

Quality Assurance – Quality control view point on pharmaceutical preparations in hard gelatin capsules

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In my opinion one of the most outstanding achievements quality assurance - quality control people have obtained in the modern pharmaceutical industry is their involvement since the very first steps of research and development of a new pharmaceutical formulation (PR&D).

The opportunity of interacting with the PR&D men from the start off has given us the possibility of offering our timely suggestions to make the formulation sometimes more practical and more rational. This way it will be avoided making possible later revisions and adjustments which would cost the company both in terms of waste of time and further investments.

During my presentation I will especially dwell on the considerations the quality assurance - quality control can bring to the attention of PR&D people in deciding the final form and then the composition of a dry product for which the choice is between capsules and tablets presentation.

Assuming that of course there should be no stability or incompatibility problem between the active principle and the capsule components, assuming also that we should not be faced by other limiting factors which might discourage or even prevent the utilization of the capsules themselves: let me say that control people prefer the capsules presentation.

Let me now look at the reasons behind such a set preference and later I will be more articulated about the limiting factors I mentioned above, from my point of view the first issue playing a very important role in favor of the capsules presentation is the lesser complexity in the formulations, lesser complexity means greater safety too. In fact it's quite understandable that the least variable factors we introduce, the most capable we are to assure the reproducibility lot and the conformity of the product to the established specifications. An article about this issue has been published not long ago.

This article reported the outcome of a survey aiming just to compare the formulations of the same active principles present on the market both in capsule and tablet form. The survey results showed that averagely the tablets formulation required a number of excipients 3 to 4 times higher than the capsules' one.

I draw your attention on the fact that I am referring to uncoated tablets. In fact it is clear that if I dealt with the coated ones, the ratio would get worse and worse. Another important factor we have to take into account is the utilization of solvents some of which are regarded as highly risky by the health authorities. Such solvents are often necessary for those tablets that on the other hand are the main part, the production cycle of which requires granulations and/or firm coating. I do believe that many of you have experienced, at your own expenses, those difficulties which are often encountered in reducing later the residual content of such solvents in the finished product below the few PPM allowed by the health authorities, nor we would forget about those certainly more complex problems the analyst faces during the development and the validation of tablet formulations.

A greater number of excipients surely means longer times for studying both the compatibility and the stability of the formulation itself and often this involves some major problems in the analytical development of the assays and tests.

We are shifting now the subject to the analytical side which is the second factor, just as important as the first one, in favor of the capsules formulation. I mean the quality control related problems.

Let me show you the different tests quality assurance - quality control daily perform on a routine basis, depending whether the product is in capsules or in tablets.

In case of tablets:

(the following parameters have to be taken into consideration and normally tested)

in-process control

- residual solvents from granulation
- potency of the mixture
- weight variation in compressing
- friability
- hardness
- disintegration time
- thickness

assays/tests on the finished product

- appearance
- content uniformity
- microcount and pathogens
- dissolution rate

In case of capsules:

in-process control

- potency of the powder mixture
- weight variation
- proper capsules sealing
- disintegration time

on the finished product

- appearance
- dissolution rate
- microcount and pathogens

As it's gathered through the above data, there is a remarkable difference in problems between capsules and tablets as far as quality assurance - quality control are concerned.

Even more so considering that these recent years the health authorities in USA and in the EEC countries have become ever more demanding, and rightly so in my opinion, in

terms of requirements and assurance about product bioavailability, lots reproducibility and validation of both methods and machineries.

I think that, based on the reasons I have so far mentioned, it is quite clear that the capsules have many advantages versus the tablets as for the bioavailability and the reproducibility; and speaking about validation it is again worth comparing tablets versus capsules as regards the complexity of the respective manufacturing processes (see the enclosed validation schemes).

This comparison goes to prove that it is more difficult to carry out validation for the tablets manufacturing process rather than for the capsules' one.

It is just as clear that there is a greater effort by quality assurance - quality control, in terms of times and therefore in terms of costs. Such effort is made not only in the tablets formulation set-up but especially in the routine controls and inspections performed on the full scale production. Just to give you some information related to the industrial production only, I will tell you that our lot standard times show that the tablets production takes 15 to 22 % bigger effort compared to the lot standard time required by the capsules manufacturing.

These percentages do raise at 24% as far as the greater effort by quality assurance - quality control is concerned in terms of time demand per lot. Summarizing all I have said so far, we have seen how many factors are in favor of capsules, namely greater formulation simplicity and consequently a greater safety, limited complexity of both chemical-physical and analytical problems as well as reduced validation requirements.

But as I hinted at the start of my introduction there are also some limiting factors related to the capsules utilization. Consequently such factors play a part in favor of the tablets formulation. The main limiting aspect is found for instance whenever high dosages are required, or whenever we have materials with considerable bulk volume, or yet with those products, such as for instance hypnotic or antianxiety drugs requiring an as low as possible dosage and for which doctors often prescribe to start off with just half dose. It is quite clear that only tablets give the practical chance of cutting the dose in half. In addition there are other negative or at least limiting factors to be kept into consideration. For instance the speed of the filling machines is surely slower than the one of the tableting machines (there is roughly a 50% difference).

The capsules cost is another factor to be considered. Last, but certainly not least, is the capsules defectiveness degree. Defects such as presence of holes or splits or cuttings inside the capsules or capsules with double caps or telescoped present some critical factors which no doubt can affect the productivity. In fact such defects are usually graded with very low AQL in every laboratory. Finally what both the capsules manufacturers and the users have to keep in the utmost consideration is the moisture content of the capsules. It is therefore absolutely important to thoroughly monitor the packaging materials, the transportation and storage conditions of the capsules since their either exceeding or short humidity contents could cause serious utilization problems.

I intended to make an assessment about the most important pros and cons of either capsules or tablets formulation and I hope I have made my opening statement clear enough, when I said that quality assurance - quality control people favor the capsules formulation.