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PROCESS AND DOSAGE FORM CONTROLTS : FORMULATION FACTORS

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ABSTRACTS

During the last decades, there have been considerable developments in the field of pharmaceutics, pharmaceutical technology and product manufacture.

The trend of the pharmaceutical industry is, like in most of the sophisticated industries, to produce, day after day, a better product, and as final goal, to manufacture continueously a perfect drug dosage form.

A few years ago, the defaults were counted in "percent". After that, it was in per "thousand". Now it is often expressed in "per million", or even for very high series (for example empty hard gelatine capsules) the trend is "per billion". Such an evaluation can only be achieved with a complete control of the whole manufacturing process.

The requirement for pharmaceutical dosage form are numerous (1): adequate biopharmaceutical profile, ease of manufacture, quality assurance (the dosage form must contain the correct quantity of

the correct drug, and liberate it at the correct place, at the correct time, and in the correct quantity, with the correct speed), stability, ...

These requirements can only be fulfilled with a perfect knowledge of the drug and the dosage form, from the beginning of the development of the dosage form (formulation) to the end of the manufacturing process (production and final product control).

It is the aim of the present lecture to show how important are the formulation factors and what is their influence on the processing and the dosage form control.

INTRODUCTION

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Guidelines for the Formulation

The first aim of the formulation is a good liberation profile in order to obtain an effective drug. This profile has to be well defined before any development of the formula. If the target of the drug is not well known, the development cannot be made in a logical manner.

The second important area in drug formulation concerns adverse reactions or side effects. The dose of the drug must be selected in the therapeutic range (high enough to be effective, low enough to avoid unwished side effects).

The third aim in formulation concerns the use of the product by the patient. A dosage form can only be safe and effective if the medication is taken by the patient according to the prescribed regimen. And it is obvious that if the medicine is inconvenient to take, requires frequent dosing, has an unpleasant taste or gives raise to side effects, the patient may fail to comply with the doctor's instructions. Some studies have indicated that from 20 to 80 % of patients fail to take their medication correctly. Old people, illiterate and mentally confused people present special problems in this respect. The design of a more acceptable dosage form, that is convenient to use (for example once a day dosing forms) is required for these cases.

Even when the drug is formulated well to ensure patient compliance, a dosage form cannot be considered as completely safe as long as it has not been used and produced the required effect: Every one has in mind the misuse of paracetamol capsules in U.S.A., and the needed change in the formulation of the product (locked capsules, formulation into tablets) in order to warranty the safety of the dosage form on the market. The formulation of a drug into a dosage form is essential for the future success of the

product. The word "success" means here commercial success, and a production made on a large scale without major problems.

Two selected examples, taken in the solid dosage form technology, can illustrate the influence of formulation factors on the process control and on the dosage form control.

Conventional Tablets

For a large number of years tablets and capsules have been the delivery system of choice for oral administration. Manufacturing of tablets and capsules is considered as an old technology, known over one century. These dosage forms should now be regarded as simple, well known, and without any particular problem. The reality is quite different. The simple example of paracetamol tablets can illustrate this reality:

Paracetamol is a drug substance that give rise to tablets which have a tendency to capping (2). As the amount of drug per dose unit is relatively high, a decision must be taken on the way of manufacturing : direct tableting or granulation and compression. This decision often depends on the kind of production material available in the factory, and the calculation of the final cost, considering the time needed for the production.

It is well known that the quality of raw material has a very high influence on the kind of manufacturing process which can be choosen for the production of the tablets : some show very poor tableting properties; others are designed for direct tableting, and their flow properties as well as their compression properties are excellent (3). The dissolution properties and the bioavailability can also be completely different from one supplier to the other (4). Beside the drug, a formulation of a paracetamol tablet needs some excipients. A good choice of adequate excipients is something essential in the development of a dosage form, especially when it is intented to market it in several countries.

Some years ago, HESS (5) has described the problem of the choice of excipients for an international use. These excipients

must meet the physico-chemical requirements for the dosage form, but several additional factors must also be considered (no adverse reaction, approval by regulatory agencies, well defined chemical and physical properties, analytical and microbiological purity, supply and international availability).

So HESS has classified the excipients for international use into different categories :

- Excipients described in Pharmacopeias;
- Excipients used for foodstuffs;
- Excipients used for cosmetics (topical preparations);
- Newer excipients, with no official status, but already registred with certain health authorities;
- Completely new excipient, used for the first time in the pharmaceutical field

The most favourable case is this of an excipient described in one of the major pharmacopeias: no special problem, due to the excipient, should arise for the registration of a formulation containing such a product. On the other extremity, the use of a new excipient, even if its technological properties are exceptionally good, should be decided with caution, because such an excipient is considered as a new product, and has to be investigated in the same manner than a new drug (toxicological data, a.s.o.....) The development of the formulation can be made in a scientific manner by mean of some preformulation studies (6, 7) and these studies facilitate the choice of the different excipients. Some publications comparing the properties of different excipients are also useful for the selection on the adequate product (8, 9, 10, 11)

During all the formulation the final dissolution profile of the tablet, and the easiness of manufacturing and control must be kept in mind. Some of the effects of formulation and process variables on the properties of paracetamol tablets have for instance been studied by NASIPURI and al. (12). The simple example of paracetamol tablets shows how important it is to

optimize the formulation in order to facilitate the production and the control of the final dosage form.

Sustained Release Pellets

The second example is obviously more complicated : it concerns the manufacturing of sustained release pellets. There are a variety of reasons for wanting a long action formulation. The most important ones are a reduction of side effects, the provision of a constant therapy for the patient and a hope for a better degree of compliance by the patient, due to a reduced frequency of dosage. Today the most popular form of sustained release is the coated particulate system: pellets that can be incorporated into capsules or tablets.

These systems present several advantages : the material is well distributed in the gastrointestinal tract and the liberation of drug is an average of the liberation from many individual pellets, so that the liberation profile is usually regular; the coating can be varied in nature and in thickness so as to provide a coating sensitive or non sensitive to pH. This system, which is able to give a really adequate liberation profile, must be developed under strict conditions, unless the wished result cannot be reached. During the stage of formulation of the dosage form, many decisions have to be taken, and all have an essential effect on the final product.

As for paracetamol tablets, first of all, the pure drug (raw metarial) must be selected. Either it is an in-house production, and all the insurances must be given that the manufacturing processing of this drug will not be changed in a significant manner between the step of formulation (where a few kilos are used), the step of pilot batches, and the final industrial production of the dosage form (where, hopefully, tons will be used every month). Or it is a drug purchased for the market : hereto, it must be insured from the beginning that a continuous quality of drug can be purchased, whatever the quantities needed may be.

Without such an insurance, any development of a sustained release pellet will give rise, one day or an other, to manufacturing or bioavailability problems wher the quality of the raw material changes. Supposing that a drug of constant quality is available, the first step of the manufacturing of pellets is a wet granulation, followed by extrusion and spheronisation, For these steps, the use of excipients is required. Here all what has been mentioned previously for the choice of excipients for international use is still valid.

Moreover the final formula of a pellet is usually more complicated than that of a simple tablet, so that some analytical difficulties can appear for the control of the final product: the formulation should take this point into account, and one should have an idea on the feasibility of the analytical end control when the formulation is developed: the use, in the same formulation, of several excipients which are similar on a chemical point of view, will certainly not make the final quality control easy. Once the spherical pellets are formed, a first analytical development is made to analyze the granule content. Such an in-process control is essential, because the final dosage form is manufactured in different steps, and each of these steps has to fulfill some precise requirements, or the whole following manufacturing makes no sense. More than in other solid dosage forms productions, in pellet production, the in-process controls must be developed with a special care.

Usually neutral granules are also produced, which will be mixed with the active ones in order to reach the correct quantity of drug per dose unit. These neutral granules should be identical to the active ones, in size, shape, and composition, in order to allow a perfect homogeneity and an easy final control. If the spherical granules meet the analytical requirement (adequate quantity of drug, no degradation of it, correct liberation profile), the granules are coated : hereto the choice of the polymer allowing a continuous liberation of the drug is very important. Only few polymers are described in Pharmacopeias (for example

HPMC or ethylcellulose), so that the choice is limited. Some of these excipients are classified as "GRAS" (Generally recognized as safe), and their use is more easily accepted by the authorities. The choice of the kind of solvent used (organic or aqueous) can also have a high influence on the kind of material to be used for the production, and the controls to make during the processing and on the final product (for example concentration of dangerous solvents in the air of the production unit, content in residual solvents of the finished product, ...) At the end of this production step, the granules are controlled, and the in vitro dissolution profile is checked. Either the granules meet the requirement, and this step of the production is ended, or they do not liberate the drug in the required manner. If the release is too fast, the granules are covered with additional coating. More complicated is the case of granules with a release with is to slow : these granules have to be mixed with other ones, specially manufactured to have a quicker release which compensates the release of the original granules. After all these steps of manufacture and control of the pellets comes the final operation: filling of the granules into capsules. This part is not very special, but needs some controls too : weight uniformity during filling; weight and dissolution profile of the finished capsules; .... The complete development of a sustained release formulation is a tedious work where all the mentioned factors have to be taken into account.

In order to simplify this work, and avoid unnecessary experiments, the development of the formulation is nowadays no longer conducted in an empirical manner, with trials and errors. The use of computers allows a modeling of most problems. On the other hand a factorial design of the experiments, and a principal components analysis of the results gives now a better view of the behaviour of the system constituted by the pharmaceutical dosage form. The experimental results obtained from the development of a product can sometimes be used to simplify the development of an other, similar one.

On any batch, a final quality control takes place. In fact such a control should be unnecessary if the whole production is organized in order to produce a product without defect. But the regulation still requires a control of the finished product. The formulation factors have a great influence on the manner on which these controls can be realized. All the manufacturing has to be realized according to the good manufacturing pratices : the design of the manufacturing material is essential in this matter, in order to facilitate the respect of the G.M.P., and to reach a reduction of production costs by simplification of the final controls.

CONCLUSION

With two selected examples, it has been shown that the the formulation factors are essential to achieve a good process and to facilitate the in-process and the final controls.

The formulation step has often been neglected in the past, because at the moment of the formulation, the future of the product seems uncertain. Many small formulation mistakes have to be paid by the manufacturer during all the commercial life of the product.

A better perception of the important part of the formulation in the final success of a dosage form should, in the next future, allow to have more and more consideration for this important initial step.

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