An attempt to adopt the workflow of the automotive and aircraft industry for the design of drug delivery vehicles

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Abstract

A prerequisite to adopt the workflow of the aircraft industry for the design of drug vehicles such as tablets consists in the availability of a F-CAD (Formulation-Computer Aided Design) platform to be able to design and test *in silico* the drug carrier vehicle. Such a workflow corresponds to a very rigorous interpretation of a "Right, First Time" concept starting at Clinical Phase I. Based on a Quality by Design (QbD) approach it is important to follow ICH Q8 (R2) recommendations to explore the formulation design space *in silico* or in reality by manufacturing laboratory batches. The successful implementation of the workflow needs a harmonization of equipment. For this reason, the Pressster™ equipment was applied for the development of a 80 mg Nifedipine extended release tablet formulation, simulating mechanically a high speed rotary press. Following the guideline of ICH Q8 R(2), the mathematical model that describes the properties of the tablet formulation was applied. Thus, the mathematical model of the 3×3 design served as a virtual design tool. Applying the software STAVEX 5.2 this tool proved to be very versatile. However, it was not possible to substitute all features of F-CAD of CINCAP.

Keywords: extended release formulation, compaction, *in silico* modeling, Quality by Design (QbD), solid dosage form

1. Preface

The authors dedicate this paper to Ampol Mitrevej, Head of the Industrial Pharmacy at the Faculty of Pharmacy at Mahidol University (Bangkok) and to Werner Glatt, President and Founder of the Glatt Group (Binzen, Germany).

Werner Glatt often stopped over in Thailand visiting Ampol Mitrevej when traveling to Japan for business meetings with President Takeshi Takashima of Powrex Corp. Werner Glatt is the recipient of the Reichstein Award Medal. Before him Prof. William I. Higuchi (University of Utah, Salt Lake City) and the Nobel Laureates Prof. Dr. Rolf Zinkernagel (University of Zurich) and Prof. Richard Ernst (Federal Institute of Technology of Zurich) were recipients.

Werner Glatt received his award in 2002 (see **Fig.1**a-1c) for his contribution as a promotor of innovative pharmaceutical technologies from Prof. Hans Leuenberger, former president of the Swiss Society of Pharmaceutical Sciences. The Reichstein Medal (see Fig.1a) is related to the fact, that Nobel Laureate Thadeus Reichstein was a former Head of the Institute of Pharmacy of the University of Basel before he received the Nobel prize in 1950. The medal is very special as it consists of 120 g of 20-carat pure gold created by Klaus Wilhelm Engel(Willy Engel AG), jeweler and goldshmith in Thun (see Fig. 1b), Willy Engel AG became famous as manufacturer of official state gifts for the Swiss Federal Government in Bern and for foreign heads of state.

Werner Glatt and his Glatt group received the attention of the press already in 1994 by the Innovation Award dedicated to the Pharmaceutical Institute of the University of Basel. This award sponsored by the Governments of Basel-City and Basel Country consists of a multi-colored glass panel still serving as a decoration on the second floor of Pharmaceutical Technology in the new building of the Pharmacenter established in 2000 of the University of Basel.

Werner Glatt was known as a great admirer of Japan, i.e. a country, which according to his idea integrates successfully its high-class traditional culture with concepts of an advanced society promoting excellence in science and technology. Werner Glatt passed away in 2014. At that time, Hans Leuenberger, co-authoring this paper, was prevented to give the eulogy as he was in Vienna to deliver as the only invited speaker a presentation in honor of the 10th Anniversary of the Galenus Private Foundation (http://www.galenusprivatstiftung.at). Thus, unfortunately, he could not cancel at short notice his honorary presentation in front of the heads of the Institutes of Pharmacy of the German speaking countries of Europe, i.e. Austria, Germany and Switzerland. Such a cancellation would not have been in the spirits of Werner Glatt, as a great and generous person promoting Pharmaceutical Technology and the Science of Galenus. For this reason, Hans Leuenberger and the co-authors of this paper, among others his grandson Jay Nowak, are happy to be able to dedicate this contribution to Werner Glatt. In addition, Hans Leuenberger is positively impressed that his grandson likes especially Green Tea, the traditional culture of Japan and shows many other positive traits of his grandfather which will help to push forward the group of Glatt companies.

It was a wish of Prof. Ampol Mitrevej to travel to Basel to see how his PhD students Duangmanee Maneerojpakdee and Koson Saetung (see Fig. 1e) are doing and to meet again Werner Glatt. It was not possible to realize physically his desire but his wish maybe fulfilled with the dedication of this paper to him and to Werner Glatt. As Duangmanee Maneerojpakdee was working for her PhD at the University of Mahidol and at the University of Basel the co-authors are happy, that the editor-in-chief Naomi Hashizume did agree to have two corresponding authors for this contribution.

2. Introduction

2.1 Quality by Design and Development Costs

Quality by Design (QbD) according to the guideline ICH Q8 (R2) [2] the International Conference on Harmonization (ICH) guidance Q8 (R2) and development costs involved are important issues. Thus, it is crucial to investigate whether development costs can be reduced in the pharmaceutical industry by adopting the workflow of the automotive or aircraft industry. In this context, the "Right, First Time" concept [3] is a tool for a quality improvement program, which includes an extensive use of PAT (Process Analytical Technology) [4] devices to control processes, the application of SPC (Statistical Process Control), of fishbone diagrams and of Pareto analysis [3] etc. The main goal of all these activities consists in achieving a Six Sigma quality of the marketed product. Steve Hammond [3] of Pfizer showed that a comprehensive Right First Time concept assures product quality, enhances supply reliability, improves cost, reduces inventory, reduces cycle time, improves capacity utilization, increases job satisfaction and last but not least transforms the organization from reactive through proactive to being predictive, enhancing strategic effectiveness of manufacturing [3]. According to Leuenberger et al [5] a rigorous interpretation of the concept Right First Time includes in addition, as a requirement, that the drug delivery vehicle for Clinical Phase I corresponds already to the prototype of the final marketed dosage form such as a tablet or capsule formulation.

This request is different from the current workflow, which does not request a Six Sigma quality for the samples manufactured for Clinical Phases I and II due to the high number of interesting drug substances (API) in the respective pipeline, which creates

Fig. 1 a Reichstein Medal manufactured by Willy Engel AG in Thun (Switzerland, see Fig. 1 b)

Fig. 1 b Thun, Historical City in the Swiss Alps

Fig. 1 c Werner Glatt and Prof. Hans Leuenberger, former president of the Swiss Society of Pharm. Sciences

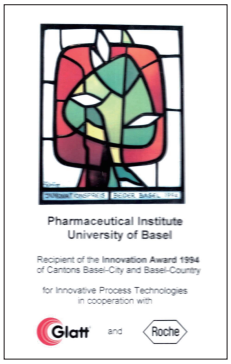

Fig. 1 d Innovation Award of the Governments of the Cantons Basel-City and Basel-Country

Fig. 1 e Prof. Ampol Mitrevej (second from left), Prof. Hans Leuenberger (third from left) at Mahidol University and the two PhD students Ms. Duangmanee Maneerojpakdee (to the left) and Mr. Koson Saetung (to the right), who spent 6 months at the University of Basel during their PhD studies at Mahidol University

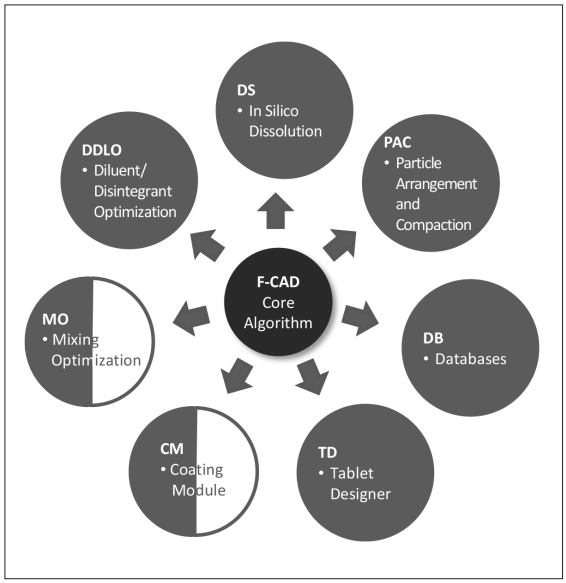

Fig. 2a Program modules of F-CAD[9]

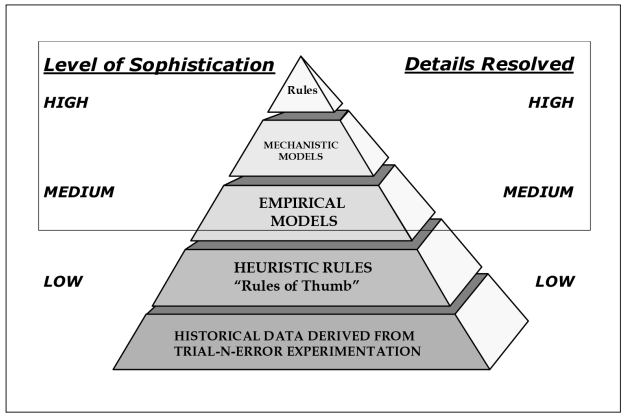

Fig. 2b Knowledge pyramid according to A.S. Hussain[14]

additional costs for APIs, which do not survive the early clinical phases [6]. Thus, the concept of using a "service dosage form" being a simple capsule or tablet formulation for the clinical phases I and II is questioned in this proposal. In case that for the first clinical phase a market ready drug delivery prototype either as a capsule or as a tablet is designed and tested *in silico* all formulation activities are kept within the same formulation design space during all clinical phases.

This rigorous "Right, First Time" concept can be realized if the pharmaceutical industry adopts the workflow of the automotive and aircraft industry. In this context, the paper is a follow-up study of the contribution "The impact of the digital revolution on the future of pharmaceutical formulation science" (invited paper, special issue "Industrial Pharmaceutical Science") [6]. For the implementation of this workflow, it is necessary to design and test first *in silico* a market ready tablet prototype of Six Sigma quality already for Clinical Phase I and to harmonize the equipment and processes of the R&D department with the manufacturing department. Thus, losses due to poor formulations and processes can be avoided, which on a worldwide scale created according to Benson and MacCabe [7] costs up to 9 Billion $ (USD) in 2004.

The focus of this paper is a rigorous interpretation of the formulation design space enforcing a harmonization of the equipment and processes between the R&D formulation department and the production [6]. Thus, for manufacturing small-scale tablet batches a mechanical simulator of a high-speed rotary press of the production department is needed such as the Presster™. In other words, F-CAD (Formulation-Computer Aided Design) of CINCAP [6] is a necessary but not a sufficient condition for an optimal implementation of the workflow of the automotive and aircraft industry by the pharmaceutical industry. According to the knowledge of the authors, only the software platform F-CAD (Formulation-Computer Aided Design) of CINCAP is currently available to design and test *in-silico* solid dosage forms such as capsule or tablet formulations for pharmaceutical originator companies.

2.2 F-CAD (Formulation-Computer Aided Design) of CINCAP

The inventor of the software platform F-CAD is Dr. Maxim Puchkov [8] who developed all the program modules in **Fig. 2a**. He is an excellent programmer using parallel computing for the implementation of the C.A. (cellular automaton) approach and obtained a PhD in chemical engineering at Mendeleyev University of Chemical Technology of Russia (MUCTR) under the supervision of Prof. Natalia Menshutina. During his postdoc time at the Institute of Pharmaceutical Technology of the University of Basel, it was not difficult for him to become a pharmaceutical engineer and a formulation scientist. In 2006, he founded together with the corresponding author the start-up company CINCAP GmbH (Center for Innovation in Computer Aided Pharmaceutics) with the office located at that time in the Institute for Innovation in Industrial Pharmacy in CH-4148 Pfeffingen, Switzerland. In this office the supercomputer, an NVIDIA Tesla (http://www.nvidia.com/object/tesla-supercomputing-solutions.html), was installed. He created the 3D C.A. core algorithm [8] for designing and testing solid dosage forms with the focus on the dissolution profile of the respective API (see Fig. 2a [9]).

At the same time, Maxim Puchkov gave a support to the PhD students Etienne Krausbauer and Go Kimura to test F-CAD as a part of their PhD thesis, supervised by the corresponding author. Go Kimura prepared his PhD thesis at the University of Basel during his sabbatical leave from Shionogi Ltd (Osaka, Japan). The PhD thesis work of Krausbauer [10] and of Kimura [11] can be accessed without problems on the server of the University of Basel. The corresponding author was asked by Prof. Joerg Huwyler, his successor as Head of Pharmaceutical Technology at the University of Basel, if Maxim Puchkov could give him a support as an assistant supervising the practical pharmaceutical technological laboratory work of pharmacy students. Currently Dr. Maxim Puchkov is working full time for his habilitation thesis at the University of Basel under the supervision of Prof. Huwyler. F-CAD could be tested by different pharmaceutical companies further to presentations by the corresponding author or to contract research work done by the start-up company CINCAP on behalf of smaller, medium and large size pharmaceutical companies. Most of the time F-CAD was used for designing a bioequivalent market ready tablet formulation for Clinical Phase III to replace the capsule formulation by a simple service dosage form used for the Clinical Phases I and II in case of an originator company. In fact, this task did not differ from the contract research work done on behalf of generic companies to show that the generic formulation is bioequivalent with the originator product. The goal of such a contract research work, which was done by the inventor Dr. Maxim Puchkov when he was working full time for the start-up company, consisted in designing a tablet formulation that shows an *in vitro* dissolution profile being identical with that of the capsule service dosage form used in Clinical Phase I and II. In case of a generic formulation the dissolution profile needs to be identical with the corresponding one of the originator product. Due to confidentiality agreements these

contract research reports unfortunately could not be published, but it was possible to establish the proof of concept [12]. The results of such a contract research work facilitate also the scale-up exercises [9, 13]. After his PhD thesis at the University of Basel Dr. Go Kimura was interested in a license to use the F-CAD platform for the regular industrial development of Shionogi formulations at Shionogi Ltd. (Osaka, Japan). The C.A. algorithm is the method of choice and is a first principle approach, which deserves to be at the top of the knowledge pyramid (see Fig. 2b [14]).

The corresponding author was invited by Fleming Europe to organize the workshop "Process Scale-up in the Pharmaceutical Industry", International Masterclass, Cologne, Oct. 14–16, 2015 [15]. On October 16, Reiji Yokoyama, a scientist on sabbatical leave from Shionogi Ltd. (Osaka, Japan) staying at the University of Basel, gave a "life presentation of F-CAD" explaining and showing the different F-CAD modules of Fig. 2a. It is evident that the F-CAD formulations need a validation by laboratory experiments. Due to the fact that the calculated dissolution profile of the first virtual F-CAD formulation is calibrated with a corresponding result of a laboratory batch, it can be expected that the subsequently calculated virtual formulations within the *in silico* formulation design space comply with dissolution profiles of the real laboratory batches.

Unfortunately, D. Maneerojpakdee did not have time, during her stay at the University of Basel for partial fulfillment of her PhD degree at Mahidol University in Bangkok, to use F-CAD for the designing and manufacturing the 80 mg Nifedipine extended release formulation. Thus, the question arises, whether it is possible to substitute F-CAD of CINCAP as a virtual development tool by using the mathematical model resulting from the experimental design being part of the guidelines of ICH Q8 (R2)?

2.3 The mathematical model of a central composite design as a predecessor of F-CAD

Based on a Quality by Design (QbD) approach it is important to follow ICH Q8 (R2) guidelines to explore the formulation design space. This exploration can take place *in silico* or in reality in a laboratory environment. Both techniques are today technically feasible. For this reason, D. Maneerojpakdee tested, as a virtual development tool, the quadratic model equation of the 3-level full factorial design, i.e. a 3×3 design, which needs a minimum of laboratory work. In this context, the study of Leuenberger [16, 17] in 1978 served as an example for a virtual formulation design tool based on 5 factors x_1 = ratio of two fillers, x_2 = disintegrant, x_3 = lubricant, x_4 = binder, x_5 = tableting pressure. This mathematical model does not belong to the class of mechanistic models (see Fig. 2b) but is a first approximation of a mechanistic model. The study of Leuenberger in 1978 covers the effect of 5 different excipients of the composition on the drug substance and one process parameter (tableting pressure). Despite the fact that factor $x_5 = x_1 x_2 x_3 x_4$ was confounded with the 4-fold interaction, 27 lab formulations were needed to explore the design space of this laboratory tablet formulation to study hardness (see **Table 1**), friability, disintegration time and the dissolution rate profile [16, 17].

Table 1 shows an excellent prediction of the hardness values with negligible differences between the experimental and calculated values, i.e. the residual values are oscillating between-1.9 N and +2.0 N, with 14 values below 0 and 13 values above 0 out of totally 27 values.

The amount of laboratory work involved was however too expensive, taking into account that at an early development stage, at the time of Clinical Phase I, only a small amount of the precious drug substance (API) is available. As it is not sure that this drug substance will survive early toxicological studies, the willingness to invest money in this substance is limited. On the other hand,

Table 1 Experimentally measured and predicted hardness values [N] of the 27 tablet batches[17]

Formulation	Hardness (calc.)	Hardness (exp.)	Difference (exp.-calc.)
1	22.62	22.90	0.28
2	26.84	26.70	-0.16
3	59.84	59.60	-0.24
4	40.10	40.20	0.10
5	29.71	30.00	0.29
6	28.87	29.50	0.63
7	35.67	36.20	0.53
8	63.32	63.40	0.08
9	33.48	32.80	-0.69
10	26.74	26.40	-0.34
11	47.64	47.20	-0.44
12	76.58	77.60	-0.98
13	29.81	29.90	0.09
14	30.16	29.80	-0.36
15	67.36	66.90	-0.47
16	49.62	49.50	-0.12
17	45.17	45.40	0.23
18	48.67	49.10	0.43
19	13.52	13.40	-0.08
20	54.88	55.60	0.72
21	41.37	42.70	1.33
22	41.11	40.50	-0.61
23	41.18	40.00	-1.18
24	52.09	54.00	1.91
25	62.60	64.00	1.40
26	41.67	41.00	-0.67
27	46.36	44.50	-1.86

the quadratic model based on a central composite design taking care of five factors did very well the job of a virtual formulation tool. Table 1 shows the quality and precision of the model for the tablet property hardness. Thus, in case of a generic drug development, there is enough drug substance available and this virtual development tool should be able to substitute F-CAD to explore the formulation design space for manufacturing tablets with an adequate hardness, i.e. a hardness > 50 N, and a friability < 0.5% for further processing (see **Fig. 3** [17]).

Fig. 3 shows the contour plots of tablet hardness H (N) and tablet friability F (%) within the same formulation design space, visualizing the acceptable range H > 50N and F < 0.5% of appropriate formulations [17]. It is important to notice that the appropriate formulation design space for an acceptable hardness remains almost unchanged if an acceptable friability is also required. Other types of responses of a tablet formulation such as the API dissolution profile in a simulated gastric fluid (SGF) may not fulfill the necessary specifications in the same formulation design space as in the case of the API dissolution profile in simulated intestinal fluid (SIF). The set theory [6] defines such a case of non-overlapping regions (areas, spaces) as disjoint.

It is a question of special interest whether a simple 3×3 design is able to characterize in a sufficient way the formulation design space? It needs a lot of knowledge and experience of the formulator to reduce the number of relevant factors to extract enough knowledge from a 3×3 design. If each factor is defined as a ratio of two excipients, it is possible to investigate a maximum of 4 components of a composition. It is a major goal of this study to test the quadratic model of a 3×3 design as a virtual formulation tool investigating the behavior of 4 components (excipients) in a tablet formulation. For this purpose, it is a prerequisite to evaluate the results of a 3×3 design with a software tool, which includes in addition a diagnostics of the model chosen, i.e. a report on the goodness of fit and model deviations as well as a check if a standard transformation may yield a better mathematical model of the tablet property studied. In case of

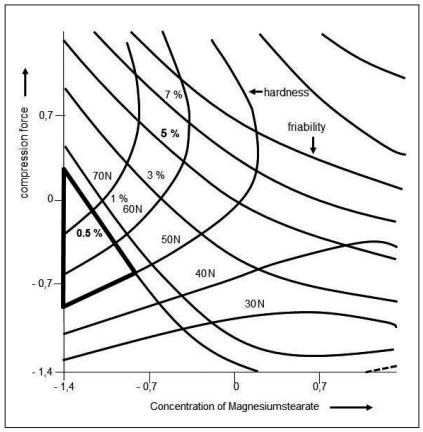

Fig. 3 Contour plots of tablet hardness H [N] and tablet friability F [%] within the same formulation design space showing the acceptable range H > 50N, F < 0.5% of appropriate formulations[16]. In this context, it is important that the desired specifications of the responses H and F belong to the same formulation design space

Table 1, in 1978 the STAVEX software was not available. The current STAVEX 5.2 software suggests in the case of the hardness values of Table 1 to use the standard transformation y => y^2 to achieve a higher quality of the model, which leads to the diagnostic report from "fit is good" (R^2 = 0.91, R_c^2= 0.89) to "fit is very good" (R^2 = 0.94, R_c^2= 0.91). In practice the label of "fit is good" is already very good (see Table 1) as the deviations of the hardness are in the range of −1.9 N to +2.0 N (see Table 1 [17]).

As mentioned above, the workflow of the automotive and aircraft industry differs from the pharmaceutical industry as follows: The automotive, resp. aircraft industry designs and test first fully *in silico* the market ready delivery system, i.e. a limousine or an aircraft. Thus, the first prototype subsequently constructed has already a very high quality close to Six Sigma. Thus, the variability of the dissolution profile would be as small as in case of a tablet formulation for Clinical Phase III allowing already during Phase I to detect a narrow therapeutic range of the API [6].

In this context, the goal of adopting the workflow of the automotive and aircraft industry the content of this paper is a follow-up study of [6] with the following goals:

1) The main goal respectively hypothesis of this paper is to test the quadratic model of the basic 3×3 design as a surrogate of F-CAD, i.e. whether such a limited amount of laboratory work allows to design an test a market ready tablet formulation already for Clinical Phase I. With other words, the paper corresponds to a feasibility study in case of lacking the availability of using an advanced technology such as F-CAD.
2) A further goal of the present study is to use the Presster™ equipment as a PAT (Process Analytical Technology [4, 6]) device and as mechanical simulator of a high speed press in the production department. Thus, an essential part of the goal "harmonization of equipment and processes" (see [6]) is covered.
3) Last but not least, it is important to choose for this feasibility study a challenging project. For this purpose the task chosen consists in the development of an optimal 80 mg Nifedipine extended release formulation for patients of the corresponding BMI (Body Mass Index).
4) In addition the formulation should comply with the USP 32 monography (test 4 [18] for SGF and test 2 [18] for SIF) required for the 60 mg Nifedipine Extended Release Formulation.

Nifedipine belongs to Class II of the Biopharmaceutical Classification System, i.e. has low water solubility but a high permeability. It is known, that PVP forms with Nifedipine a complex which enhances drug solubility.

The tablet formulation is challenging, as it needs to be compliant with test 4 and test 2 of the official monograph of USP 32 Nifedipine 60 mg extended release tablets [18].

The conditions of test 4 for the dissolution experiment in Simulated Gastric Fluid (SGF) are as follows: 900 ml buffer solution at pH 1.2 with 0.5 % Sodium Lauryl Sulfate (SLS) without enzymes using US apparatus 2 at 100 rpm stirrer rate of the paddle. The 60 mg Nifedipine extended release formulation has to comply with the following requirements in SGF regarding the % amount of API released after 1h: between 10% and 30%, after 4h: between 40% and 63% and after 12h not less than 80%.

The conditions of test 2 for the dissolution experiment in Simulated Intestinal Fluid (SIF) are as follows: 900 ml buffer solution at pH 6.8 with 10 % Sodium Lauryl Sulfate (SLS) without enzymes using US apparatus 2 at 50 rpm stirrer rate of the paddle with sinkers. The 60 mg Nifedipine extended release formulation has to comply with the following requirements in SIF regarding the % amount of API released after 3h: between 10% and 30%, after 6h: between 40% and 65% and after 12h not less than 80%.

3. Materials and Methods

3.1 Materials

Nifedipine (NI) (Sharon Bio-medicine Ltd., Mumbai, India), Microcrystalline cellulose burst 100 (MCC SANAQ®. Burst, Pharmatrans Sanaq AG, Basel, Switzerland), a polymorph of the normal Microcrystalline Cellulose, which has the property of a superdisintegrant, which was demonstrated in the PhD thesis of Michael Lanz [19] and was first described by Kumar [20]. Murad Rumman studied in his PhD thesis in detail the functionality of MCC SANAQ® Burst (= MCC Rapid) as an excipient for direct compression [21] e.g. to prepare oral dispersible tablets (ODT) or fast disintegrating pellets [22]. PVP K-30 (Kollidon 30, BASF ChemTrade GmbH, Burgbernheim, Germany); Microcrystalline cellulose PH 102 (MCC PH 102, Pharmatrans Sanaq AG, Basel, Switzerland), Ethyl cellulose (EC) (Ethocel® , Colorcon, Kent, England); Sodium lauryl sulfate (SLS) (Merck, Darmstadt, Germany). Magnesium stearate (Mg-St) (Lot No. K2 41155, Actelion Pharma Schweiz AG, Allschwil, Switzerland) was used as a lubricant for tableting by lubrication of the die used in the Presster™, equipment.

3.2 Methods

Tableting

The Nifedipine tablets were prepared by direct compression method. Nifedipine and PVP K-30 were weighed and mixed using mortar and pestle for 5 min, then filled in turbula mixer. The other excipients were added to the prior mixture and blended for 5 min. Tablets were compressed with Presster™ at the speed of 10,800, 54,000 and 108,000 TPH using a flat faced punch tool of diameter 10 mm. Tablets were compressed to a target weight of 400 mg.

Manufacturing conditions for tableting was described in previous publications [1, 11, 23, 24]. For each compression cycle the die and the punches were lubricated manually with a cotton stick immersed in Magnesium stearate.

Determination of the hardness

Tablet hardness was determined from the force required to fracture tablets by diametrical compression using a tablet hardness tester (8M, Dr. Schleuniger Pharmatron, Solothurn, Switzerland). Mean hardness of 3 tablets ± SD from each formulation was reported as tablet hardness.

Determination of the disintegration time

Disintegration tester USP (DT 2, SOTAX, Allschwil, Basel, Switzerland) was used for determining the disintegration time. Thousand milliliters distilled water was used as disintegration medium and the temperature was set at 37± 0.5℃. The time taken until no material from any of the tablets remained on the mesh was recorded. The average disintegration time ± SD of six tablets was calculated for each batch.

Determination of the dissolution profile

For the determination of the dissolution profile of Nifedipine the method of the USP 32 monography for the 60 mg Nifedipine [18] extended release formulation was adapted to 80mg Nifedipine. For this reason, 80 mg Nifedipine was solubilized in SGF (Simulated Gastric Fluid) with 3% SLS (Sodium Lauryl Sulfate) instead of 0.5% SLS [18]. As 80 mg Nifedipine could be also solubilized with 3% SLS in SIF (Simulated Intestinal Fluid), the dissolution experiments were carried out with 3% SLS. Only after the return of Duangmanee Maneerojpakdee. to Thailand, it became evident that the method of USP 32 allows in case of SIF the addition of 10% SLS. Thus, it will be necessary to repeat the dissolution experiments of the 80 mg Nifedipine extended release formulation in SIF with 10% SLS.

Dissolution studies were conducted in triplicate in 900 mL of SGF and SIF with 3% sodium lauryl sulfate at 37 ± 0.5℃. The rotating paddle dissolution apparatus was used and the revolution speed of the paddle was 100 rpm, respectively 50 rpm. The samples were withdrawn after predetermined time intervals. The samples were assayed for Nifedipine concentration by UV/VIS spectrophotometer at the wavelength of 265 nm.

3.3 3-level full factorial design for a preliminary study of Nifedipine tablets

A 3×3 full factorial design was applied to this study using the Pressster™ equipment as a Process Analytical Tool (PAT) for a technological screening program of the 9 formulations and for preparing 9 different tablet batches in the context of the topic of harmonization of the equipment and the processes (Leuenberger & Leuenberger [6]). The composition consisted of Nifedipine as drug substance, PVP K-30 as a solubilizing agent of Nifedipine in 3 different ratios, two types of fillers (MCC PH 102, MCC Burst) in also 3 different ratios. This 3×3 design was used to study the effect of 3 tableting speeds on the hardness and disintegration time of the 9 tablet batches manufactured. The independent coded and uncoded variables (factors) in the experimental design are shown in **Table 2** using the standard representation of a 3×3 design (Table 2).

The experimental results (see **Appendix Table A**1a to A1d) were evaluated using the commercial software STAVEX 5.0, (AICOS Technologies AG, Efringerstr. 32, CH-4057 Basel, Switzerland) which allows to plot the responses as contour plots for each tableting speed considered.

Table 2 Coded and uncoded (ratios [% w/w]) variables in a 3-level full factorial design of stage 1: Preliminary study on the effect of tableting speed concerning the harmonization of the equipment between the R&D and production department

No.	Coded Variable		Uncoded Variable	
	$A = x_1$	$B = x_2$	Ratio Nifedipine / PVP K-30 (mg)	Ratio MCC burst / MCC PH 102 (mg)
1	-1	-1	30:170	10:190
2	0	-1	60:140	10:190
3	+1	-1	90:110	10:190
4	-1	0	30:170	100:100
5	0	0	60:140	100:100
6	+1	0	90:110	100:100
7	-1	+1	30:170	190:10
8	0	+1	60:140	190:10
9	+1	+1	90:110	190:10

3.4 3-level full factorial for exploration of design space

A 3×3 factorial design was applied to this study for observing the effect of ethyl cellulose (EC) (matrix agent), PVP K-30 (complexing agent with Nifedipine), two types of MCC, i.e. MCC PH 102 as a filler and MCC SANAQ® Burst as a "superdisintegrant" . The amount of drug substance (Nifedipine = 80 mg) was kept constant. The independent factors (coded and uncoded variables) in the experimental designs are shown in **Table 3** using the standard representation of a 3×3 design. The resulting mathematical model was used to calculate and to check whether a 80 mg Nifedipine extended release formulation which complies with the requirement of the 60 mg extended release formulation of the monograph in the USP 32 [18] (test 2 and test 4) can be found in the formulation design space. For the evaluation of the following design, the commercial software STAVEX 5.2 (AICOS Technologies AG, Efringerstr. 32, CH-4057 Basel, Switzerland) was used (Table 3).

Table 3 Coded and uncoded (ratios [% w/w]) variables in a 3-level full factorial design of stage 2: Formulation design space exploration

No.	Coded variables		Uncoded variables		Nifedipine [mg]
	$A = x_1$	$B = x_2$	Ratio PVP K-30/EC [mg]	Ratio MCC Sanaq burst/ MCC PH 102 [mg]	
1	-1	-1	100:220	20:80	80
2	0	-1	160:160	20:80	80
3	+1	-1	220:100	20:80	80
4	-1	0	100:220	50:50	80
5	0	0	160:160	50:50	80
6	+1	0	220:100	50:50	80
7	-1	+1	100:220	80:20	80
8	0	+1	160:160	80:20	80
9	+1	+1	220:100	80:20	80

Preparation of Nifedipine 80 mg extended release tablets

The focus of this study is the dissolution profile of Nifedipine 80 mg extended release tablet formulations.

The Nifedipine 80 mg extended release tablets were prepared by direct compression method. Nifedipine and PVP K-30 were weighed and mixed using mortar and pestle for 5 min then filled in turbula mixer. The other excipients were added to the prior mixture and blended for 5 min. Tablets were compressed with Pressster™ at the speed of 108,000 TPH using a flat faced punch tool of diameter 10 mm. Tablets were compressed to a target weight of 500 mg.

4. Results and Discussion

4.1 The Pressster™ equipment used as a PAT device

The results of the Pressster™ equipment used as PAT device for the highest tableting speed are shown in the table A1a in the Appendix.

The peak values of the upper (UC) and lower (LC) compression roll do not show a difference as a function of tableting speed at 10,800 TPH [1] and 108,000 THP [1]. The peak ejection force increases as a function of the tableting speed [1], which leads to the conclusion that the lubrication still could be optimized. There is no trend of a sticking of the tablets to the punch surface due to the low values of the peak take off force. The manual lubrication of the die and the punches with a cotton stick and Magnesium stearate is however not optimal. Thus, the authors suggest to install in the Pressster™ equipment an external automatic lubrication system "ELS" of the company KIKUSUI (Japan) for an optimal lubrication [25, 26]. In case of the preparation of oral dispersible tablets (ODT) with a rotary press an external lubrication is the method of choice compared with an internal

lubrication. From a rigorous point of view an external lubrication should be generally preferred not only for ODT products, where the taste is an important issue, but also for all types of tablets as no adverse effect on the drug dissolution can be expected. Indeed, lubrication is required just for a technical reason: the compression process. In an optimal case the Pressster™ equipment can be used to prepare a Six Sigma quality tablet for the clinical samples of Clinical Phase I. Ideally, in case of high potent APIs for preparing clinical samples the Pressster™ needs to be within a containment for an optimal protection of the operators and for an optimal compliance with cGMP.
Such a procedure would comply with the requirements of adopting the workflow of the automotive and aircraft industry discussed in the paper of Leuenberger and Leuenberger [6].

4.2 Effect of tableting speed on tablet hardness and disintegration time

The results of the properties of the tablets manufactured with the Pressster™ equipment are listed in the Tables A1b, to A1d (see appendix).
Fig. 4a shows as contour plot the hardness values [N] of the tablets manufactured with the Pressster™, as a function of the tableting speed. The sensitivity of the hardness values of the tablets becomes more important at the highest speed. It is evident that at the highest speed the variability of the hardness and disintegration time values are significantly different from the variability at lower speed.
Fig. 4b shows the contour plot obtained for the disintegration time of the tablets manufactured with the Pressster™, as a function of the tableting speed. The disintegration time values of the tablets with respect to the factor values seem to show a similar behavior as the hardness values (see Fig. 4a and 4b). Thus, a regression analysis shows a linear dependence between the disintegration time Y(Dis) values [sec] and the hardness X (H) [N]:

$$Y\,(Dis) = -393.6 + 15.1X(H) \text{ with } R^2 = 0.894 \qquad (4.2\text{–}1)$$

Unfortunately, in an industrial environment there is usually no time for a detailed study and for a mechanistic explanation of such phenomena. The findings comply with the results detected by Lars Rehoric, a former PhD student analyzing "BIG DATA" of a comprehensive collection of tablet batch records at Roche pharmaceuticals in Basel [27]. This correlation is not surprising, as the relationship between the hardness and the porosity of a compact is of mechanistic nature: The Hardness (Ryshkevitch equation [28, 29]) and the disintegration time [11, 24] are a function of the porosity. However, in general, it has to be kept in mind, that the results of an analysis of a collection of tablet batch records have only a limited value, due to the fact, that "correlations" do not have always a rational cause showing just a spurious relationship. Children being very young learn throughout Europe and America, that the stork delivers newborns to their mothers. In this context, the corresponding author could show to students in pharmaceutical technology the significant correlation between the decreasing number of storks in the French region of Alsace near Basel and the decreasing number of newborn babies in the same region. Such a spurious relationship is a problem analyzing "BIG DATA" of batch records. (Fig. 4a and 4b)

4.3 Dissolution profiles of the 80 mg Nifedipine Extended Release Formulations

Fig. 5 shows the dissolution profiles of the 80 mg Nifedipine Extended Release Formulations in simulated gastric fluid (SGF) with 3% SLS respectively in simulated intestinal fluid (SIF). The tablet properties of the 80 mg Nifedipine Extended Release Formulations are listed in Table A1e of Appendix 1.
Based on R^2 values of the regression analysis the dissolution

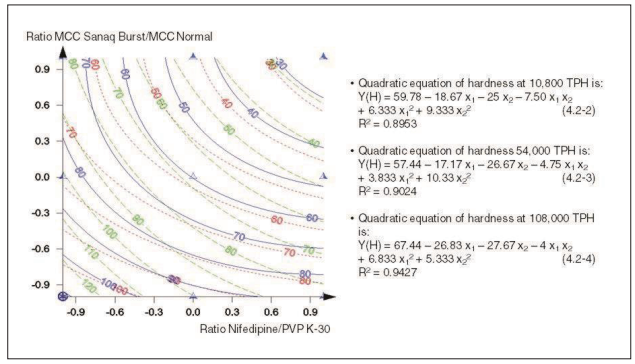

Fig. 4 a Hardness [N] of the tablets as a function of the tableting speed (blue =10,800TPH, red=54,000TPH and green=108,000TPH). For tableting speeds between 10,800TPH and 54,000TPH the hardness values do not change in an important way, but at the highest tableting speed (108,000TPH) the hardness values of the tablets are ca. 20% higher, which may be an effect of work hardening. The mathematical model for tablet hardness Y (H), as a function of the tableting speed is shown at the right of Fig. 4 a

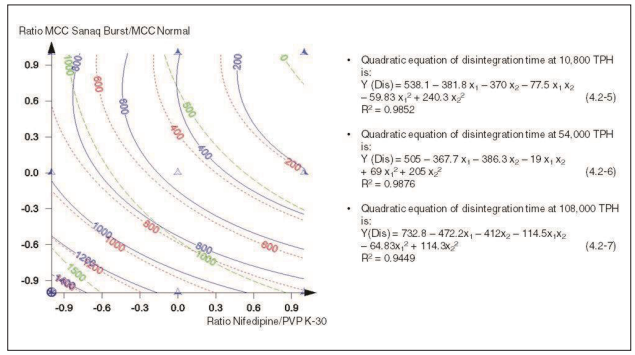

Fig. 4 b Effect of the tableting speed on the disintegration time of the tablets manufactured With the Pressster™ (blue=10,800TPH, red=54,000TPH and green=108,000TPH) .Only in case of the highest speed the disintegration time value differs significantly from the values at the two lower speeds. This behavior seems to be a result of the proportionality between the values of hardness and disintegration time. The mathematical model for tablet disintegration time Y (Dis), as a function of the tableting speed is shown at the right of Fig 4 b

profiles [28] can be described better by using the Higuchi equation than using a zero order kinetic model [1]. However, it has to be taken into account that the Higuchi equation is only valid in the range of 0% to 60% of drug released. For this reason, the Hixon–Crowell model for the dissolution profiles of Fig. 5a and 5b was used, which is exact in the whole dissolution range. The knowledge of this model is important for the virtual evaluation of the amount of API released after 1h, 4h and 12h in SGF and after 3h, 6h and 12h in SIF (see chapter 4.4 and 4.5). (Fig. 5a and 5b)

4.4 Evaluation of the amount (%) of API released after 1h, 4h, and 12h in SGF and after 3h, 6h and 12h in SIF for the nine formulations of the 3x3 design

Table 4 shows as results of the 9 formulations the amount of API dissolved after 1h, 4h and 12h in SGF and after 3h, 6h and 12h in SIF. The results of table 5 were used for an evaluation with STAVEX 5.2.

Case of SGF

Fig. 6a and 6b show the evaluation for the amount of API (%) dissolved after 1h and 4h for SGF and 3h and 6h for SIF respectively.

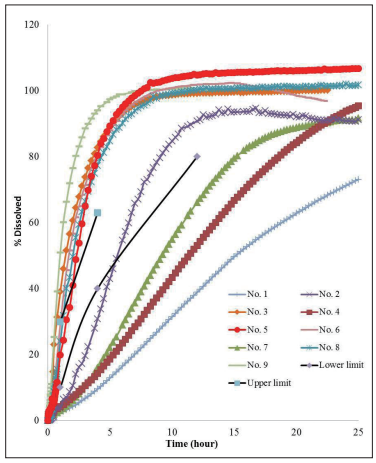

Fig. 5a Dissolution profiles of nine formulations of 80 mg Nifedipine extended release tablets in SGF with 3% SLS. According to the standard order of a 3×3 design neither formulation No.5 nor No.2 complies with the requirements of the USP monograph (test 4[18]). It is important to notice that formulation No.4 (see Fig. 5b) does not comply either

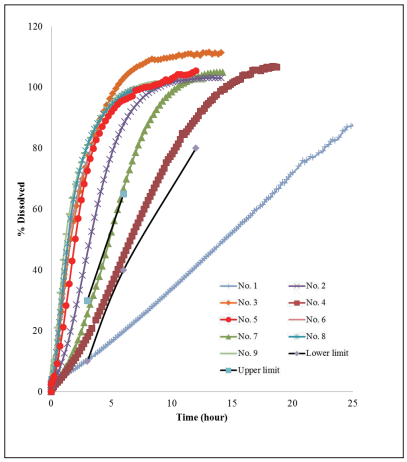

Fig. 5b Dissolution profiles of nine formulations of 80 mg Nifedipine extended release tablets in SIF with 3% SLS with the upper and lower limit of test 2[18]. According to the standard order of a 3×3 design (see Table 4) formulation No.2 does not comply. The formulation No.4 and No.7 are candidates to comply test 2 of the official monography[18]

In case of Fig. 6a (to the left) the STAVEX 5.2 evaluation yielded the goodness of fit values R^2 = 0.90584 and R_c^2 = 0.74892 and the diagnosis "goodness of fit is mediocre" as R_c^2 was lower than 0.8. The following model equation was obtained for the amount of API (%) released in SGF after 1h, i.e. for $Y_{1h\ SGF}$ (%):

$$Y_{1h\ SGF}\ (\%) = 14.11 + 18.32x_1 + 5.465x_2 + 5.582x_1^2 + 2.672x_2^2 + 2.808x_1x_2 \quad (4.4\text{-}1)$$

A suitable formulation close to 10% API dissolved after 1h could for instance be located at x_1^* = −0.2 and x_2^* = −0.5 in the formulation design space (see Fig. 6a, to the left).
In case of Fig. 6a (to the right) the STAVEX 5.2 evaluation yielded again the diagnosis "goodness of fit is mediocre" with R^2 = 0.91153 and R_c^2 = 0.76407, and the following model equation for the amount of API (%) released in SGF after 4h, i.e. for $Y_{4h\ SGF}$ (%):

$$Y_{4h\ SGF}\ (\%) = 67.43 + 36.38x_1 + 10.7x_2 - 13.26x_1^2 - 6.843x_2^2 + 1.213x_1x_2 \quad (4.4\text{-}2)$$

Table 4 Dissolution results of the 9 formulations studied[1] with respect to test 4 (for SGF) and test 2 (for SIF) in case of USP 32 monography for 60 mg Nifedipine extended release formulation

No.	in SGF			in SIF		
	1h	4h	12h	3h	6h	12h
1	2.29	9.51	38.84	10.36	19.8	41.07
2	3.77	30.81	90.86	45.40	87.7	102.8
3	39.06	82.81	99.14	75.7	102.8	110.7
4	4.20	14.26	53.11	18.02	44.5	89.4
5	19.92	80.42	104.78	72.7	95.8	105.5
6	29.38	81.07	101.86	77.3	97.1	100.7[1]
7	2.96	15.90	66.12	25.6	66.8	103.2
8	23.99	77.36	100.22	80.6	97.5	99.6[1]
9	50.96	94.05	100.60	81.0	98.1	102.1

[1] *Measured at 8.37 h*

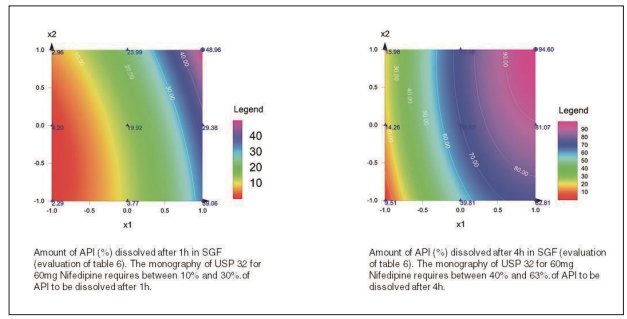

Fig. 6a Amount of API dissolved after 1h (to the left) and 4h in SGF (to the right)

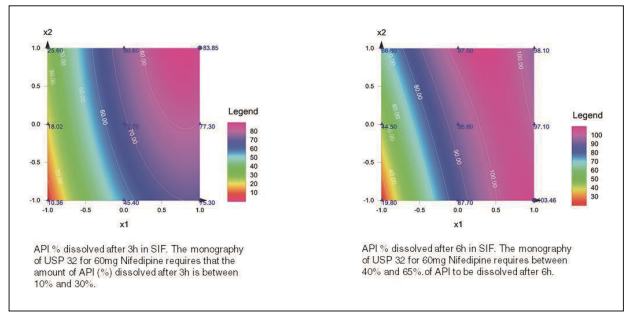

Fig. 6b Amount of API dissolved after 3h and 6h in SIF

A suitable formulation close to 50% API dissolved after 4h could for instance be located at x_1^* = −0.2 and x_2^* = −0.5 in the formulation design space (Fig. 6a, to the right).

Case of SIF

Fig. 6b (to the left, respectively to the right) show the evaluation for SIF of the amount of API (%) dissolved after 3h resp. 6h.
In case of Fig. 6b (to the left) the STAVEX 5.2 evaluation yielded the diagnosis "goodness of fit is very good" with R^2 = 0.96364, R_c^2 = 0.90304 and the following model equation for the amount of API (%) released in SIF after 3h, i.e. for $Y_{3h\ SIF}$ (%):

$$Y_{3h\ SIF}\ (\%) = 68.21 + 29.94x_1 + 9.357x_2 - 18.3x_1^2 - 2.868x_2^2 + 2.385x_1x_2 \quad (4.4\text{-}3)$$

A suitable formulation with the result of close to 20 % API dissolved after 3 h could be located at x_1^* = −1.0 and x_2^* = 0.0, corresponding to formulation No. 4.
It is important to realize that this location is quite different from the formulation located at x_1^* = −0.2 and x_2^* = −0.5, which does not comply with the requirements in SIF (see Fig. 6b).
In case of Fig. 6b (to the right) the STAVEX 5.2 evaluation yielded the diagnosis "goodness of fit is very good" with R^2 = 0.99148, R_c^2 = 0.97728 and the following model equation for the amount of API

(%) released in SIF after 6h, i.e. for $Y_{6h\ SIF}$ (%):

$$Y_{6h\ SIF}\ (\%) = 93.9 + 27.82x_1 + 8.683x_2 - 22.15x_1^2 - 0.35x_2^2 - 12.82x_1x_2 \quad (4.4\text{-}4)$$

A suitable formulation close to 40 % API dissolved after 6h could be located at $x_1^* = -1.0$ and $x_2^* = 0.0$, corresponding to formulation No. 4. It is important to realize that this location is quite different from the formulation located at $x_1^* = -0.2$ and $x_2^* = -0.5$, which does not comply with the requirements in SIF (see Fig. 6b, to the right). In fact, a close study of the evaluation of Fig. 6a and 6b show, that there is no location, respectively formulation, in the explored formulation design space, which fulfills simultaneously the requirements of test 2 and test 4 of the monography of the 60 mg Nifedipine Extended Release Formulation in USP 32 [18]. In the mathematical language the set theory explains, that we have two regions within the formulation design space, which are not overlapping, i.e. the regions are disjoint [6]. Thus, this result differs completely from the case of the tablet property hardness and friability, where a common region of the formulation design space complying with the requirements for hardness and friability could be identified (see Fig. 3).

The Hixon – Crowell model

Due to the fact that the Higuchi model [30], which can be described by a linear regression line of API released as a function of $\sqrt{t}$, is only correct between 0% and 60 % of API, the classical Hixon-Crowell model was used, i.e. API [%] (Y) not released corresponds to (cube root law, see **Table 5**a):

$$Y^{1/3}{}_{\text{API NOT RELEASED}} = 1 - kt \quad (4.4\text{-}5)$$

This model has the advantage that the intercept $Y_0^{1/3}$ is well defined and that the equation is valid from 0% of API released to 100% released. At the time t=0, the intercept $Y_0^{1/3}$ should be equal to one or close to one. The difference between the intercept calculated (= $Y_0^{1/3}$) in **Table 7**a and the theoretical value for t=0 being equal to one is related to the presence of a lag-time t_{lag} and due to the variability of data. The lag-time t_{lag} is calculated as follows:

$$t_{lag} = (Y_0^{1/3} - 1.0)/k \quad (4.4\text{-}6)$$

It is evident that t_{lag} is related to k, i.e. a formulation with slow diffusion/dissolution shows an important lag-time such as formulation No.4 and No.7 in SGF and in SIF (see Table 5b).

Fig. 7 show the result of the STAVEX evaluation of k of the Hixon-Crowell equation in SGF, respectively in SIF (see **Table 6**).

In case of API dissolution profile in SGF the STAVEX 5.2 platform suggested to use a standard transformation for obtaining a better diagnostics than after the first cycle, which was "mediocre" . The second cycle yielded the diagnostic "fit is very good" and the following model equation for k_{SGF}:

$$(-k_{SGF})^{-1/2} = 3.236 - 1.929x_1 - 0.7103x_2 + 1.284x_1^2 + 02839x_2^2 + 0.4045x_1x_2 \quad (4.4\text{-}7)$$

For the formulation chosen ($x_1^* = -0.2$ and $x_2^* = -0.5$)
the value for $(-k_{SGF})^{-1/2*} = -4.1398\ h^{1/2}$, i.e. $-k_{SGF}{}^{-1*} = 17.138$, i.e. $k_{SGF}{}^* = -0.05834\ h^{-1}$. This $k_{SGF}{}^*$ value leads to the following results after 1h, respectively 4h:

$Y^{1/3}$ = API (%) not released after 1 h ($Y^{1/3}{}_{\text{API NOT RELEASED}} = 1 - kt$):

$Y^{1/3} = 1 - k_{SGF}{}^* = 0.94165$, Y = 0.835, i.e. after 1 h the amount of API released = 16.5%. According to test 4 after 1 h a minimum of 10% and a maximum of 30% needs to be released. Thus, the result of 16.5% is fully compliant.

$Y^{1/3}$ = API (%) not released after 4 h ($Y^{1/3}{}_{\text{API NOT RELEASED}} = 1 - kt$):

$Y^{1/3} = 1 - kt$ (4h) = 0.76664 Y = 0.4505 i.e. after 4h the amount of API released = 54.94 %

According to test 4 after 4 h a minimum of 40% and a maximum of 63% needs to be released. The result of 54.94 % in SGF is fully

Table 5a Hixon-Crowell model as an alternative to the dissolution profiles of Fig. 5a[1] and Fig. 5b[1] described by the cube root law $Y^{1/3}$ (not dissolved=1 – kt)

No.	Classic Cube root model in SGF			Classic Cube root model in SIF		
	Slope k [h^{-1}]	Intercept $Y_0^{1/3}$	R^2	Slope k[h^{-1}]	Intercept $Y_0^{1/3}$	R^2
1	-0.0157	1.03	0.9990	-0.0188	1.0487	0.9788
2	-0.0561	1.09	0.9983	-0.0912	1.0757	0.9881
3	-0.1070	0.96	0.9923	-0.1325	1.0165	0.9752
4	-0.0247	1.06	0.9956	-0.0458	1.0819	0.9857
5	-0.1191	1.06	0.9947	-0.1327	1.0523	0.9969
6	-0.1099	0.99	0.9864	-0.1279	0.9931	0.9922
7	-0.0322	1.08	0.9923	-0.0687	1.1055	0.9952
8	-0.1003	1.00	0.9933	-0.1561	1.0261	0.9957
9	-0.1946	0.99	0.9987	-0.1421	0.9788	0.9863

Table 5b Lag-time t_{lag} for the formulations No.4 and No.7 in SGF and SIF according to eq. (4.4-6)

No.	Classic Cube root model in SGF			Classic Cube root model in SIF		
	Slope k [h^{-1}]	Intercept $Y_0^{1/3}$	t_{lag} [h]	Slope k[h^{-1}]	Intercept $Y_0^{1/3}$	t_{lag} [h]
4	-0.0247	1.06	2.4h	-0.0458	1.0819	1.8h
7	-0.0322	1.08	2.4h	-0.0687	1.1055	1.4h

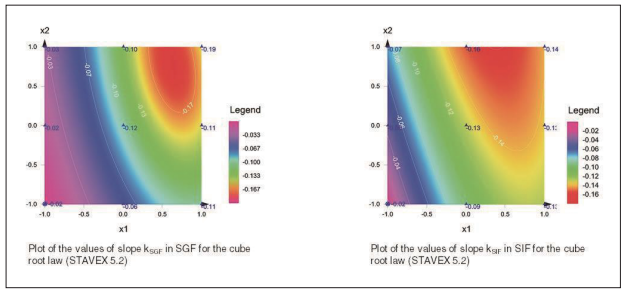

Fig. 7 Hixon-Crowell model for SGF and SIF dissolution profiles (STAVEX evaluation of slope k)

Table 6 Summary amount API dissolved for CR_4, CR_7, $CR_{4/7}$ (uncoated) and final coated oblong tablet $CR_{4/7}$

		Coated Oblong Tablet. CR_4	*Coated Oblong Tablet. CR_7*	*Uncoated Oblong Tablet. $CR_{4/7}$*	*Oblong Tablet. $CR_{4/7}$ (coated)*
	hour	*$Y(\%)_{released:}$*	*$Y(\%)_{released:}$*	*$Y(\%)_{released:}$*	*$Y(\%)_{released:}$*
In SGF	1h	31.2%	27.96%	3.58%*)	28.58%
	4h	41.26	40.98%[1)]	12.6%**)	37.6%[3)]
	12h	81.11%	81.11%	61.3%**)	86.3%
In SIF	3h	18.02%	25.6%	22.6%**)	22.6%
	6h	44.5%	66.8%[2)]	58.7%**)	58.4%
	12h	89.4%	89.4%	93.5%**)	93.5%
			[1)] At the limit of the specification (>40%) [2)] Limit = 65%, i.e. out of specification!	**) interpolated (amount released within t_{lag} > 1h). **) calculated according to eq. (4.4.- 7), respectively (4.4.-8) with an intercept of 1.07, respectively 1.09.*	*[3)] critical estimate*
		Estimated results of the dissolution profile of an 80 mg Nifedipine extended release oblong tablet formulation coated with 27% of API in the outer layer for immediate release. The combination *with formulation No. 4 (CR_4)* for the controlled release part fulfills the requirements in SIF but not in SGF.	Estimated results of the dissolution profile of an 80 mg Nifedipine extended release oblong tablet formulation coated with 25% of API in the outer layer for immediate release. The combination *with formulation No. 7 (CR_7)* for the controlled release part does not fulfill the requirements in SIF but critically in SGF.	k_{SGF} = 0.02845 k_{SIF} = 0.05725	Estimated results of the dissolution profile of an 80 mg Nifedipine extended release oblong tablet formulation coated with 25% of API in the outer layer for immediate release. The in silico release rate of $CR_{4/7}$ in SGF, respectively in SGF was calculated according to the equations for k_{SGF} (eq. 4.4.-7), resp. for k_{SIF} (eq. 4.4.-8) using as intercept[*)] the interpolated value between CR_4 & CR_7 of 1.07 in SGF, respectively a value of 1.09 in SIF.

compliant for the formulation with $x_1^* = -0.2$ and $x_2^* = -0.5$.
In case of API dissolution profile in SIF the STAVEX 5.2 platform suggested to use a standard transformation for obtaining a better model than after the first cycle. The second cycle accordingly yielded the diagnostics "fit is very good" with better R^2 values ($R^2 = 0.99117$, corrected goodness of fit $R_c^2 = 0.97641$) than in case of the first cycle.
The Hixon-Crowell model equation (of the second cycle) for k_{SIF} in case of SIF:

$$-k_{SIF}^{1/2} = -0.3576 - 0.08089x_1 - 0.03851x_2 + 0.06848x_1^2 + 0.005761x_2^2 + 0.02801x_1x_2 \quad (4.4.-8)$$

The evaluation of the formulation with $x_1^* = -0.2$ and $x_2^* = -0.5$, which complies with test 4 in SGF yields the value for $k_{SIF}^* = -0.09934\ h^{-1}$ in SIF. The exact model of the Hixon-Crowell equation in SIF allows to predict the amount of API (%) released after 3h and 6h:
In case of 3h the amount of API % released is equal to 65.4% for $k=-0.0994\ h^{-1}$. Thus, the result does not comply.
The following results need a special consideration: The best tablet formulation for test 2 is equal to formulation No. 4 (see Fig. 5b) and a separate best tablet formulation for test 4 can be found in the formulation design space in the neighborhood of tablet formulation No. 5 and No. 2 (see Fig. 5a).
Thus, the results so far lead to the first very important conclusion: It is not possible to find within the complete formulation design space a single tablet formulation, which complies simultaneously with test 2 and test 4.
What are the consequences of these findings? Is it necessary to start again this project from zero and to forget about the work done so far? Does such a fact contribute to the high losses [7] of time and money reported by MacCabe and Benson? Is it possible to find a solution for such a problem, which can show up during the development of a generic formulation, as all specifications of the originator formulation need to comply? This point is the topic of the next chapter.

4.5 Proposal for an optimal 80mg Nifedipine Extended Release tablet formulation, which fulfills simultaneously the tests No. 2 and No. 4

How can this problem be resolved? The work of a formulation scientist resembles the one of a detective, especially if the formulation scientist is working for a generic company. In other words, a formulation scientist working first in a generic company has the opportunity to get an optimal experience and training to become a real specialist in formulation science, which is an advantage in an originator company. The specifications in the monography of USP 32 [18] correspond to the test results of a single tablet formulation. Thus, the originator single tablet must consist of two parts with different release rates, such a tablet having an outer layer (coat) and an inner core. The coat will release rapidly the API in SGF, so that after 1h a minimum of 10% of API is released in SGF according to test 4. The API of the inner core is part of the hydrophilic matrix. Thus, the inner core of the tablet releases the API at a lower rate in order to fulfill the requirements of test 2. Due to the fact, that some of the prepared controlled release formulations have an important lag-time an immediate release coating is the method of choice. As an alternative formulation a bi-layer tablet with different release rates could lead to similar results, i.e., a percentage of API will be released immediately by layer 1 and layer 2 serves as an extended release formulation. Due to the fact, that the transit time is approx. 2h in the fluid of the stomach (SGF) and approx. 10h in the intestinal fluid (SIF), the formulation of the core of the coated tablet or tablet layer 2 becomes the focus of interest. In this context, the upper and lower specifications in SIF of Fig. 5b limit the formulation design space of interest. The formulations No. 4 and No. 7 are located within this limited space. Thus, the two formulations should be first studied for a "combination drug" with layer 1 = immediate release and layer 2 as controlled release, resp. a coating for immediate release and a core of controlled release. The part of immediate release can consist of a Nifedipine-PVP complex showing a high solubility and the controlled release part can be a formulation identical to No. 4, i.e. CR_4 : ($x_1 = -1$, $x_2 = 0$) or to No.7, i.e. CR_7: ($x_1 = -1$, $x_2 = +1$) or as a third alternative a formulation in between $CR_{4/7}$: ($x_1 = -1$, $x_2 = +0.5$).
CR_4: According to Table 6, it is necessary to use 27% [w/w] of the API of the inner core for an immediate release coating of e.g. an oblong (500 mg) tablet to achieve an amount of API released after 12h in SGF > 80% (see Table 6).
CR_7: According to Table 6, it is necessary to use 25% [w/w] of the API of the inner core for an immediate release coating of e.g. an oblong (500 mg) tablet to achieve an amount of API released after 12h in SGF > 80% (see Table 6). The following release rates result in SGF and SIF for the formulations CR_4, CR_7 and $CR_{4/7}$ (see Table 6).
The combination of 25% of API as immediate release part with formulation $CR_{4/7}$ for the controlled release part has the chance to fulfill the requirements in SIF and in SGF, but the result after 4h looks to be critical. However, due to the fact, that the specific surface of an oblong tablet is higher than a bi-layer tablet, a coated oblong tablet will have a slightly faster dissolution profile. Thus, the coated oblong tablet will be likely to comply with test 2 and test 4. Finally yet importantly, this formulation needs to be validated by a laboratory batch.

5. Conclusions

The guidelines [3] of ICH Q8(R2), especially, the use of experimental design for the exploration of the formulation design space including the application of STAVEX 5.2 for the *in silico* description of the important responses of the formulations in the complete design space are extremely fruitful.
The Presster™ equipment used for the harmonization of processes and equipment shows to be an excellent PAT device to test the sensitivity of tablet formulations to the tableting speed. As an optimal 80 mg Nifedipine formulation, the following procedure is suggested: Direct compaction of an oblong tablet consisting of the formulation $CR_{4/7}$ with the coordinates ($x_1 = -1$, $x_2 = +0.5$), i.e. $x_1 = 100 : 220$ = ratio PVP K-30/EC [mg] and $x_2 = 65 : 35$ = ratio MCC Sanaq burst/ MCC PH 102 [mg] with 55 mg Nifedipine per oblong tablet. After applying an aqueous solution of PVP/Nifedipine complex with 25 mg Nifedipine each tablet contains 80 mg API and 25 mg is released immediately. As an alternative for adding classically 0.5% Magnesium stearate an external lubrication system can be used.

The study shows clearly that in an industrial environment there is no time for basic research during the development phases. Thus, an industrial pharmacist cannot enjoy to study and explain interesting phenomena, which occur during the development phases. The motivation of a formulation scientist consists in achieving a high quality of the dosage form in a short time. Thus, time to market plays an important role. This looks to be just a commercial point of view but has a high societal impact if the number of successful introduction of new APIs and therapies is increased. This is the reason, why FDA pushes forward the concept of "Right, First Time" [6]. Such a holistic approach avoids losing sight of the wood for trees. Thus, for the advancement of pharmaceutical science a close cooperation between industry and academia is a prerequisite. Indeed, it is the task of academia or of a spin-off start-up company to develop the virtual tools for a better understanding of the processes and formulations. F-CAD

as a virtual tool is able to serve as a "learning suite" [5, 12] and is able to predict the important properties of a solid dosage form after calibration [6]. The classical approach according to the guidelines of ICH Q8 (R2) describing the formulation design space needs much more laboratory experiments and is by nature retrospective as the prediction is primarily based on an interpolation with the formulation design space.

Already a simple 3×3 design with only 9 lab batches gives a helpful insight in the formulation design space. In this context, it is important to take into account the set theory [6]. Thus, special actions are needed as shown in this present study if the relevant responses do not overlap in design space regions being disjoint. In order to avoid redundant experiments creating unnecessary costs the set theory urges that an originator company should start the first clinical trials with the same dosage form as marketed later [6].

Curiosity was the driving force for research of the experimental work of D. Maneerojpakdee: In this context she regrets that she had no time to apply F-CAD in parallel during her stay in Basel, especially as she could have done the same experiments *in silico* and compared the results. In addition, F-CAD is able to predict the effect of the drug particle size and of the shape of the tablet on the dissolution profile [8], which differs in case of a bi-layer or a coated tablet. In addition, It is also possible to test and calculate the final porosity of the tablet formulation on the release rate. F-CAD needing for the calibration step a minimum of one batch manufactured in the laboratory should allow saving a lot of money for laboratory work.
Last, but not least, the findings of this paper may give an incentive to test the benefits of F-CAD by a third party.
For the training of future industrial pharmacists in academia and or in an industrial environment it would be of special interest to compare if the same result of the optimal formulation of a 80 mg Nifedipine extended release formulation is obtained and last but not least to compare the costs of this developing project:

- By following strictly the guidelines of ICH Q8 (R2)
- By following the intuition of an experienced formulator (without using experimental design)
- By the application of F-CAD

The results push forward the idea of adopting the workflow of the automotive and aircraft industry by the pharmaceutical industry: However, only the practical implementation of the workflow of the automotive and aircraft industry will lead to the proof of concept that the application of a virtual formulation tool and the harmonization of the equipment between the R&D and production labs are mandatory to reduce the annual billion dollars of losses due to poor formulations and poor processes [7].

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7. Appendix

Table A 1a PAT data obtained from Presster™ of Nifedipine tablets at a speed of 108,000 (TPH=tablets per hour), each value represents the mean± SD (n=3). PAT data include peak values of the upper (UC) and lower (LC) compression roll, the values of the peak ejection force and the values of the peak take-off force. Runs according to Table 2.

No.	UCPeak (kN)	LCPeak (kN)	Peak ejection (N)	Peak take-off (N)
1	7.1±0.0	7.7±0.1	182.8±15.7	0.9±0.0
2	6.1±0.3	6.7±0.3	167.8±6.5	1.0±0.3
3	5.7±2.1	6.2±0.1	172.2±9.0	0.9±0.2
4	7.1±0.2	7.8±0.2	173.6±10.4	0.9±0.1
5	6.7±0.3	7.4±0.3	165.9±3.1	0.9±0.1
6	6.0±0.1	6.5±0.1	152.9±4.9	0.9±0.2
7	7.4±0.3	8.1±0.4	177.5±10.0	0.8±0.1
8	6.6±0.2	7.3±0.2	181.1±2.8	0.9±0.2
9	6.3±0.1	6.8±0.2	168.1±3.3	1.0±0.2

Table A 1b The tablet weight, thickness, diameter, hardness and disintegration time of Nifedipine tablets at 108,000 TPH, each value represents the mean±SD (n=3). Runs according to Table 2

No.	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Disintegrationtime (sec)
1	402.7±0.9	4.76±0.02	10.06±0.01	131±13	1639±76
2	401.1±2.0	4.81±0.06	10.08±0.01	92±28	1217±242
3	401.3±0.7	4.76±0.02	10.07±0.01	92±4	1051±348
4	401.0±1.8	4.81±0.06	10.07±0.00	101±12	1300±227
5	401.7±1.0	4.79±0.03	10.08±0.01	81±9	927±43
6	400.2±1.0	4.83±0.03	10.11±0.02	34±18	101±17
7	401.0±1.3	4.85±0.04	10.09±0.00	82±14	1099±20
8	401.5±2.0	4.89±0.03	10.12±0.01	40±7	283±48
9	401.2±0.7	4.86±0.03	10.12±0.01	27±6	53±11

Table A 1c The tablet weight, thickness, diameter, hardness and disintegration time of NI tablets at 54,000 TPH, each value represents the mean ±SD (n=3). Runs according to Table 2

No.	Weight(mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Disintegratiotime (sec)
1	401.7±1.1	4.83±0.01	10.07±0.01	108±2	1463±40
2	402.0±1.7	4.85±0.02	10.07±0.00	87±4	1116±50
3	400.7±1.2	4.74±0.02	10.07±0.00	96±3	848±78
4	401.0±1.6	4.88±0.02	10.08±0.01	87±3	1018±28
5	401.4±3.1	4.87±0.02	10.08±0.01	66±3	517±91
6	401.7±1.1	4.84±0.01	10.11±0.00	31±2	118±21
7	401.2±0.9	4.89±0.02	10.09±0.00	61±3	754±64
8	399.8±2.0	4.89±0.02	10.10±0.01	40±1	292±13
9	401.5±1.4	4.85±0.01	10.11±0.01	30±1	63±4

Table A 1d The tablet weight, thickness, diameter, hardness and disintegration time of NI tablets at 10,800 TPH, each value represents the mean±SD (n=3). Runs according to Table 2

No.	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Disintegration time (sec)
1	400.5±2.2	4.83±0.02	10.07±0.01	110±6	1446±60
2	401.1±2.1	4.83±0.01	10.07±0.00	85±5	1197±47
3	400.4±0.8	4.74±0.01	10.06±0.00	100±4	922±11
4	402.8±0.9	4.86±0.01	10.07±0.01	92±3	1068±23
5	401.1±2.8	4.85±0.02	10.08±0.01	70±2	531±56
6	401.3±1.0	4.82±0.01	10.11±0.01	32±2	135±32
7	401.9±1.9	4.88±0.01	10.88±0.00	71±1	906±67
8	401.3±2.0	4.89±0.01	10.09±0.01	43±3	367±37
9	400.4±1.6	4.83±0.01	10.11±0.00	31±1	72±4

Table A 1e The tablet weight, thickness, diameter, hardness and disintegration time of Nifedipine 80 mg extended release tablets, each value represents the mean±SD (n=3). Runs according to Table 3

No.	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (N)	Disint. Time (sec)
1	501.9±1.1	6.28±0.02	10.05±0.01	111±6	-
2	500.3±0.9	6.34±0.05	10.06±0.01	88±4	-
3	499.8±0.2	6.34±0.02	10.08±0.00	66±1	-
4	500.9±0.8	6.32±0.04	10.05±0.01	94±5	-
5	498.9±1.6	6.42±0.02	10.07±0.00	67±2	-
6	501.7±0.8	6.40±0.04	10.08±0.01	71±2	-
7	500.7±2.3	6.30±0.01	10.05±0.01	85±4	-
8	499.4±1.4	6.39±0.03	10.07±0.01	82±1	-
9	500.1±0.7	6.43±0.03	10.09±0.00	52±2	>1800

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