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From "Functional Excipients" towards "Drug Carrier Systems"

ABSTRACT

The paper describes the state of the art and actual trends in the area of pharmaceutical functional excipients, taking into account the impact of FDA's PAT (Process Analytical Technology) initiative. The new requirements mean, that the formulator is requested to explain the specific choice and the functionality of the excipient. The formulator needs to have a clear "understanding of the formulation" and of the unit operations ("process understanding") used in the manufacturing process. The performance of functional excipients can only be assessed as a constituent of the specific formulation and unit operation. Special tools are necessary, such as the design of experiments, the use of artificial neural networks and the application of percolation theory for the design of dosage forms.

INTRODUCTION

The role of functional excipients and the bioavailability of solid dosage forms

The champion of all medical products on the market are tablets or hard gelatine capsules, i.e. solid dosage forms for oral use (1). In the ideal case, the dosage form delivers the drug precisely with the right quantity in the right quality at the right site, at the right time to the body of the patient. If this is not the case, undesirable side effects can occur (see Figure 1). In this context, the choice, the function and the amount of excipients in the formulation play a major role (2).

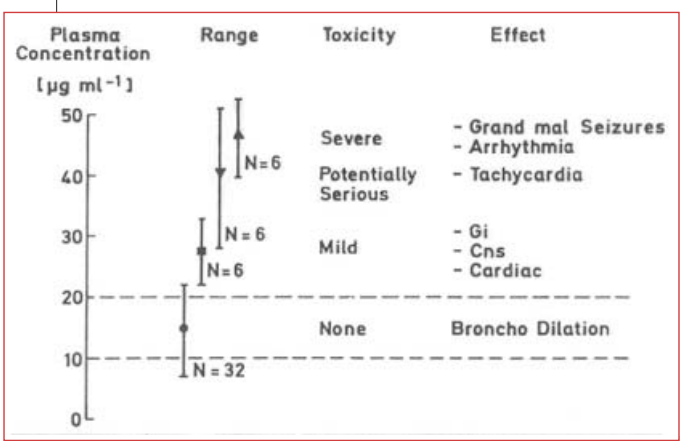

Figure 1, Theophylline plasma concentration with a narrow therapeutic window between 10 and 20_g ml-1 (1)

The task of dosage form design can be compared with the task of designing an aircraft, which delivers all passengers at the right time to the right destination (1). However, the drug cannot be delivered in its "native" form, i.e. "naked". The drug needs to be "dressed" to achieve an optimal bioavailability. Many other problems have to be resolved at the same time such as to achieve a sufficient shelf life, i.e. physical and chemical stability etc. Unfortunately, it is in general not possible to take a "prefabricated dress off the rack" and a "tailor made" formulation needs to be designed. In this context the choice of the functional excipients, the choice of the "dress", i.e. of the formulation, is essential for an optimal dosage form.

The myth of inert functional excipients

The statements "inert" and "functional" are sometimes in contradiction. It is evident, that the excipient needs to be chemically and physically compatible with the drug substance. Everybody knows that it is important to know whether the active substance is polymorph, i.e. shows different crystalline structures with different physico-chemical properties, such as water solubility, wettability, compactability etc. However, it is surprising that the question of different polymorphs of excipients do not seem to play so far the same role. This issue may change in future. It is assumed that an excipient has no intrinsic pharmacological or toxicological effect being "generally recognised as safe" (GRAS – list). On the other hand it is well known, that certain excipients, e.g. antioxidants such as vitamin C and E are in fact biologically active substances.
Not so long ago it became evident, that certain excipients and certain drugs can saturate the p-glycoprotein efflux-system in the intestine. A saturation of the efflux-pump can induce drug interactions in case of a co-medication (3, 4). A shocking example has been the discovery that ordinary grapefruit or orange juice, used as an excipient for taste masking or being part of food up-take is able to block the p-glycoprotein system in the intestine (5). These findings strongly underpin the requirement to insist on a science-based approach in designing optimal and robust formulations.

The quality and the performance of functional excipients

It is still an unsolved problem to assess properly the quality and performance of a functional excipient. The author of this paper was involved in a working party of Ciba-Geigy, F. Hoffmann-La Roche and Sandoz

putting together the properties and functionalities of pharmaceutical excipients in a "catalogue of pharmaceutical excipients". This list was later extended and published as "Handbook of Pharmaceutical Excipients" (6). The Fiedler Encyclopaedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas (7), is an interesting source of information. However many data are just provided by manufacturers, specifying the properties of the pharmaceutical excipient in a certificate. The existing documentation is often not sufficient. In this respect, it is a pity that in academia only a few research groups are working in the important field to get a better physico-chemical and technological description of the behaviour of pharmaceutical excipients (8, 9). It is important to notice that from a scientific point of view it is not possible to declare that a chemically identical excipient of manufacturer A is much better than, or has the same quality as, the one of manufacturer B as its functionality depends also on its physical properties and on the specific formulation of the specific drug. Unfortunately, due to the high costs of toxicological studies it is difficult for manufacturers to introduce on the market new excipients.

Functional, multi-functional, composite excipients and drug carriers

Most excipients exhibit not only one singular function. A typical example is lactose, which is not only a filler but makes at the same time the formulation more hydrophilic, which is an important issue concerning disintegration and dissolution of a solid dosage form. The following example serves as an illustration (2). In case of a capsule formulation in early clinical trials for dose range finding it is clear that initially only a low amount of active substance is used. Subsequently the amount of drug substance is increased at the expense of lactose (2).

Figure 2 shows the dissolution profile for the drug substance for three different drug contents of a capsule formulation for a specific drug. In case of the first low dose, a rapid dissolution was observed, however an important slow down of the dissolution rate occurred at higher drug loads. What happened? In case of the low dosage, lactose acted as an excellent hydrophilizing agent, embedding as perfect filler the total of all drug particles, forming a drug in lactose formulation. With the increasing amount of the drug substance with its poor wettability the composition became in the end lactose in drug formulation, where the excipient lactose lost its function as a hydrophilizing agent.

In order to avoid such failures it is important to take into account percolation theory (see chapter 2).

Besides of lactose there are other excipients, where the function depends on the concentration of the excipient in the formulation. Starch can be used in low concentrations as a disintegrant and in high concentrations as a matrix for hydrophilic long acting dosage forms (10). The manufacturers of excipients are aware that many excipients are intrinsically multifunctional. Thus composite or co-processed excipients for direct compression, capsule and dry powder inhaler formulations are offered on the market.

The objective is to improve the functionality and to mask undesired properties of the individual excipient. Co-processed excipients for direct compression consist of up to three excipients, Cellactose 80 (Lactose & Powder Cellulose), ProSolv (Microcrystalline Cellulose & Silicon Dioxide), Xylitab (Xylitol & NaCarboxymethylecellulose), DCL40 (Lactose anh. & Lactitol), Ludipress (Lactose & PVP & PVP cl). The same philosophy can be applied to improve properties of drugs such as vitamin C or paracetamol coprocessed with a low amount of excipient to get a direct compressible drug.

From a principal point of view, each excipient is a kind of "drug carrier". This concept becomes clearly evident in case of pellets, which are subsequently loaded with the drug substance and eventually subsequently film coated for taste masking or controlled release purposes. Thus, placebo pellets such as Cellets® (consisting of microcrystalline cellulose), Balocel® (consisting of microcrystalline cellulose, lactose and NaCarboxymethylcellulose) can be considered as drug carrier systems with features going beyond the co-processed excipients.

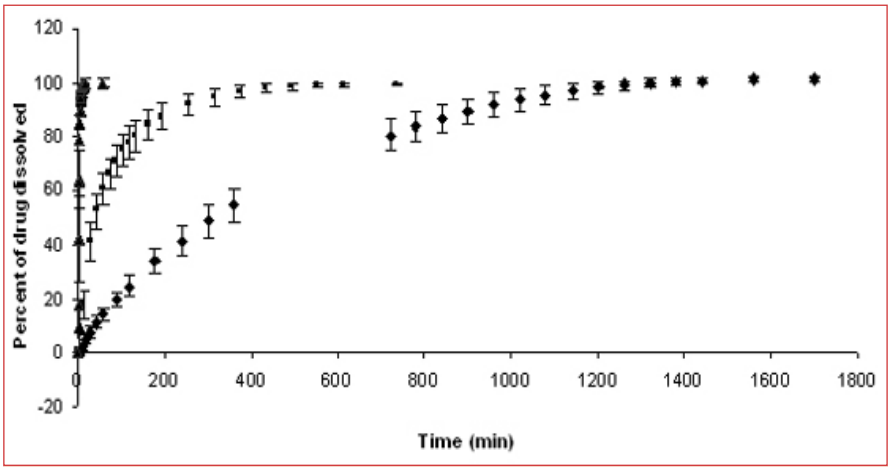

Figure 2, Dissolution profile (2) for the drug substance for three different drugs (p : 10 percent(w/w); < : 50 percent(w/w); u : 70 percent(w/w).

POWERFUL TOOLS IN FORMULATION AND PROCESS RESEARCH FOR THE DEVELOPMENT OF OPTIMAL AND ROBUST DOSAGE FORMS

The application of percolation theory

Percolation theory is one of the few tools to study on a scientific firm base the behaviour of complex formulations consisting of a number of functional excipients (1, 2). For a better understanding, a drug formulation can be analysed as a two-component, i.e. drug/matrix carrier-system. The basic equation of percolation theory is a simple power law:

$$X = S(p - p_c)^q \qquad (1)$$

X = any system property, e.g. effective diffusion coefficient Deff of a controlled release dosage form
S = scaling factor
p = drug concentration (drug load), e.g. in the carrier matrix consisting of a water insoluble excipient such as ethylcellulose (9)
pc = percolation threshold, critical drug concentration where the drug particles start to form an "infinite" cluster, i.e. a continuous phase, connecting all surfaces of the matrix tablet exposed to the intestinal fluids
q = critical exponent

The percolation threshold pc depends on the microstructure of the system, i.e. on the underlying coordination number between drug and excipient particles. The critical exponent q depends only on the Euclidean dimension of the process studied and is, for a number of processes, a universal constant introducing an order in a chaotic system.
The proof of concept of universality of different critical exponents q for different pharmaceutical processes such as the dissolution in case of controlled release systems (9) or the disintegration of a tablet (10) will be a breakthrough in the area of a science-based approach in dosage form design.

The development of expert systems

The use of design of experiments such as factorial design, response surface methodology and the application of artificial neural networks (ANN) allow describing in an excellent way the behaviour of a complex system such as a formulation. In many cases, the conclusions can be compared to an analysis of variance. In this respect, it is important to realize that also an "unsuccessful" case i.e. that only a minor part of the total variance can be explained by known experimental factors is a very valuable result.
This means that an important experimental factor is hidden or that an important unit operation is not under control (2).
The combination of these methods of experimental design with established scientific laws is the starting point of expert systems (1).

CONCLUSIONS

Functional excipients, co-processed excipients and pellets as drug carriers will play in future a more important role. The focus will be on a high standard of quality of the excipients with appropriate specifications. There is a need to evaluate the performance of excipients - not only in bulk, but also in different formulations. Powerful development tools such as the application of percolation theory (12) and expert systems (2) will be helpful for a better understanding of the formulations to fulfil the properties of a robust dosage form required by the health authorities.

REFERENCES AND NOTES

1. H. Leuenberger, M. Lanz, *Advanced Powder Technol.* **16**, 3-25, (2005)
2. H. Leuenberger, *Chimia* **60**, 40-45, (2006)
3. M. Verschraagen, C.H.W. Koks, J.H.M. Schettens, J.H. Beijnen, *Pharm. Res.* **93**, 301-306, (1999)
4. S.W. Wang, J. Moragle, C. McNulty, D Putnam, H. Chen, *J. Pharm. Sci.* **93**, 2755-2767, (2004)
5. R. Tian, N. Koyatu, H. Takanaga, H. Matsuo, H. Ohtani and Y. Sawada, *Pharm.Res.* **19**, 802-809, (2002)
6. *Handbook of pharmaceutical excipients*, Pharmaceutical Press, 1986, 1-375
7. H.P. Fiedler, *Fiedler Encyclopaedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas*, Editio Cantor, 2006, 1-1738
8. P. Kleinebudde, *Pharm. Res.* **14**, 804-809, (1997)
9. Ossi Korhonen, Pasi Raatikainen, Päivi Harjunen, Johanna Nakari, Eero Suihko, Soili Peltonen, Mika Vidgren and Petteri Paronen, *Pharm. Res.* **17**, 1138-1143, (2000)
10. R. Luginbuehl, H. Leuenberger, *Pharm. Acta Helv.* **69**, 127-134, (1994)
11. H. Leuenberger, J.D. Bonny, M. Kolb, *Int. J. Pharm.* **115**, 217-224, (1995)
12. E.M. Alvaro, I. Caraballo, *Pharm. Res.* **21**, 875- 881, (2004)

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