the capsules gave a slower rate of absorption. The opposite effect was obtained for a capsule formulation of heptabarbital, which gave a more rapid absorption than the tablet formulation, although the extent of absorption from the capsule was only 83% of that from the tablet. The formulations here did, in fact, differ, because the tablet contained the heptabarbital in the form of the free acid whereas the capsules contained the sodium salt. These three examples do, however, illustrate that capsule formulations can be deficient in their rate and extent of absorption in comparison with tablets.

That it is possible to formulate capsules and tablets containing drugs with known bioavailability problems, in such a manner that they are equally effective, has been demonstrated for clofibrate. A capsule and a tablet formulation of oxytetracycline were also both absorbed to the same extent - a decreased availability found in some tablet formulations being related to the form of tablet coating used.

Some specific commercial tablet and capsule formulations of phenytoin did not differ significantly in extent or rate of absorption, nor in therapeutic efficacy. A study of the metabolite plasma levels and the sodium to potassium ratio in urinary excretion after administration of spironolactone to dogs showed that an uncoated tablet and a capsule were bioequivalent, but that a coated tablet had a reduced bioavailability.

Table 1: Tablet and capsule formulations (qs = quantity of water is sufficient to granulate the tablet)

<table>
<thead>
<tr>
<th>Raw material</th>
<th>Tablet 1 core (mg)</th>
<th>Tablet 2 core (mg)</th>
<th>Capsule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibasic calcium (Emcompress) phosphate (DCP)</td>
<td>—</td>
<td>188.00</td>
<td>—</td>
</tr>
<tr>
<td>Microcrystalline cellulose (MC)</td>
<td>100.00</td>
<td>—</td>
<td>100.00</td>
</tr>
<tr>
<td>Pregelatinized starch (PGS)</td>
<td>88.00</td>
<td>—</td>
<td>88.00</td>
</tr>
<tr>
<td>Purified water (PW)</td>
<td>qs</td>
<td>—</td>
<td>qs</td>
</tr>
<tr>
<td>Magnesium stearate (MS)</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>190.00</td>
<td>190.00</td>
<td>200.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cat</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl methycellulose (HPMC)</td>
<td>3.00</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose (HPC)</td>
<td>3.00</td>
</tr>
<tr>
<td>Titanium dioxide (TD)</td>
<td>2.35</td>
</tr>
<tr>
<td>Talc (T)</td>
<td>1.50</td>
</tr>
<tr>
<td>Iron oxide (FeO)</td>
<td>0.15</td>
</tr>
<tr>
<td>Purified water (PW)</td>
<td>qs</td>
</tr>
<tr>
<td>Capsule shell</td>
<td>45.00</td>
</tr>
<tr>
<td>Total Cost</td>
<td>200.00</td>
</tr>
</tbody>
</table>
A capsule formulation containing fine particles (5-50 µm) of this drug gave equivalent, or in some instances higher, metabolite plasma levels than a commercial tablet. A study of commercial formulations of methaqualone established comparability between some tablet and capsule formulations, although no strict statistical comparisons were made. A warning note was sounded however, in that one tablet that was tested gave significantly higher plasma levels than all other preparations. Further work confirmed that tablets can differ in bioavailability, and that capsules can equal or exceed them in performance, but no formulation details are given to account for these differences.10, 11

Nitrofurantoin tablets gave greater urinary excretion and faster absorption rates than capsules containing the same drug. Here, the explanation was that the drug in the capsule was in the form of ‘macrocrystals’ and was provided by a study of urinary excretion of nitrofurantoin from 14 commercially available products. A commercial tablet formulation existed that gave even lower urinary excretion than that from either of the capsules tested. In vitro dissolution/dyalysis confirmation of the in vivo results was found possible for 50 mg dosage forms but not for 100 mg tablets and capsules.12, 13

Diphenhydramine hydrochloride has been tested using widely differing dosage forms and its bioavailability appears to be unaffected. The formulations studied in humans included a tablet, a hard gelatin capsule and a soft gelatin capsule containing either an oil/wax mixture or poly(ethylene) glycol, each with and without Tween 80.14 The bioavailabilities of these set formulations did not differ significantly, so simple comparison of tablet and capsule formulations of such a drug fails to decide the question of which to use.15

The advantages of hard gelatin capsules over coated tablets are

- more possibilities to develop controlled-release products
- suitable for low melting point drugs – smaller dosage form
- perceived as being more effective
- perceived as being easier to swallow
- more possibilities for product identification (printing)
- less stress on drug during manufacture compared with wet granulation
- suitable as a container for sprinkle pellets
- suitable for inhalation products.

The disadvantages of hard gelatin capsules over coated tablets are

- lower production speed
- perceived as being more expensive
- higher volume pack
- perceived as being more difficult to swallow by older patients
- greater weight variation
- hygroscopic materials pick up moisture from shell
- more difficult to enteric coat less standardized production methods (tamping, dosator)
- shape and size limited
- supplier dependent.

This article looks specifically at one aspect of this conflict concerning the relative costs in terms of development time, raw materials, production equipment, buildings and validation for the manufacture of a dry-filled capsule and a film-coated tablet.

There is a general belief within the pharmaceutical industry that tablets are easier and cheaper to produce on a production scale than hard shell gelatin capsules. This has arisen from two basic issues:

1. Tablet technology has developed at a greater rate than capsule filling technology. An example of this is the rotary tablet press capable of producing 1000-2000 tablet/min that has been available since the early 1930s, whereas an equivalent capsule filling machine did not become available until the 1970s.

2. The cost of the excipients used in the formulation is cheaper for tablets than for capsules. This is certainly true, as the capsule shell is the most expensive. If a comparison is made of the costs of an uncoated, white round compressed tablet, then it is difficult to establish a preference for the capsule formulation (the objective used to be to formulate all new tablet products as white, round and biconvex).
However, this criterion has now changed and many major pharmaceutical companies produce coloured film-coated tablets in a variety of shapes, a much more expensive operation.

There are a number of reasons for this, and some examples are

- coated tablets are easier to handle and pack in high-speed packaging lines
- elimination of particles and dust from tablet surface (improved containment)
- protection from atmospheric oxidation, moisture and improved stability
- identification of the company logo to doctor and patient
- makes it more difficult for generic companies to compete.

The technology of film coating has now developed to an extent that it can be accomplished reasonably quickly and simply. However, it is not without a cost and it adds risk of failure to the manufacturing operation.

This article will examine and quantify some of the costs using two examples of film-coated tablets compared with a dry powder product filled into a hard shell gelatin capsule. The two tablet formulations used were

- wet granulated film-coated tablet (Tablet 1)
- directly compressed film-coated tablet (Tablet 2).

Formulation

Initially, NCEs are usually only available in very small quantities (less than 10 g). In the early stage of formulation, this quantity is used to undertake pre-formulation studies, assess bioavailability, develop dosage strengths and initiate some stability studies.

The quickest way to do this is to use a capsule and many companies will start with a capsule formulation and then, at a later stage, convert this formulation into a tablet. It is simple to mix a number of powders together or just use the active material in the capsule for these purposes.

The three formulations compared in this article are shown in Table 1. For the purposes of this study the cost of the active ingredient has been ignored. Table 2 shows the cost of the raw materials and the cost of producing batches of 100000 dosage units.

An examination of Table 1 shows that the excipients cost almost four times as much for a capsule as for a tablet. It is also interesting to note that there

![Table 2: Raw material and batch costs per 100000 (all costs are in US dollars).](image)
is little difference between a directly compressed tablet and a wet granulated tablet and, in fact, that the directly compressed tablet is more expensive. However, this is only a small part of the overall cost in manufacturing a dosage unit. Each of the following costs will be examined in some detail:

- process equipment and processing times
- building and process utilities
- analytical
- manning levels
- validation.

**Process equipment costs**

The process flow for the manufacture of a wet granulated filmcoated tablet is shown in Figure 1. Figure 2 shows a comparable process for filling hard shell gelatin capsules. The process for the manufacture of a directly compressible tablet will be similar to Figure 1 but will eliminate the following steps:

- dry mix (one of the unit operations)
- paste preparation
- granulation
- fluid bed drying
- size classification.

The equipment required for each of these processes is shown in Table 3 together with the appropriate costs.
It can be seen from Table 3 that there is a considerable saving in capital equipment if a capsule is filled rather than a tablet manufactured, and that the capsule has an approximate 23% saving even over the directly compressed tablet.

An examination of Figures 1 and 2 also shows considerable differences in the number of steps required to produce the product ready for compressing into a tablet or filling into a capsule.

In these examples it is assumed that Tablet 2 and the capsule require the same number of processing steps to reach this point. Three hours is allowed for these operations.

Tablet 1 requires five additional steps to proceed through wet granulation, drying and size classification. Eight hours is allowed for these additional stages.

Tablet machines generally have much higher outputs than capsule fillers. Here it is assumed that a capsule machine operates at a filling speed of 2000 capsules per min and a tablet press operates at twice this speed (that is, 4000 tablets per min). The relative times for this part of the process are 50 min and 25 min respectively.

After compression, both tablets require film coating. Four hours has been assumed for the preparation of the film coating suspension/solution and the coating operation. Manning costs have been allocated at $75/h. This is summarized in Table 4.

It is also assumed that the packaging of the final film-coated tablet and the filled capsule will require very similar equipment, for example, blister packs, and that this equipment will require similar floor space, manning levels and utilities. For this reason the costs of this part of the manufacturing operation are considered to be the same and are therefore ignored in this comparative evaluation.

Table 5 illustrates the point that, under the assumptions made and considering only the excipient costs and processing times, the order of costs is now: Tablet 1 > Capsule > Tablet 2 So far no account has been taken of capital, building, analytical and validation costs.

Table 3 quantifies the equipment costs, but does not consider building and process utilities. It shows that it is more than 50% cheaper to manufacture a capsule product compared with Tablet 1, and for Tablet 2 the saving is still more than 20%. If the
equipment is written off over five years and interest rates are 10%, then, taking the capsule as base level, the company can save against Tablet 1 more than $849000 and against Tablet 2, $147000.

Building layout and process utilities

Figures 3 and 4 show two building layouts, one for tablets and one for capsules. The standard finishes used to design and equip each building are the same. An examination of these two figures shows that the Capsule Facility is 25% smaller than the Tablet Facility. The costs to design, construct and equip these facilities, omitting process equipment, is assumed to be $2000 per square metre.

There are four services that are costly to install and operate:
- purified water (PW) system
- compressed air
- vacuum
- heating, ventilating and air conditioning (HVAC).

For the processes under discussion it could be argued that PW is unnecessary for the capsule process, however, in reality it will be installed, albeit on a smaller scale, as it may be required in cleaning operations.

Compressed air is required on both processes whereas vacuum is only required in capsule filling to separate the empty shells. Here again, a vacuum system will be installed in a tablet plant as it can also be used for powder transfer operations and cleaning operations.

A typical PW system designed to provide one cubic metre of water/h would cost, with installation, $30-40000. It is also an essential requirement for aqueous film coating to monitor and maintain levels within the pharmacopoeia specification. Compressed air of the required quality is also a costly utility to maintain. The requirements for film coating in a coating pan with batch sizes of 100 kg are 20 m$^3$/h at 20-40 psi (2-3 bar). This air must have a low particle count, be bacteria free and have a low moisture level (less than 1.0%) as it is used to atomize and spray the film onto the tablet. A typical system with a compressor, 0.2 µm filter, dryer, receiver and stainless steel pipework system, would cost approximately $60-70000. For the purpose of this study HVAC is considered to be constant for both systems. It is recognized that, for various products, both tablets and capsules, special conditions may be required for products that are moisture sensitive, but here it is considered that all products will be produced under standard conditions of 50% relative humidity (±20%) and at a temperature of 20°C (±2 °C). It is also a requirement for film coating that large volumes of drying air are required.

The equipment to provide this air is included in the capital requirement (Table 3), and the heat required in the general building and overhead costs. All these costs have been included in the $2000/m$^2$ estimate.
Figure 3: Tablet manufacturing facility

Figure 4: Capsule filling facility
An estimated saving of 25%, based on the footprint of the building using Figures 3 and 4, has been made. The total cost saving in a floor area reduction of 312 m² is more than $600000. On a write-off period of 20 years this amounts to an investment saving of more than $1000000.

Validation and analytical costs

An examination of the formulae for each of the products under discussion shows that in Tablet 1 there are nine ingredients, Tablet 2 has eight ingredients and the capsule (including the shell) has four. Analytical rates can be rated at $150/h and it would be reasonable to assume that, if each ingredient requires three workhours of (QC) input, the cost of Tablet 1 is $4050, Tablet 2, $3600 and the capsule $1800.

Validation is now a major requirement for all pharmaceutical processes. Its cost has been estimated at up to 20% of the total installed cost of any project. The level depends very much on the complexity of the process, the degree of computerisation and the number of products requiring validation. Validation is a total concept and applies to all elements of the facility, its operators, their training, analytical procedures, calibration of instruments, engineering and supervision.

The total size of the manufacturing area for the capsule facility (omitting offices and canteen for example) is 1248 m² at a cost of $2.49 million and, on the same basis, the tablet facility is $3.12 million.

If, for the purposes of this exercise, an allowance of 10% is made for validation and only the building infrastructure and equipment is considered, then the difference between the processes amounts to $600000 for equipment and $630000 for the building, 10% of 1.23 million is $123000.

Conclusion

This article has evaluated and quantified a number of costs associated with filling capsules and the process for manufacturing film-coated tablets. It has shown that the investment for capsules is much less than that required for a tablet manufacturing facility, and that it is cheaper to operate and control, and minimizes inventory levels. Only when the cost of excipients is considered in isolation does the tablet process have an advantage.

References