ARTICLES

A systematic pharmaceutical technology drug-excipient screening program for pre-formulation studies

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Summary

A systematic pharmaceutical technology drug-excipient screening program is a prerequisite for the development of a six sigma quality solid dosage form. The main goal of this paper consisted in establishing such a screening program for the preparing high quality samples for Clinical Phase I and II. The existing chemical drug-excipient compatibility studies served as an inspiration. The systematic pharmaceutical technology drug-excipient screening program should be able to define clearly the formulation design space, which should not be changed from Clinical Phase I to registration. For this purpose it is a prerequisite that the samples for Clinical Phase I and II are prepared with a mechanical simulator of a high speed press such as the Presster™. This tool is used as a PAT (Process Analytical Technology) device to study tableting problems, which depend on the choice of drug and excipient and to study, whether the formulation is suitable for mass production regarding Clinical Phase III and IV after registration.

As an exemplary the screening program is used for the development of an optimal formulation of orally disintegrating paracetamol tablet with the main focus on the disintegration time. It is evident that the application of this screening program is not limited to orally dispersible tablets but can be used for any types of tablets.

The effect of compaction speed, ratio of paracetamol and lactose, and ratio of granulated MCC Sanaq® Burst 100 with 3% of PVP and MCC normal on hardness and disintegration time were elucidated. A full factorial design was used to design an experiment. The tablets composing of 0.5% w/w magnesium stearate as a lubricant showed a capping, while no capping in the formulation composing 1% w/w stearic acid and 1% w/w LubriSanaq®. The tablets composing 1% w/w LubriSanaq® showed the lowest ejection force. The systematic pharmaceutical technology drug-excipient screening program showed the optimal formulation of orally disintegrating paracetamol tablets disintegrates within 11 seconds. This formulation was composed of paracetamol and lactose in the ratio of 3:1 (300 mg/100 mg), MCC Sanaq® Burst with 3% PVP and MCC Normal in the ratio of 3:1 (75 mg/25 mg), and 1% LubriSanaq® as a lubricant. The paper shows as well the limits of such a systematic pharmaceutical technology screening program as the design of experiments do not allow the detection of abrupt changes of quality attributes, respectively the critical concentrations of ingredients, which are responsible. A chemical imaging system is proposed for the determination of critical concentrations.

Keywords Right First Time, Pharmaceutical technology drug-excipient screening program, Orally disintegrating tablets (ODTs), Critical concentrations, Percolation theory.

Introduction

The pharmaceutical companies spend the highest percentage of revenues in the research and development of new drugs [1]. Research and development process is costly and lengthy, while

the number of new drugs reaching the market declined [2, 3]. "Right, First Time" concept is adopted in pharmaceutical industry to reduce cost and time in product development. "Right, First Time" is to develop pharmaceutical products in high quality such as six-sigma quality to the market. A rigorous interpretation of " Right, First Time" leads to the prerequisite to develop six-sigma quality dosage form at the stage of pre-formulation studies and uses that dosage form in the first clinical trial [4].

In this context, it is essential, that depending on the physico-chemical properties of the drug substance the right excipients are chosen not only with respect to the *chemical compatibility* but also with respect to the *tableting process*.

For the development of a systematic pharmaceutical drug-excipient screening program the chemical drug excipient compatibility test procedure is a prerequisite and a suitable example is recalled as part of the introduction.

Chemical drug-excipient compatibility

Different types of chemical drug-excipient compatibility program exist for a long time. Often the compatibility was tested using a binary mixture of the drug and an excipient selected, which does not give an answer, whether the final tableting mixture could show chemical interactions between all ingredients, which may contribute to a stabilization. In this context it is most important that a drug can show in a binary drug-excipient stress test negative results [5], but in a mixture with more than one functional excipients positive results (see **Table 1**a, 1b).

Table 1b shows all possible combinations of functional excipient needed to prepare a tablet formulation. Due to interactions it is evident that the mixtures show very different results. Thus, it can be extrapolated that for a systematic pharmaceutical technology test powder mixtures consisting of the drug substance and the excipient needed for tableting should be tested with a suitable design of experiments. In the above case of the chemical drug compatibility test it is evident, that the combination, i.e. the mixture No.8 shows practical no degradation. However, for principal reasons a careful statistical evaluation is recommended:

The values of Table 1b (stress test for 4 weeks at 50 °C) were used to establish a mathematical model simulating the amount of intact drug substance with the help of STAVEX 5.3. Thus, the mathematical model is based on the result of all samples leading to a better estimate than the individually tested experimental result. Thus, the model recommends not only mixture No.8 but to make a choice between mixture No.3 and No.8 [6].

The STAVEX 5.3 [6] evaluation of the drug excipient compatibility stress recommends the following excipients (No.3): Lactose, Magnesium stearate, Cornstarch, PVP, dry atmosphere and (No.8): Mannitol, Magnesium stearate, Microcrystalline cellulose, HPMC, dry atmosphere. Thus, the formulator will probably choose Lactose, Magnesium stearate, Cornstarch and PVP adding to the packed tablets a silica gel sachet as a desiccant. The results of the mathematical model simulating the stress test of the formulation for 4 weeks at 50 °C are summarized in **Table 2** (see predicted values). According to the diagnostics of STAVEX 5.3 the fit is very good (Goodness of fit: R^2 = 0.99316; corrected goodness of fit: R_C^2 = 0.98291).

Table 1a Example of a drug-excipient chemical compatibility program in a drug-excipient mixture of different functional excipients using a 2^{5-1} Factorial Design [5]

A (filler)	(−) lactose	70%w/w
	(+) mannitol	70% w/w
B (lubricant)	(−) stearic acid	5% w/w
	(+) Mg-stearate	5% w/w
C (disintegrant)	(−) cornstarch	20%w/w
	(+) microcrystalline cellulose	20%w/w
D (binder)	(−) polyvinylpyrrolidone	5% w/w
	(+) hydroxypropylmethylcellulose	5% w/w
E (moisture) E = ABCD	(−) without H_2O	+ 0%w/w
	(+) with H_2O	+ 3% w/w

Table 1b Example of a result of a stress test at 50°C and at 4°C, the mixture No.8 shows after 4 weeks at 50°C practically no degradation, but mixture No.10 shows less than 50% of the intact drug substance

	A	B	C	D	E	50° C	4° C
1 = e	−	−	−	−	+	59.6	100
2 = a	+	−	−	−	−	86.4	98.3
3 = b	−	+	−	−	−	95.0	98.7
4 = abe	+	+	−	−	+	97.0	96.5
5 = c	−	−	+	−	−	83.4	96.6
6 = ace	+	−	+	−	+	53.8	96.7
7 = ce	−	+	+	−	+	93.7	98.5
8 = abc	+	+	+	−	−	**99.7**	96.9
9 = d	−	−	−	+	−	54.1	97.9
10 = ade	+	−	−	+	+	**45.8**	99.0
11 = bde	−	+	−	+	+	92.8	95.3
12 = abd	+	+	−	+	−	96.1	98.0
13 = cde	−	−	+	+	+	53.6	98.7
14 = acd	+	−	+	+	−	64.7	99.6
15 = bcd	−	+	+	+	−	94.0	96.4
16 = abcd	+	+	+	+	+	96.3	97.2

Table 2 Predictions and model deviations

Run	Observation	Predicted	Model dev.
1	59.60	60.10	−0.50
2	86.40	88.30	−1.90
3	95.00	97.35	−2.35
4	97.00	95.35	1.65
5	83.40	81.50	1.90
6	53.80	53.30	0.50
7	93.70	95.35	−1.65
8	99.70	97.35	2.35
9	54.10	56.00	−1.90
10	45.80	46.30	−0.50
11	92.80	94.55	−1.75
12	96.10	95.05	1.05
13	53.60	53.10	0.50
14	64.70	62.80	1.90
15	94.00	95.05	−1.05
16	96.30	94.55	1.75

Sum of squared model deviations = 40.26
Estimate of mean model deviation = 2.5904

Such a mathematical model of the chemical drug excipient compatibility test is exemplary for the desired systematic pharmaceutical technology drug-excipient screening program.

A systematic pharmaceutical technology drug-excipient screening program

In the context that the innovative pharmaceutical companies adopt the workflow of the automotive and aircraft industry [7, 8] the first prototype of the drug delivery vehicle should have for the first clinical trials [7] a six sigma quality. In an ideal case, the desired six-sigma quality dosage form can be developed by using an appropriate software, such as F-CAD (Formulation-Computer Aided Design) or an equivalent program to reduce time consuming and expensive laboratory work [7, 8].

For an optimal application of F-CAD, it requires (1) physico-chemical characterization of the drug substance and of the functional excipient used in dosage form design, (2) chemical and physical drug-excipient compatibility study, (3) automated accelerated stability test program for shelf life estimation of the final marketed solid dosage form, (4) a pharmaceutical technology drug-excipient screening program and (5) the knowledge of tableting and other problems, which can occur during scale-up [9, 10].

Thus, the focus of this paper is a systematic pharmaceutical technology drug–excipient screening program, which covers point (4) and (5) of the above requirements.

Although a physico–chemical characterization of the drug substance and of the functional excipients, and chemical drug–excipient compatibility program can be found in literatures, the lack of a systematic pharmaceutical technology drug–excipient screening program results in no meaningful results from a literature search. In principle, a standard galenical drug–excipient screening program can be designed by preparing a tablet composing of the drug substance and filler in different ratios combined with additional auxiliary substances such as a disintegrant and lubricant in appropriate concentrations.

With respect to the fact, that the tablet formulation needs to be manufactured in the production department, it is a prerequisite to use an instrumented tableting device, capable of simulating mechanically a high speed rotary tableting machine such as the Pressster™ for studying in the detail of tableting process [8, 11, 12, 13].

Fig.1 Pressster™ as a mechanical simulator of a high speed rotary press [11]

In this paper the Pressster™ is used as a PAT (Process Analytical Technology [14]) tool to study the properties of the tablet formulation. This device is a prerequisite for designing a systematic drug excipient screening program. The compulsory goal is the capability to develop and manufacture as a first formulation for Clinical Phase I a six sigma quality tablet [7]. This screening program defines for the rest of the development time till registration the design space according to ICH Q8. Thus, there is a chance to reduce time to market and to avoid losses of time and money due to formulation problems. In this context Benson and McCabe calculated in 2004 annual losses of 90 billion $ worldwide [15]. The development of a six–sigma quality of the tablet formulation allows to detect drugs having a narrow therapeutic range [7] see Fig.2. Thus, the high attrition rate during Clinical Phase I can be reduced [7].

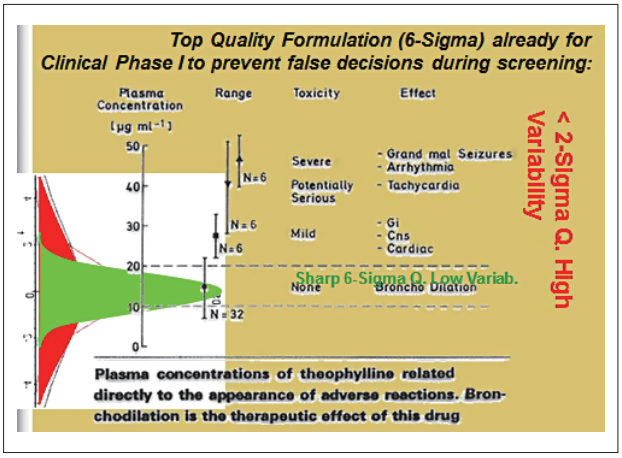

Fig.2 Drug with a low therapeutic range: Only a low variability of the dissolution profile will show a low variability of the plasma levels for detecting the therapeutic effect and that side effects can be avoided [7]

For the pharmaceutical technology drug–excipient screening program it is essential that during the compression cycle at different tableting speeds among others [11] the following parameters can be measured:

Upper and lower compression peak force, max. upper and lower punch displacement, peak ejection force, peak take off force, elastic recovery and work of compaction. It is important to use the Pressster™ and to collect the results of all batch records for an appropriate description of the quality attributes of the formulation used in all Clinical trials. It is recommended to prepare the samples for Clinical Phase I and Phase II with the Pressster™. It is essential to compare these results of the properties of the tablets, which need to include the results of the dissolution rate with the results of the samples manufactured with a high speed press for Clinical Phase III. Thus, the CMC documentation and the registration process will be facilitated.

For an exemplary demonstration of such a systematic pharmaceutical drug–excipient screening program an oral dispersible paracetamol tablet formulation is chosen as a model drug delivery system.

A paracetamol oral dispersible tablet formulation

The European Pharmacopoeia [16] describes an orally disintegrating tablets (ODTs) as a tablet to be placed in the mouth where it disperses rapidly before swallowing and which disintegrates in less than 3 minutes while according to the FDA [17]; ODTs should have an in vitro disintegration time of 30 seconds or less. ODTs can disintegrate in only a small amount of water in the oral cavity without chewing. Therefore, it is easy to administer this kind of tablets to elderly, bed–ridden patients, or infants who have problems swallowing tablets and capsules [18]. In our study, we used a systematic pharmaceutical technology drug–excipient screening program to develop optimal orally disintegrating paracetamol tablets.

Material

Paracetamol from Rhodia, USA, Lactose monohydrate (Lactose pulvis H_2O®) from Paul Brem AG, Switzerland, Microcrystalline cellulose (Avicel PH102®) from FMC, Philadelphia, USA, Magnesium stearate and stearic acid from Novartis Pharma, Switzerland, Microcrystalline cellulose (MCC) Sanaq® Burst 100 and LubriSanaq® from Pharmatrans–Sanaq AG, Switzerland.

Method

An orally disintegrating paracetamol tablet composed of paracetamol as an active ingredient, lactose and microcrystalline cellulose (MCC) as diluents, granulated MCC Sanaq® Burst 100 with 3% of polyvinylpyrrolidone (PVP) as a multifunctional excipient, and lubricant. A full factorial design was used to design an experiment for screening the optimal formulation. The effect of ratio of paracetamol and lactose, and ratio of granulated MCC Sanaq® Burst 100 with 3% of PVP and MCC normal on hardness and disintegration time were studied. The ratios of paracetamol/lactose were studied at three difference ratios, i.e., 0.3 (100 mg/300 mg), 1.0 (200 mg/200 mg) and 3.0 (300 mg/100 mg). The ratios of granulated MCC Sanaq® Burst 100 with 3% PVP/MCC normal were studied at three difference ratios, i.e., 0.3 (25 mg/75 mg), 1.0 (50 mg/50 mg) and 3.0 (75 mg/25 mg). Paracetamol, lactose and granulated MCC Sanaq® Burst 100 with 3% PVP were mixed in turbula mixer for 5 minutes. Magnesium stearate as a lubricant

Table 3 The full factorial design for a galenical drug-excipient screening program

Formulation	Coded variables		Uncoded variables	
	A	B	Ratio of Paracetamol/Lactose	Ratio of granulated MCC Sanaq® burst 100/MCC normal
A1	0	− 1	1.0(200mg/200mg)	0.3(25mg/75mg)
A2	0	1	1.0(200mg/200mg)	3.0(75mg/25mg)
A3	1	0	3.0(300mg/100mg)	1.0(50mg/50mg)
A4	− 1	1	0.3(100mg/300mg)	3.0(75mg/25mg)
A5	0	0	1.0(200mg/200mg)	1.0(50mg/50mg)
A6	1	− 1	3.0(300mg/100mg)	0.3(25mg/75mg)
A7	− 1	− 1	0.3(100mg/300mg)	0.3(25mg/75mg)
A8	1	1	3.0(300mg/100mg)	3.0(75mg/25mg)
A9	− 1	0	0.3(100mg/300mg)	1.0(50mg/50mg)

was applied to die by using cotton stick. 10 mm flat faced punches were used in the study. 500 mg of paracetamol tablets were prepared by the Presster™ at two difference compaction speeds, i.e. 10,800 and 100,600 tablets/hour. The fastest disintegrating tablet formulation was used to study the effect of type of lubricant on the hardness and disintegration time of paracetamol tablets. Three types of lubricants, i.e., magnesium stearate, stearic acid and LubriSanaq® (sodium stearyl fumarate) were studied. For the evaluation of the results of the design of experiments the software STAVEX 5.3. [6] was used.

Results and discussion

The results showed that compaction speed had a significant effect on the hardness ($p<0.05$) but no effect on the disintegration time of orally disintegrating paracetamol tablets. The increase of compaction speed resulted in the decrease of hardness due to less time available for the material to consolidate by plastic deformation at high speed of compaction [19] (**Fig.3**a).

The ratio of paracetamol/lactose had a significant effect on the hardness and disintegration time of the tablets ($p<0.05$). The increase of ratio of paracetamol/lactose resulted in the decrease of hardness because of the poor compactibility of paracetamol [20] (Fig.3a). At the low amount of disintegrant, MCC Sanaq® Burst 100, the increase of ratio of paracetamol/lactose resulted in increase of disintegration time because the high amount of paracetamol retarded water penetration into the tablets. However, at the high amount of MCC Sanaq® Burst 100 in the formulation, the increase of ratio of paracetamol/lactose resulted in decrease of disintegration time due to the decrease of tablet hardness (Fig.3b). The ratio of granulated MCC Sanaq® Burst 100 with 3 % PVP/MCC Normal had no effect on the hardness of paracetamol tablets but had an effect on the disintegration time ($p<0.05$). The increase of ratio of granulated MCC Sanaq® Burst 100 with 3 % PVP/MCC Normal resulted in the decrease of disintegration time due to the increase of disintegrant in the formulation (Fig.3b). Therefore, the optimal formulation should have high ratio of granulated MCC Sanaq Burst/MCC Normal for fast disintegration. It should also have the optimal ratio of paracetamol/lactose. The fastest disintegrating tablet formulation, that disintegrated all within 11 seconds, composed of paracetamol/lactose in the ratio of 300 mg/100 mg, and MCC Sanaq® Burst with 3% PVP/MCC Normal in the ratio of 75 mg/25 mg.

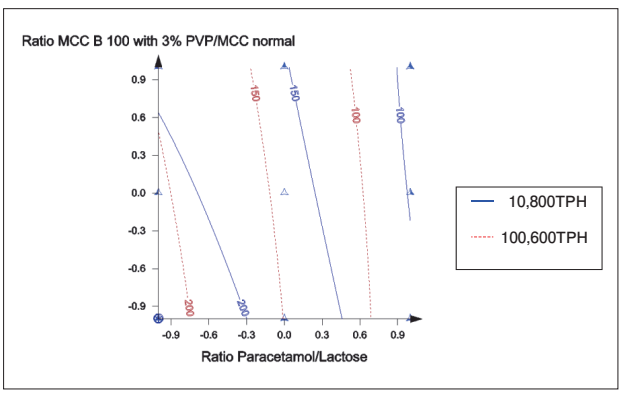

Fig.3a The contour plot of hardness (Z), the coded variables of Paracetamol/Lactose ratio (X) and the coded variable of Sanaq® Burst 100 MCC granules with 3% PVP/normal MCC ratio (Y) at two different compaction speeds (10,800 and 100,600 tablets/hour)

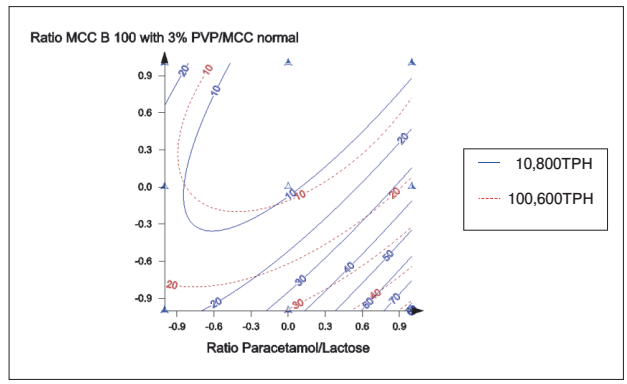

Fig.3b The contour plot of disintegration time (Z), the coded variables of Paracetamol/Lactose ratio (X) and the coded variable of Sanaq® Burst 100 MCC granules with 3% PVP/normal MCC ratio (Y) at two different compaction speeds (10,800 and 100,600 tablets/hour)

The fastest disintegrating tablet formulation that composed of paracetamol/lactose in the ratio of 300 mg/100 mg, and MCC Sanaq® Burst with 3% PVP/MCC normal in the ratio of 75 mg/25 mg was used to study the effect of lubricant on hardness and disintegration time of orally disintegrating paracetamol tablet. The mixer of paracetamol, lactose and granulated MCC Sanaq® Burst 100 with 3% PVP was mixed with lubricant (0.5% w/w magnesium stearate or 1.0% w/w stearic acid or 1.0% w/w LubriSanaq®) for 1 min by using turbula mixer. The mixer was compacted in high speed (100,600 tablets/hour) by Presster™. There was a capping in the tablets using magnesium stearate as a lubricant but no capping in stearic acid and LubriSanaq® added formulation. The capping of the tablets using magnesium stearate as a lubricant correlated to the percentage of elastic recovery that was quite high, as you can see in the **Table 4**. The effect of 1.0% w/w stearic acid and 1.0% w/w LubriSanaq® on hardness and disintegration time were not different. Both 1.0% w/w stearic acid and 1.0% w/w LubriSanaq® added formulations showed a short disintegration time within 12 and 11 seconds, respectively. However, the ejection force of the tablets composing of 1.0% w/w LubriSanaq® was lower than the tablets composing of 1.0% w/w stearic acid.

Table 4 The compaction data and evaluation results of fast disintegrating paracetamol tablets composing difference types of lubricant

Measurement	Lubricant		
	0.5% Mg Stearate	1.0% Stearic Acid	1.0% LubriSanaq®
Upper Compression Peak (kN)	57.4	57.0	55.3
Lower Compression Peak (kN)	54.9	54.6	53.1
Max. upper punch displacement (mm)	2.8	2.8	2.8
Max. lower punch displacement (mm)	7.9	8.0	8.2
Peak Ejection (N)	950.1	1,109.1	881.1
Peak Take-off (N)	2.2	2.9	3.2
Elastic Recovery (%)	11.2	10.7	10.6
Work of Compaction (Joules)	32.3	31.8	32.4
Weight (mg)	Capping	503.1	502.6
Thickness (mm)		4.9	5.1
Hardness (N)		70	70
Disintegration time (sec)		12	11

What are the limits of the systematic pharmaceutical technology drug-excipient screening?

The proposed screening program is not limited to oral dispersible tablet with the focus on a fast disintegration time and on a taste masking, which was not the theme of the above study. The main points are to avoid tableting problems such as capping and sticking and to optimize the quality of the dosage form, i.e. to have a very short disintegration time. In case of another solid dosage form the focus will be different and in general the dissolution profile plays the most important role (see Fig.2). However, the above pharmaceutical technology program does not allow the determination of critical concentrations or percolation thresholds [21]. It is known, that system properties can change abruptly and significantly. Thus, it is important for the formulator to know the critical concentrations of the ingredients. Unfortunately, these concentrations depend on the particle size distributions of the ingredients (drug substance, excipient). Thus, if the formulation contains an ingredient with the critical concentration the tablet properties may show at and in the neighborhood of this percolation threshold a high variability. Thus, if the particle size distribution changes from batch to batch or due to different manufacturing processes the tablet property can change to such an extent, that the original specifications are no longer satisfied. An example is shown in case of a Mefenamic acid (MA) [13] in the next chapter.

The impact of the percolation thresholds

During pre-formulation studies it is important to detect percolation thresholds, i.e. critical concentrations [21] of the ingredients (drug substance, excipient) which are used in the formulation. At the critical concentration, a geometrical phase transition occurs and the tablet property often changes discontinuously. Thus, if a recipe is characterized by a critical concentration of an ingredient, the formulation is not robust but shows a high variability of specific tablet properties. This problem may become often only evident during the scale-up process or by using a slightly different quality of the respective ingredient (drug substance, excipient) involved. Unfortunately, the impact of percolation theory is not yet part of ICH Q8 or equivalent guidelines for the industrial development of solid dosage forms [13]. In principle, the percolation thresholds of three dimensions (3D) system can be calculated with an appropriate software numerically, if the particle volume size and respective shapes are known. Due to the fact, that batch to batch differences may exist it is recommended to determine percolation thresholds by the visual inspection of the tablet using Near Infrared (NIR) Imaging (see **Fig.4** [13, 22]). The Mefenamic acid tablet formulations studied [13] are listed in **Table 5**.

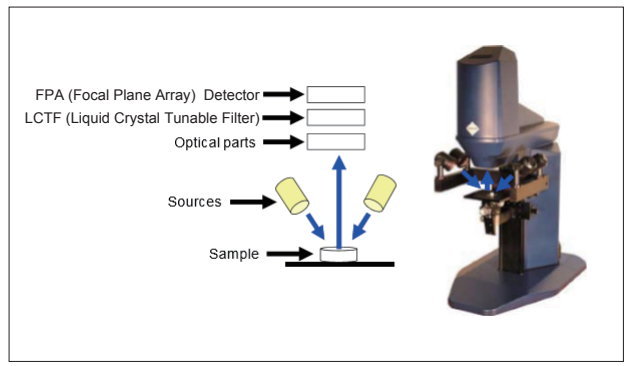

Fig.4 Chemical imaging system (Sapphire, Malvern Instruments [13, 22, 23]).

The chemical imaging system allows determining the size of the

Table 5 Composition of the tablets A to H [13] consisting of MA, LA and MS (to the left). Middle: tensile strength (TS) after compression with 7 kN max. force. To the right: Mean domain (cluster) size. Note that V/V % are used with respect to the fact that at the percolation threshold a geometrical phase transition occurs

	MA	LA	MS	TS (N/cm²) (n = 6-7)	Mean domain size (μm)		
					MA	LA	MS
A	0.0	69.7	30.3	103 ± 3.20	-	104	94.3
B	12.0	61.4	26.6	128 ± 4.64	171	95.2	83.4
C	23.5	53.4	23.1	133 ± 3.60	193	97.1	74.0
D	34.5	45.7	19.8	132 ± 3.89	211	104	83.0
E	45.0	38.4	16.6	134 ± 3.35	211	111	85.3
F	55.1	31.3	13.6	143 ± 7.14	177	123	81.4
G	64.8	24.6	10.6	142 ± 4.76	137	138	74.8
H	74.1	18.1	7.8	143 ± 3.52	83.2	118	82.9

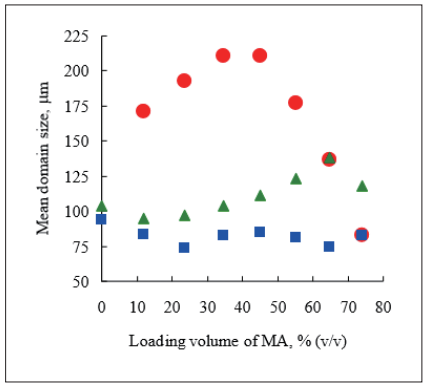

Fig.5 Mean domain size of MA (full circles) of Lactose (triangles) and maize starch (squares)

domains at the tablet surface and its mean diameter. As the NIR used in this study cannot penetrate the whole tablet the calculation of the mean cluster size can only be determined close to the surface of the tablet. Thus, it is not possible to use the equation below [24], which describes the mean cluster size S(p) of the ingredients of all clusters within the complete volume of the compressed tablet:

$$S(p) \propto |p - p_c|^{-\gamma} \text{ for } p \rightarrow p_c$$

The universal critical exponent γ in 3D would be equal to 1.8 [13]. On the other hand, the result can be used to determine the percolation thresholds in 3D (see **Fig.5**) for Lactose (LA) and Mefenamic acid (MA). No clear peak could be found for Maize starch (MS).

The maximum cluster or domain size for MA is located between 45% and 55% (V/V) and for Lactose (see Table 5 tablet G) is close to 24.6 % (V/V). According to the percolation theory [24] the mean cluster size shows a maximum at the percolation threshold.

The tensile strength plotted in **Fig.6** as a function of the volumetric drug content shows a discontinuity or step function close to the percolation threshold of MA. Thus, MA is responsible for the high value of the tensile strength. Depending on the type of formulation dramatic changes can happen as reported [25] previously (see **Fig.7**).

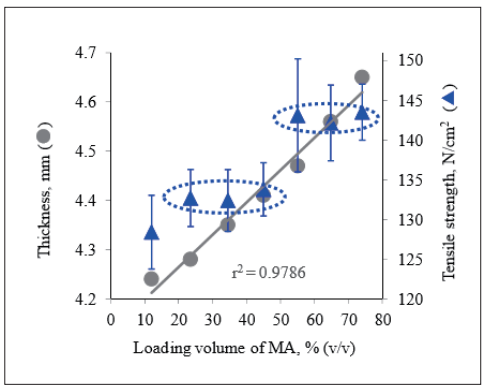

Fig.6 Thickness and Tensile Strength of MA tablets compressed at 7 kN [13]

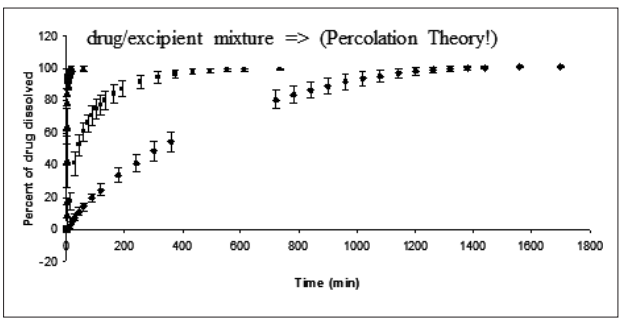

Fig.7 Dramatic change of the drug dissolution profile after crossing a critical concentration (percolation threshold) [25]

The non-robust capsule formulation contains a hydrophobic drug, which needs to be embedded in a hydrophilic environment such as lactose to become wetted and to get fast in solution. This is the case for the mixture to the left side of the three dissolution profiles (low dose 16 mg drug embedded in Lactose powder capsule formulation): Middle curve: 79 mg drug substance: The hydrophobic drug substance has percolated the system, which became as a whole less wetted. Curve at the right: The hydrophilic lactose is completely embedded in the hydrophobic drug, which dissolves very slowly [25].

Conclusion

In practice a new drug formulation often shows the signature of the formulator having a good experience in selecting his/her preferred excipients and processes. Such an approach depends heavily on the skill and experience of the formulator. In order to avoid during a later phase of the development undesirable technical surprises a systematic pharmaceutical technology drug – excipient screening program is presented which was inspired by the traditional use of a chemical drug-excipient compatibility test, which is today an integral part of a pre-formulation study. Using such a systematic pharmaceutical technology drug-excipient screening program, we developed the optimal formulation of orally disintegrating paracetamol tablet composing of paracetamol/lactose in the ratio of 300 mg/100 mg, MCC Sanaq® Burst with 3% PVP/MCC Normal in the ratio of 75 mg/25 mg and 1% LubriSanaq® as a lubricant. The tablets could disintegrate in very short time, in 11 seconds. For this purpose the use of a mechanical simulator of a high speed press is a prerequisite. Ideally, the use of the systematic pharmaceutical technology drug-excipient screening program is complemented by an appropriate F-CAD (Formulation-Computer Aided Design) software [7, 8] and by a software taking care of pharmacokinetic and pharmacodynamics properties such as GastroPlus™ [26].

The application of a systematic pharmaceutical technology screening program is not limited to the design of an orally dispersible tablet formulation but can be used in general for the design of solid dosage forms. Guidelines for the formulation development such as ICH Q8 request the use of design of experiments (DOE). Depending on the type of DOE (simple factorial design, composite designs etc.) the results of DOE can be described with a linear, semi-linear or quadratic mathematical model. Such a model corresponds to an approximation of the real function similar to the fact that a Tayler expansion of the function f (x, y, z) is an approximation of the real function. Thus, the usual DOE are not always able to detect abrupt changes in a real function (see Fig.6). For this purpose, it is important to get an a priori knowledge of critical concentrations of the ingredients (drug, excipient). Critical concentrations correspond to percolation thresholds of percolation theory. Dramatic effects can be expected, if the ingredients used show significant differences in their physico-chemical behavior (brittle versus plastic or hydrophobic versus hydrophilic, swelling versus dissolving etc.). Only a deep knowledge acquired during the pre-formulation studies, which include a systematic pharma technology drug-excipient screening program and the knowledge of critical concentrations will lead to correct decisions for a save formulation development.

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