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Implementing virtual R&D reality in industry: *In-silico* design and testing of solid dosage forms

Hans Leuenberger^{1*}, Michael N. Leuenberger² and Maxim Puchkov³

Summary

Approximately 80% of all drug delivery systems are solid dosage forms such as tablets, film tablets, controlled release formulations, pellets, instant soluble preparations, powders for nasal, bronchial or pulmonary administration. The paper describes how to speed-up the development of solid dosage forms, to save money, and to improve quality. The idea is to replace expensive laboratory experiments by doing in-silico experiments. Thus, it is possible to design and test robust solid dosage forms for the market already in clinical phase I instead in the end of phase II, and, respectively in early phase III. The paper shows that in-silico experiments can really replace laboratory experiments and can efficiently improve process understanding and the functionality of excipients in a complex formulation. The in-silico experiments are performed by using software and hardware package F-CAD (Formulation – Computer-Aided Design) developed by CINCAP GmbH. Interestingly F-CAD uses the same concepts in case of immediate release and controlled release formulations. F-CAD utilizes a special core module based on cellular automata and cannot be compared to existing “Expert Systems”. Discrete element methods (DEM) complement the F-CAD core module and permit to visualize in-silico “1:1” laboratory experiments such as the coating of tablets in a drum. For this software a high performance computer hardware is necessary. Virtual research & development reality (e-R&D) should be complemented in industry by virtual manufacturing reality (e-manufacturing) to facilitate scale-up processes. Thanks to a VES, i. e. a “Virtual Equipment Simulator” laboratory personnel can be trained in-silico like aircraft pilots using a flight-simulator. Such training should reduce the number of rejected batches and should contribute efficiently to a faster time-to-market. The application of in-silico design and testing of solid dosage forms is an innovative tool for fulfilling the requirements of PAT (Process Analytical Technology) and the Quality by Design Initiative of FDA.

Keywords

Drug delivery systems, dosage form design, in-silico design and experiments, PAT and quality by design, faster time-to-market, e-research and e-development (e-R&D), proof of concept, e-manufacturing, process and formulation understanding

1. Introduction:

The need to reduce time-to-market and to realize cost savings in R&D

1.1 The complex task to introduce a new product into the market

The Fig. 1 shows a typical diagram, that only one out of 10000 molecules extensively tested in the discovery phase reaches successfully the market. Between the discovery of an interesting drug substance and the introduction of the final marketed dosage form of the successful drug substance a complexity of activities and tests are involved. The financial expenditures are estimated to be ca. 1 billion USD for a company to introduce a new medication into the market. This amount has to cover also the costs of the interesting drug substances, which failed during the development and did not reach the market. This fact limits companies to reduce the price of their medications on the market in order to be able to continue R&D activities. Thus if the costs of R&D can be reduced in the end all partners of the health service system can take an advantage. If the time-to-market can be reduced, then substantial savings can be achieved. Let us assume, that a new, successful medication may contribute to the sales volume of a company in the first year on the market 365 million USD. Thus, each day earlier on the market means 1 million more on sales. In case of a new approach using an e-Development (see the study of PricewaterhouseCoopers “Pharma 2020” [1, 2]) substantial savings are predicted without taking into

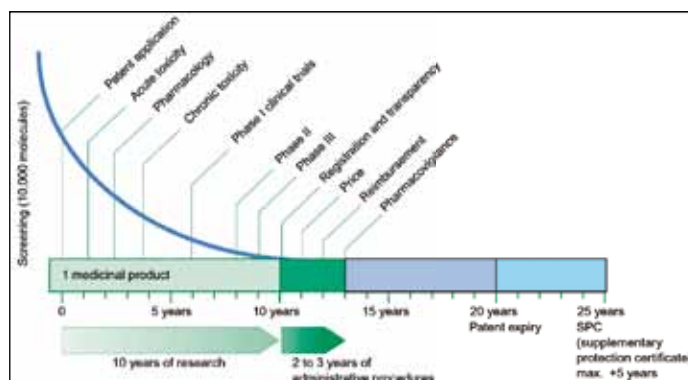


Figure 1: Time schedule and activities involved to introduce a new medical product on the market starting from 10,000 screened molecules (Courtesy: Dr. J. Werani, Pfizer Inc.).

¹ Ifiip GmbH, Institute for innovation in industrial pharmacy, Birsigstr. 79, CH-4011 Basel, hans.leuenberger@ifiip.ch, www.ifiip.ch

² AMIFICAS Inc., American institute for innovative computer-aided solutions, 195 Stillwater Drive, Oviedo, FL 32765, U.S.A, mleuenbe@mail.ucf.edu, www.amificas.com

³ CINCAP GmbH, Center for innovation in computer-aided pharmaceuticals, c/o Ifiip GmbH, Birsigstrasse 79, CH-4011 Basel, maxim.puchkov@cincap.ch, www.cincap.ch

* Corresponding author, the corresponding author can be also addressed for copies of invited presentations, which are not published

account an earlier entry into the market. The paper has as a goal to describe such a new approach in the area of developing and manufacturing of solid dosage forms.

1.2 Classical approach in pharmaceutical R&D and its deficiencies

In case of a classical approach a substantial slow down concerning "time-to-market" is linked intrinsically to the workflow and sequential activities (see Fig. 1). Due to a lack of connectivity often some special problems occur at the interfaces between the different departments involved. These different groups in research, early development, pilot plant manufacturing & scale-up, or large scale manufacturing, have usually very different cultures. For this reason today a product manager needs to take care of a product from the very beginning, starting in R&D and until the large-scale manufacturing of the final marketed dosage form. In general, for early tests in the preclinical and first clinical phases a preliminary "service dosage form" is prepared, usually a hard gelatine capsule formulation. Such a "service dosage form" may be very different from the final marketed form, which is in general ready at the end of clinical phase 2 or in the beginning of clinical phase 3. Such an approach has many risks. The final marketed dosage form needs to be bioequivalent with its earlier "service dosage form". Unfortunately, it is not uncommon, that expensive "repair actions" in the development of the final marketed dosage form have to be done to achieve a bioequivalence (see Fig. 2). What happens if the early "service" dosage form was far from optimal? In such case, the final marketed dosage form needs to be corrected to the quality of the dosage form tested in clinical phase 2. Thus, the market dosage form may not have the optimal bioavailability. Such an effect creates today headaches for companies manufacturing generics. To show bioequivalence, the generic companies may need to reduce the bioavailability of their product to comply with the originator. Unfortunately only in rare and extreme situations a non-robustness of an early dosage form becomes evident already at an early clinical phase (see H. Leuenberger, M. Lanz in [3, 4] and PhD thesis Johannes von Orelli [5]). The fact, that early "service" dosage forms have often a poor quality is linked to the fact, that the company has maybe 12 or more interesting drug substance simultaneously in the development pipeline (see Fig. 2). Obviously, there are not enough resources and time slots for doing additional expensive laboratory work. Thus, it is not surprising, that the early dosage forms are far from having a six-sigma quality. This problem becomes accented due to the fact, that the formulation cannot be changed during the forthcoming clinical trials.

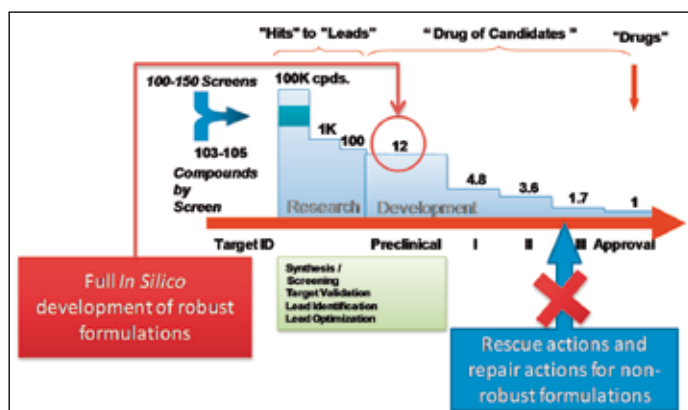


Figure 2: Typical number of drug substances in the pipeline as a function of the development phase (figure adapted, based on a presentation by Dr. A. Hussain, FDA) and CINCAP proposal for an early *in-silico* development.

1.3 Can a company afford in an early phase to develop a robust dosage form with a six-sigma quality ready for the market?

It has been generally accepted that the quality of pharmaceutical products has a quality of ca. 2-sigma. In case of a "snapshot-view",

i. e. looking at manufacturing a single batch a 2-sigma quality corresponds to ca. 4.5% defectives. Looking at a sequence of batch productions over a longer period of time the percentage of defectives of the sum of batches increases to ca. 20%. The higher value is due to drift of individual results as a consequence of measurements over an extensive time period. This poor quality boosted FDA's PAT (Process Analytical Technology) and "Quality by Design" initiative, which will have an important impact on the future concepts of R&D and manufacturing [6]. The PAT initiative has prompted the installation of additional in-process control units in the manufacturing departments for optimizing the quality. Several pharmaceutical companies in Switzerland and Germany have introduced at-line, on-line or in-line near infrared (NIR) spectroscopy control tools for nearly all process steps such as raw material identification, blending, drying and tableting [7]. Besides of NIR spectroscopy sophisticated tools such as terahertz pulsed imaging have been tested for suitability to monitor the coating process of pharmaceutical tablets [8]. Interestingly the PAT initiative did not affect with the same visibility the pharmaceutical R&D departments with their task to build-in and not to test-in the quality, but to implement quality by design (QbD) according to ICH Q8 [9]. The aim of pharmaceutical development is to design a quality product. The design space is proposed by the applicant and is subject to regulatory issues [9].

In this context the following key question arises: Is it possible to increase the quality of a product and to reduce simultaneously the costs in pharmaceutical development?

It is well known, that the quality $Q(\mu, t)$ is a function of resources μ and time t . $Q(\mu, t)$ can be expressed as an exponential asymptotic function of the following nature:

$$Q(t) = Q_{opt} (1 - \exp[-\mu t]) \quad (1)$$

With Q_{opt} = optimal quality for $t \rightarrow \infty$, μ = amount of means, i. e. tools, resources etc.. Depending on μ and time t , the "learning", resp. "optimization" process shows in the beginning a fast increase and then levels off. For this reason, the so-called "20%/80%" rule became very popular in the pharmaceutical industry. The idea of the 20%/80%-rule consists in obtaining 80% of the optimal quality with only 20% of time and resources invested. In a simplified manner, this means in practice, that one person takes simultaneously care of five projects, dedicating 20% of time and resources per project. Fig. 3 shows, that the resulting quality of the product corresponds to a sigma value of 2.34, which is very close to the reported one [6]. Even if the factor $[\mu t]$ is increased by a factor of 5, i. e. that one person dedicates 100% of the time per project, a 6-sigma value cannot be obtained. Such an approach would mean to increase the work force by five times, which is impossible for obvious reasons. Therefore, the search for new tools and means is mandatory. The authors of this paper are convinced that this is possible in the framework of an e-development concept.

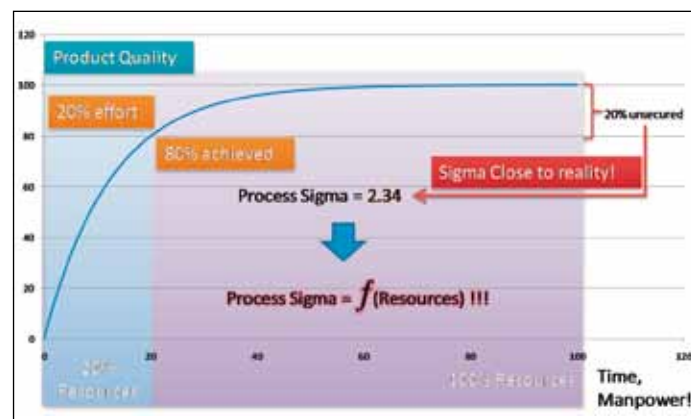


Figure 3: "Learning", resp. "Optimization" profile concerning the Quality of a product.

2. E-development concept for designing and testing of solid dosage forms

2.1 Concept of the formulation computer-aided design, F-CAD module

F-CAD [6,10], developed by CINCAP GmbH, consists of unique software modules (see Fig. 4) and has nothing to do with existing "expert systems", which can be purchased in the market. The core module is based among other on the concept of cellular automata. The core module allows to calculate dissolution profiles of the drug substance as a function of the composition and of the physico-chemical properties of the components in a formulation (solubility, swellability, effect of the particle size distribution of the drug substance and the excipients, etc.) With this concept it is also possible to calculate percolation thresholds, which play an important role in the design and the functionality of the formulation of solid dosage forms [10–13].

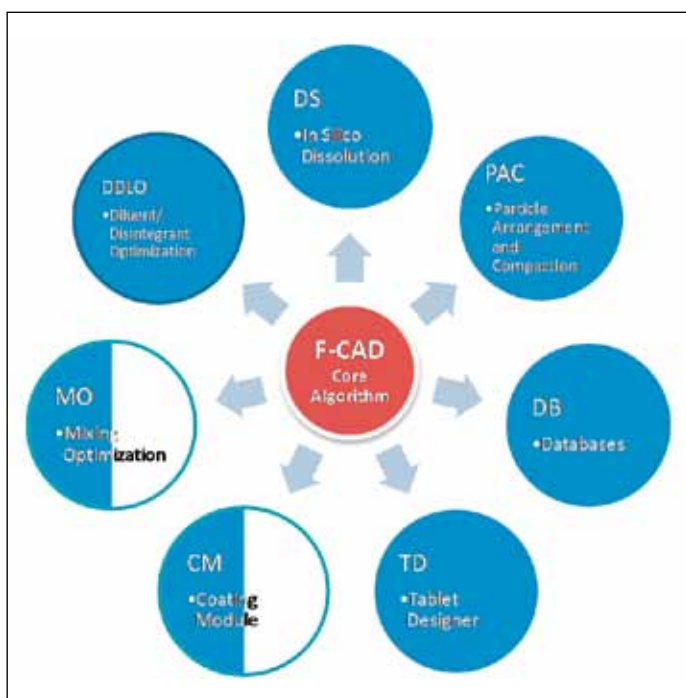


Figure 4: F-CAD software modules: the semi-filled circles indicate that this module has been complemented with discrete element methods.

It is important to keep in mind, that in this early phase of development only a minimum amount of drug substance is needed for the determination of its physico-chemical properties. The physico-chemical properties of the functional excipients are usually known.

The core module is also taking into account the shape of the dosage form. In this context, the special core module is capable of taking care of the different boundary conditions, which would be extremely difficult by solving classically sets of partial differential equations. In this respect F-CAD follows *first principles* (see Fig. 5). The software modules in Fig. 4, which are represented by semi filled circles indicate that the concept of the core module has been complemented by dedicated discrete element software modules, which allow to visualize and analyse important pharmaceutical processes such as pan coating (see Fig. 6). The capabilities of F-CAD can be summarized as follows:

- Search for an optimal and robust formulation for the market with a minimum amount of drug substance, i.e. already in an early phase of development;
- Explore the whole design space in a minimum of time;
- Define the necessary specifications of the drug substance and the excipients on a scientific base such as particle size distribution etc;

- Search for root cause in case of OoS (out of specification) problems;
- Check of equivalence in case of the exchange of an excipient by the same type having e.g. a different size distribution;
- Generate a feasibility study for the project including a sensitivity analysis to assure the robustness of the formulation;
- Establish intellectual property rights by providing results for systems before experimental confirmation;
- Effectuate only a minimum of laboratory experiments to confirm the results of the suggested formulations by F-CAD;
- Save time and money by improving quality and shortening time-to-market.

In this context F-CAD is an innovative tool being able to design and to test *in-silico* solid dosage forms.

It is interesting to compare the design of a drug delivery system with the design of a modern aircraft. Passenger airplanes and drug delivery systems have in common the following goals: a complete and safe delivery of goods at the right time to the right destination. Interestingly a modern aircraft, such as Boeing 777 or Airbus 380 is entirely designed *in-silico*. Therefore, during the development of such an aircraft savings up to 90% could be realized while improving quality [15].

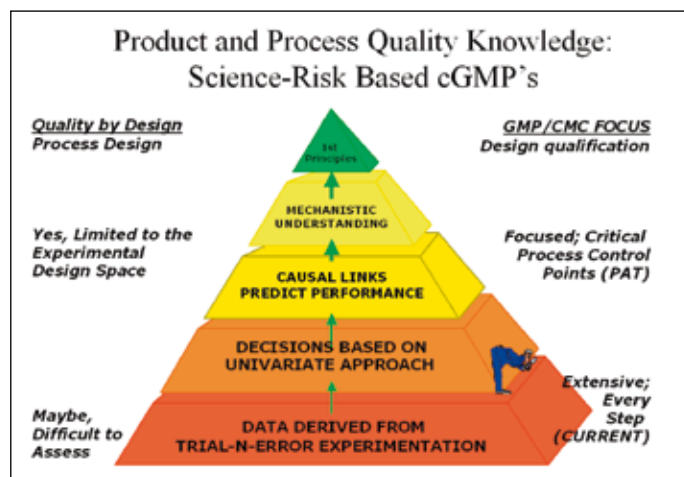


Figure 5: Knowledge Pyramid (Courtesy : Dr. A.Hussain, FDA).

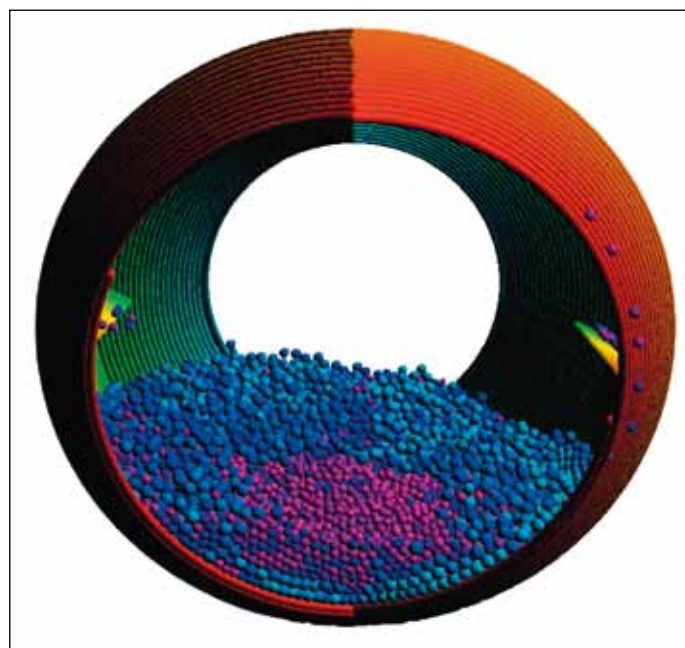


Figure 6: Snapshot view of the movement of tablets to be coated in a drum. Using discrete element methods, it is possible to visualize the effects of the geometry of the baffles inside the drum.

The most important point is that with the application of F-CAD real laboratory work concerning design and testing of solid dosage forms can be entirely done *in-silico* and performed in a very short time.

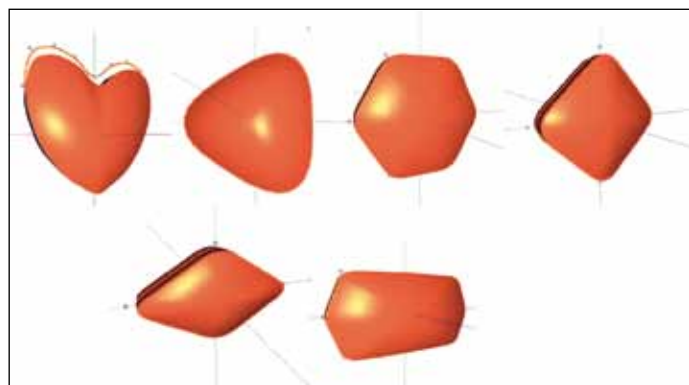


Figure 7: Different tablet shapes created by the "Tablet Designer" software module.

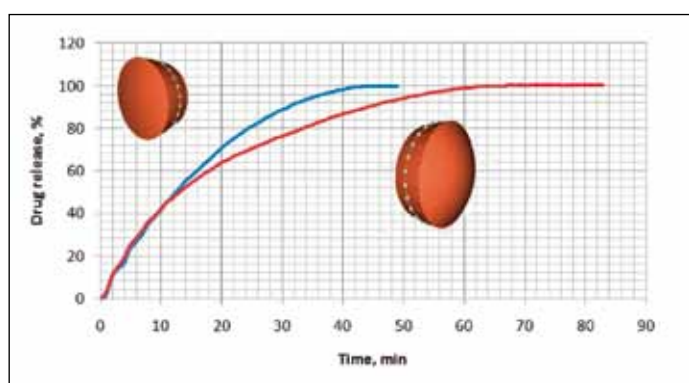


Figure 8: Calculated dissolution profiles as a function of the shape of a tablet having the same volume and the same composition.

2.2. Application of F-CAD, proof of concept of virtual R&D

2.2.1 Main application: Search for an optimal and robust solid dosage form

F-CAD can be applied already at an early phase of the development, as soon as the physico-chemical properties of the drug substance are known. On the other end, F-CAD can be used for the development of a generic. In order to use optimally the tools of F-CAD for e.g. a tablet formulation, the following procedure is recommended: 1) Definition of the desired dissolution profile of the tablet formulation (immediate release, controlled release); 2) Dose of the drug substance; 3) Desired shape of the tablet for the tablet designer, see Fig. 7; 4) List of excipients, which can be used for reasons of chemical/physical compatibility with the drug substance; 5) List of physico-chemical properties of the drug substance and excipients such as solubility, swellability, real density etc., if not already known. F-CAD can deliver a feasibility study of the desired formulation, which includes a sensitivity analysis concerning the dissolution rate profile as a function of changes in the concentrations of the components, changes in the particle size distribution of the components, the shape of the tablet etc. F-CAD can also take care of the development of a combination drug formulation and the dissolution rate of the individual drug substances, which is a challenging task [16]. Fig. 8 and 9 show dissolution rate profiles of typical applications. Depending on the properties of the drug substance the shape of the tablet can have an influence on the dissolution rate: Fig. 8 shows the influence of the shape of a tablet formulation, i.e. the volume and the composition of the formulation is completely identical. Thus if the dissolution profile is too close to a limit of an earlier specification window, already a minor change of the tablet shape may resolve such a problem. Fig. 9 shows the dissolution profile of a model formulation using caffeine as model drug substance. F-CAD has calculated the caffeine dissolution profile, which includes error bars. It has to be kept in mind that the calculated error bars contain only the contribution created by the different arrangements of the drug particles within the tablet. As in the laboratory experiment the particles are arranged at random and do not occupy in the tested

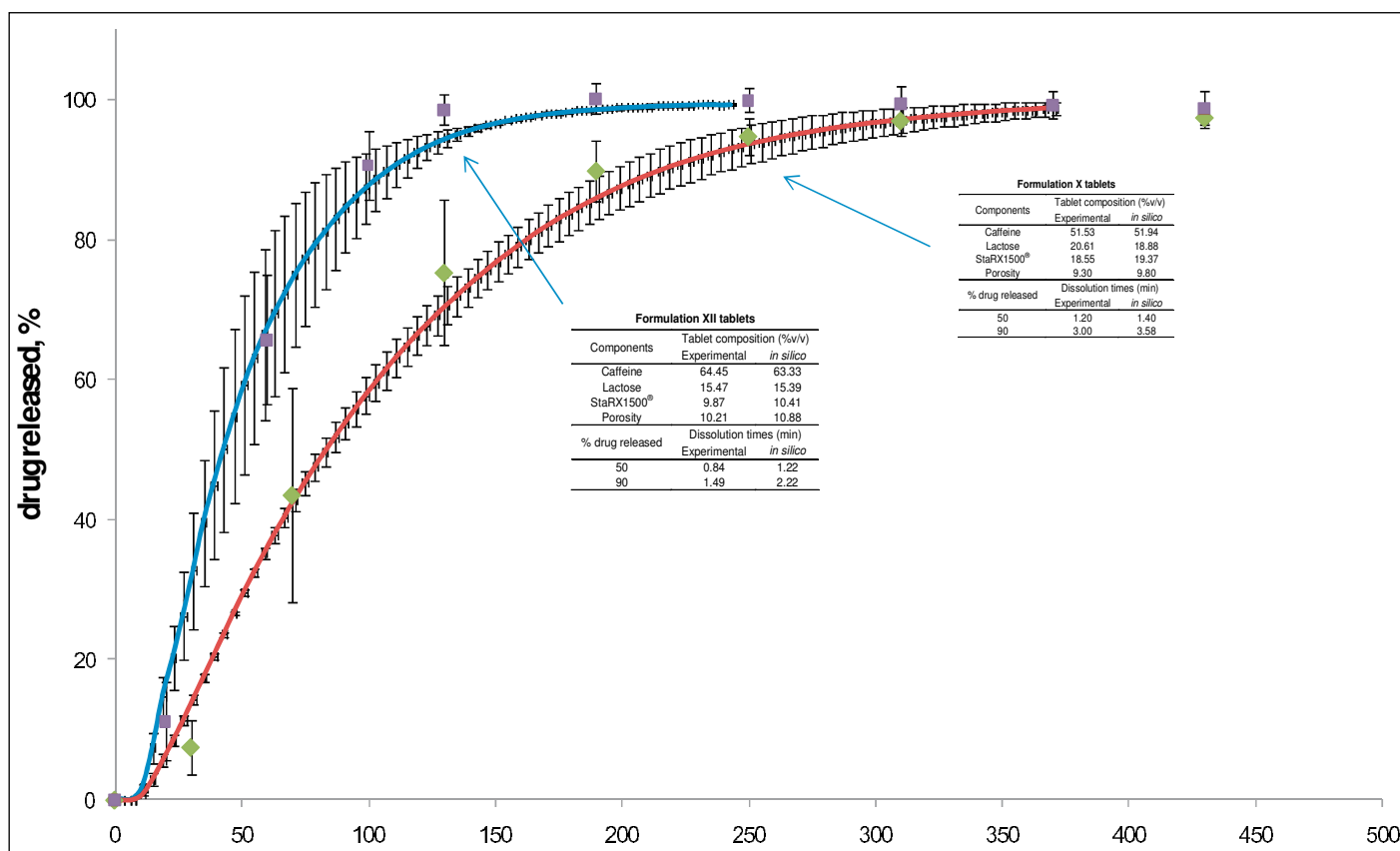


Figure 9: Calculated dissolution profile including error bars and the corresponding result of the laboratory experiment (PhD thesis Etienne Krausbauer [14]).

tablets exactly the same site. This finding supports the idea of Price-waterhouseCoopers, that such an *in-silico* approach is also helpful in research activities, i. e. the acronym virtual e-R&D is correct. The larger error bars included in Fig. 9 is the result of the real laboratory dissolution experiment. The calculated and in the laboratory experiment determined dissolution profiles show an excellent compliance. Such an excellent compliance is possible due to the fact, that F-CAD can copy 1:1 the laboratory experiment and delivers already a first estimate of the real laboratory experiment. Then a single laboratory formulation, called "calibration experiment", allows a fine-tuning of the first *in-silico* result. This "fine-tuning" can take into account laboratory-site-effects as well as the effect of the type of dissolution experiment such as USP Basket or USP paddle method.

2.2.2 Other applications and proof of virtual research reality

There are numerous other applications using F-CAD to study the behaviour of a solid dosage form, which would be out of the scope of this paper. F-CAD can e. g. be applied for dosage forms such as nanostructured micro-sized pellets [17, 18], e. g. as drug carriers for instant soluble or inhalable systems (see Fig. 10).

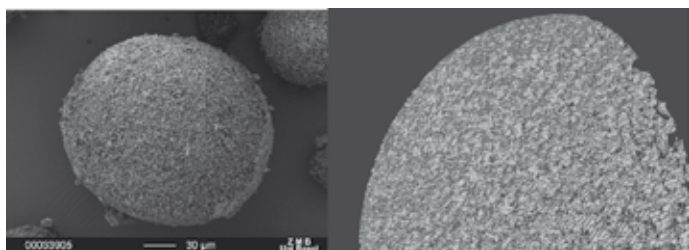


Figure 10: Real and computer generated nanostructured micropellet (laboratory data from the PhD thesis of Matthias Plitzko [17]).

Most of the other applications are linked to a specific root cause finding of a weak-point in a formulation. This task can be fulfilled by a "sensitivity analysis" of a formulation. Such studies allow to explore the design space of the formulation in a very fast time and very efficiently. The following example concerns a tablet formulation having problems with the disintegration time. The filler of this tablet formulation consisted of MCC (Microcrystalline Cellulose). The question arises if the currently used MCC can be replaced completely or partially by MCC_{rapid} of Pharmatrans Sanaq, a new microcrystalline cellulose, which facilitates the disintegration of a tablet. MCC_{rapid} is a direct compaction cellulose with filler and superdisintegrant properties, see Fig. 11. F-CAD can be used to determine, which amount of MCC_{rapid} would be

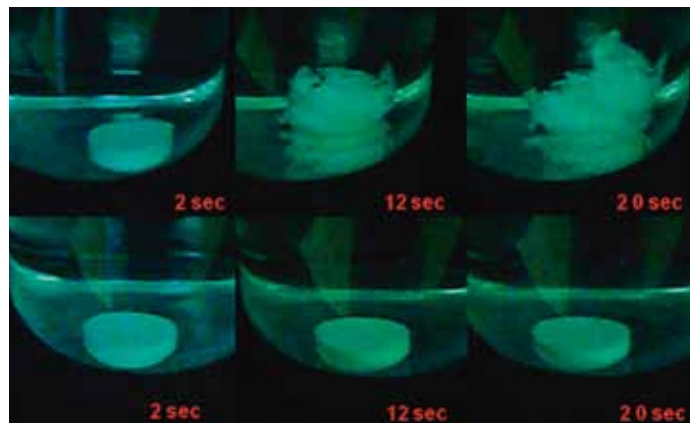


Figure 11: MCC_{rapid} tablet (PhD thesis Murad Rumman [4]) in contact with water showing a fast disintegration (above) compared to a classical MCC tablet (below).

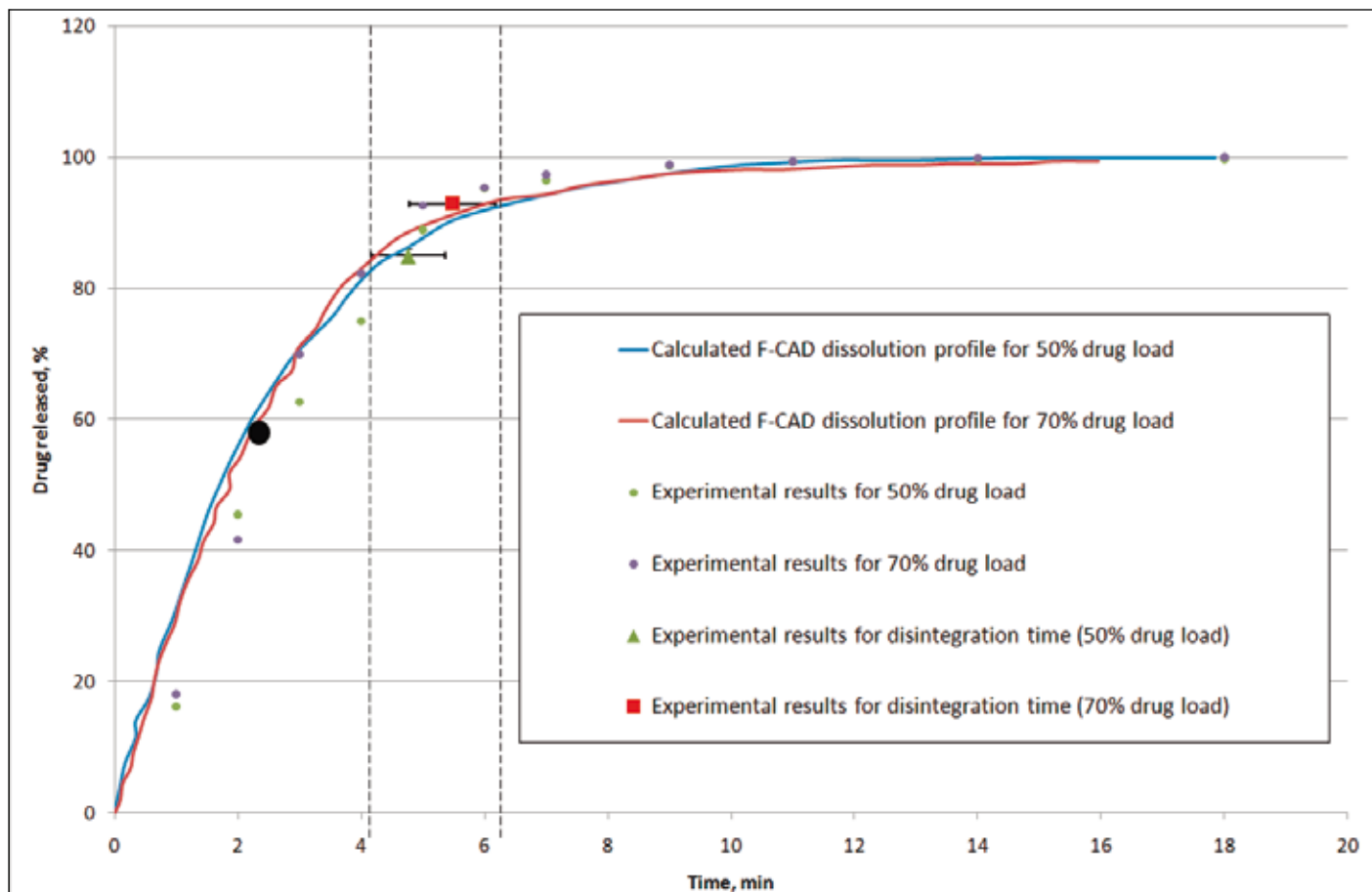


Figure 12: F-CAD calculated dissolution profiles of tablets with 50%(w/w) and 70%(w/w) drug load and laboratory data [5]. F-CAD marks in addition the specific time point (black filled circle), when the water molecules have reached the geometric center point of the tablet. Experimental disintegration of the tablets have been observed between 4 and 6 Minutes.



Figure 13: Screenshot of virtual equipment simulator (VES) for miniGlatt table-top processor.

necessary to achieve the desired disintegration time. F-CAD cannot calculate the disintegration time, which depends very much on the method used in the laboratory (with disks, without disks). However, F-CAD can calculate the time elapsed until the water molecules have reached the geometric center of the tablet. This specific time point occurs before the tablet is completely disintegrated (see Fig. 12). The effective time difference between this specific time point and the time of complete disintegration is a function of the formulation. In case of Fig. 12, the specific F-CAD time point is located at ca. 2 Min. The laboratory disintegration times range between 4 and 6 minutes. Such studies can be helpful for a better understanding of the disintegration process and the formulation. Fig. 12 shows this specific time point as a part of the dissolution profile of a tablet formulation. This capability of F-CAD is the result of its science-based core, which allows a *true mapping of the events, which happen during the laboratory experiment*. This unique property of F-CAD represents a *breakthrough* in pharmaceutical technology, to complement its scientific base of physical pharmacy [19]. This proof of concept opens a complete new research field. The authors of this paper believe that these findings are a real *premiere* in pharmaceutical literature and in the area of formulation research. Due to the complexity of a formulation with one or more drug substances and maybe 7–10 excipients such a study has a lot in common

with systems research. F-CAD shows that virtual research in solid dosage form design has become a reality. F-CAD confirms also that formulation research in classical dosage forms [20] need not be an obsolete topic.

3. Scale-up and VES, Virtual Manufacturing Reality

The scale-up process is a critical step in the development. The authors of this paper suggest to combine F-CAD with the VES tool. VES means "Virtual Equipment Simulator" [21, 22] complementing the e-R&D with the e-manufacturing. VES is a science-based tool and goes beyond classical e-manufacturing tools to optimize the cycle time, assigning manufacturing equipment for efficient use etc. VES takes into account the underlying physics such as in case of drying the thermodynamic laws (Mollier diagram etc). VES takes also into account the site-to-site specific differences of the equipment, such as heat capacity, by "fine-tuning" the calculated processes involved. This can be done exploiting the results of former experiments, respectively the results of specific laboratory experiments carried out with this apparatus. VES is a tool to train the specialist operating an important manufacturing equipment. In fact, VES has the same task as "Flight Simulator" for training pilots. It is important to keep in mind that VES is exactly describing the

behaviour of the equipment, and thus it is possible to simulate potential "crash" situations to explore technological limits. VES can be used for training purposes in a university environment but also in industry leading to a better process understanding. For educational purposes in a university environment, it is suggested to use VES in parallel with a small scale equipment such as a "MiniGlatt Fluidized Bed Table-Top Processor" (see Fig. 13), that the student can be first trained *in-silico* and subsequently verify and confirm the results in a laboratory experiment using a minimum of material. In an industrial environment it is important to keep in mind, that the behaviour of large-scale equipment can be translated 1:1 to a corresponding VES, taking into account the results of earlier batch records and settings. Thus, such a large scale VES has as a goal to be a helpful tool for facilitating scale-up exercises and to minimize risks.

4. Conclusions

Pharmaceutical solid dosage forms are complex systems consisting of the drug substance and functional auxiliary substances, which interact in a complex manner as a function of the environment. The confirmation of the *in-silico* results by laboratory experiments is very promising. The authors of this paper will be happy for comments and suggestions for further projects from the side of the pharmaceutical industry. The authors of this paper are convinced in addition, that the replacement of laboratory experiments by *in-silico* experiments is not limited to the design of solid dosage forms or airplanes. This approach should be also very helpful in designing new devices in the area of photovoltaics and quantum information technology. The proof of concept obtained in the area of dosage form design and testing lead to the conclusion, that the pharmaceutical virtual R&D approach pushed forward by PricewaterhouseCoopers has a bright future. It will be interesting to monitor, how much time is needed to apply these concepts also in systems biology to calculate the results of human clinical studies. A next goal of virtual R&D biology could be to copy *in-silico* the functions of a stem cell and its differentiation as a function of the environment. The application of e-R&D [1, 2] and e-manufacturing will revolutionize and change the landscape in pharmaceutical industry. Companies applying this new approach will have an important competitive advantage. To be successful in this approach it is not sufficient to buy such software. The important point is a close cooperation between the software provider, who needs to have an experience in the area of pharmaceutical technology and who needs to take into account the industrial in-house scientific expertise. The most efficient implementation can be realized with a strong in-house bottom-up and top-down support.

5. Acknowledgements

The authors want to thank the persons, companies and institutions, which allowed to develop, test and validate F-CAD as well as VES for solid dosage forms including *in-silico* processes such as the coating of tablets. Respecting confidentiality agreements only public available laboratory data are cited in this paper. In this context, the authors acknowledge the respective institutions and persons involved.

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