Communication:

Development strategies for herbal products reducing the influence of natural variance in dry mass on tableting properties and tablet characteristics

Ylber Qusaj [1,2*], Andreas Leng [2], Firas Alshihabi [1], Blerim Krasniqi [2] and Thierry Vandamme [1]

[1] Laboratoire de Conception et d´Application de Molécules Bioactives, Faculty of Pharmacy, University of Strasbourg, CNRS 7199, 74 route du Rhin, 67400 Illkirch, France; E-Mail: vandamme@unistra.fr
[2] Product Development Pharma, Bioforce AG, Roggwil (TG), Switzerland

* Author to whom correspondence should be addressed; E-Mail: ylber.qusaj@etu.unistra.fr; Tel.: + 41 71 454 61 53; Fax: + 41 71 454 61 61.

Abstract: One "Quality by Design" approach is the focus on the variability of the properties of the active substance. This is crucially important for active substances that are obtained from natural resources such as herbal plant material and extracts. In this paper, we present various strategies for the development of herbal products taking into account especially the natural batch to batch variability (mainly of the dry mass) for tablets that contain a fixed amount of tincture.

The following steps of the development have been evaluated for the outcome of the physico-chemical properties of the resulting tablets and intermediates: concentration of the tincture extracted from Echinacea fresh plant, loading of the concentrate onto an inert carrier, the respective wet granulation and drying step, including milling, and the adjuvant excipients for tablet compression step. The responses that were investigated are the mean particle size of the dried and milled granulates, compaction properties and disintegration time of the tablets.

Increased particle size has been shown to significant increase of the disintegration time and decrease of the compaction properties. In addition, our results exhibited that the particle size has a great dependency on the ratio of liquid to carrier during the wet granulation process. Thus, the performed strategy of the extracted tincture in correlation to its dry mass and its relation to the amount of carrier used influenced the variability on the respective parameters tested. In order to optimize those parameters, a good strategy has to be carefully chosen.

1. Introduction

In the "Quality by Design" approach, in formulation development, it is important to take into consideration the properties of the active substances and its impact on the final dosage form. This is especially important for attributes, which show a high degree of variability, which cannot be controlled by the production process itself.

Stemming from natural grown products, herbal remedies are best examples for this kind of natural variations. These variations are a complex result of several factors such as soil condition, climatic condition, vegetation time, harvesting and maceration process.

Since several years, herbal remedies are becoming more and more popular as alternatives to conventional pharmaceuticals. This is because of their broad effects and versatile use in several applications, high potency, efficacy and low side effects [1].

The most common dosage forms of herbal preparations are liquids derived from macerations, infusions and decoctions [2], with the associated problems of large dose volumes, clumsy packaging and poor stability [3]. Solid preparations or tablets on the other hand have often higher stability and are easier to standardize which adds to increase their therapeutic acceptance, efficacy and product value [4]. Tablets are simple and convenient dosage forms that enable accurate tamper proof doses to be delivered.

The formulation of herbal medicines especially using fresh plants into robust tablet forms is challenging due to the inherent poor tableting properties of most herbal extracts or powdered plant parts. In addition larger amount of the liquid used for extraction and limiting information on relevant physico-technical properties of these crude drugs in relation to the commonly used excipients can be a problem [5]. Sometimes it is necessary that tablets need to be standardised to a fixed amount of tincture per tablet. Depending on the natural variation of the dry mass of the tincture, the tablets will contain changing amounts of dry extract. Dry mass of the herbal extract is the material consisting only of the components present in the original plant or formed during the extraction process, excluding any excipients or other added substances [6]. The amount on dry extract has more or less impact on the processability during tableting and the properties of the tablets.

Here we present various strategies for the development of an herbal drug tablet with the equivalence to the tincture taking into account the natural variability's (mainly of the dry mass).

As a model for a herbal remedy we are using a tablet made from Echinacea purpurea tincture. Echinacea purpurea is a very common herbal plant and its preparations represent the most common used herbal immune modulator, with antiviral, antibacterial effect and especially used against common cold [7].

Echinacea purpurea tincture is used as a starting substance for the tablets. Then it is concentrated to form a soft extract, which is loaded onto different carrier to form granulates. After drying, milling, mixing with further excipients, the mixture will be pressed.

In this paper, we focus on the variability of the dry mass of the tincture and its influence on the compaction properties of the mixture and the disintegration time for the tablet. Furthermore, the relation between these parameters and the granule size will be discussed.

2. Materials and Methods

2.1 Materials

Echinacea purpurea extract is provided from Bioforce AG, Roggwil, Switzerland. β-cyclodextrin (β-CD); Wacker Chemie GmbH, Germany); Microcrystalline Cellulose (MCC) (JRS Pharma, Rosenberg, Germany); Lactose monohydrate (Domo, Zwolle, Netherlands) and magnesium stearate (Peter Greven, Bad Münsterreifel, Germany) were of pharmaceutical grade.

2.2 Methods

2.2.1 Preparation of liquid Echinacea purpurea extract

2.2.1.1 Evaporation of Echinacea purpurea fresh plant extract and final adjustment of the liquid amount

The solvent of Echinacea tincture was evaporated under reduced pressure at 45°C. The extract was dried in a vacuum oven at 45°C to constant weight. Subsequently, the water and ethanol were added to gain the needed experimental conditions, which represent the soft extract in our products within its respective variations which are listed in Table 2.

2.2.2 Preparation of the granulate

A granulate was prepared in a lab size high shear mixer (Kenwood) by blending of beta-cyclodextrin (β-CD) with the concentrate of Echinacea purpurea extract and subsequent mixing onto carrier (microcrystalline cellulose (MCC)) according to the design of each specific experiment (see table 2). The wet granulate was sieved through a 2 mm sieve and dried over night (14 h) at 45°C in an oven. Then, the dried granulate was milled by a rotary sieving machine (MG205, Frewitt, Switzerland, 0.63 mm sieve). The particle size was estimated as described under granules characteristics.

2.2.3 Preparation of tablets

The dried and sieved granulate was blended in a turbula mixer (Turbula, Basel, Switzerland) with adequate excipients (q.s.), and magnesium stearate (0.5 g) to result to 100.0 g of mixture, which was ready to press. Tablets (250 mg) were pressed by an eccentric tablet press (Fette Exacta 21, Fette GmbH, Schwarzenbek, Germany) equipped with 6 punches (8 mm round, oval). The speed was set at 35 rpm and the compaction force was set to achieve similar hardness for each formulation. Each batch was compressed at the different compression force levels from 6.8-7.8 in the eccentric tablet press.

2.2.4 Characterization of granulate

2.2.4.1 Particle size distribution

The particle size distribution was analysed by sieve analysis (Retsch, Germany). Sieving was performed using eight selected sieves ranged from 1000 μm to 90 μm. Particle size distribution was calculated as the ratio of sieves cumulative weight and total sample mass.

The mean particle size diameter (MPSD) (d) of each formulation was calculated with the following Equation 1:

$$\textbf{\textit{Equation 1:}} \quad \boldsymbol{d = \frac{\sum n_i x_i}{100}}$$

Where x_i is the arithmetic mean of upper and lower limit of i sieve fraction (determined by the aperture size of used sieve) and n_i is the percentage of the particles' weight of i sieve fraction [8].

2.2.5 Tablets characterization

2.2.5.1 Disintegration time

The disintegration time is the time required for a breakdown of the tablet into smaller particles that completely pass through the 2 mm screen. Procedure using the basket rack assembly with disk in disintegration tester (ZT72, Erweka, Heusenstamm, Germany). Distilled water maintained at 37±0.5°C was used as test medium. 6 tablets from each formulation were tested and the mean of 6 tablets were recorded automatically in minutes and subsequently were calculated in seconds.

2.2.5.2 Compaction properties

In order to evaluate the compaction properties of two different formulations, the maximum breaking strength has been assessed. This one represents the maximum breaking strength measured by a pneumatic tablet hardness tester (Pharmatron 4M, Schleuniger, Solothurn, Switzerland) on a sequence of increasing compaction forces. This measurement has been chosen, because this value is independent of the applied forces and hence does not need the measurement of the value of the forces applied. The mean of 6 tablets were recorded in newton (N).

2.3 Examining the effect of different liquid to carrier ratios in the granulation system

As a first step, the effect of the liquid amount and the carrier amount has been examined on the mean particle size diameter (MPSD) of the granules. The accompanied effects on compression properties and disintegration time of the respective tablet have also been assessed. For this reason, three amounts of concentrate and supportive liquids have been added to three different amounts of MCC by performing a 3 x 3 factorial design (Table 1).

Table 1. Composition of the granules by using different amounts of MCC

Sample name	Liquid amount [g]	MCC [g]
1	8.7	12.5
2	8.7	17.5
3	8.7	25
4	12.1	12.5
5	12.1	17.5
6	12.1	25
7	15.4	12.5
8	15.4	17.5
9	15.4	25

2.4 Standardisation strategies in diminishing the variability of the dry mass in the tincture

Standardisation of the concentrate is important. It allows relating the volume to its constituents and reduces variability in its properties. Depending on the amount of variables which have been standardized, the degree of freedom is reduced. In the present study, it was important to keep the ratio of ethanol/water in the liquid phase constant, so there was only the concentration that was left which could be variable or fixed. Therefore, in priority on two types of standardisation of dry mass inside the concentrate were studied: a fixed concentration standardisation and a fixed volume standardisation.

2.4.1 Concentration settings depending on the dry mass

2.4.1.1 Fixed concentration standardisation (FCS)

In this standardisation, the concentration of the dry mass within the concentrate was fixed. As the dry mass concentration in the tincture was a variable, the volume of the concentrate used for the production will change in accordance to the dry mass of the respective tincture when the product has to be adjusted according to the volume of the tincture. The fixed concentration standardisation has the advantage that the physical properties of the concentrate should be similar. However, the chemical constituents can be different from one batch to another batch due to the different chemical constituents into the tincture.

2.4.1.2 Fixed volume standardisation (FVS)

In the fixed volume standardisation, the dry mass is varying but the reduction of the volume is set by a fixed concentration factor. As an example, if 1000 kg of the tincture are concentrated by a concentration factor of 20 than it yields to 50 kg of concentrate. As the concentration of the dry mass is proportional to the dry mass of the tincture, the physical properties can be different, from a good flowing soft extract to a more viscous mass. Therefore, the concentration factor has to be thoroughly chosen, so that there is no problem for further processing. Since the same amount of concentrate reflected the same amount of tincture, the amount of concentrate used for production is always the same.

During the development of the formulation several treatments have been tested out (Table 2). As a further step, the process of granulation has to be evaluated. As there are several parameters that may show a significant influence, the principal aim was also to standardise the rules of administration of the concentrate to the carrier and the supportive liquids. First of all, the treatments for the fixed concentration standardisation concentrate have to be evaluated, followed by the treatments for fixed volume standardisation concentrates.

2.4.2 Fixed concentration standardisation

2.4.2.1 Treatment 1) Fixed carrier

The simplest method was to add the required amount of concentrate to a fixed amount of carrier. The proportion between the concentrate and the carrier can vary.

2.4.2.2 Treatment 2) Fixed carrier with compensation

In order to reduce this variation, the amount of carrier is based on the amount of concentrate in a fixed ratio. In order to compensate the loss of carrier in the formulation and to compensate different amounts in dry mass in the formulation, a certain amount of carrier has to be added afterwards to achieve always the same amount of granulate. In addition the water amount for the granulation step has been standardised by adding more water to gain a fixed amount of water.

Table 2. Parameters of the experimental setting for the development of an herbal solid dosage form

	Dry mass in tincture [%]	Dry mass in concentrate [%]	Liquid amount [g]	Carrier amount (MCC) [g]
Treatment 1: **fixed concentration - fixed carrier standardisation**				
A	1.2	43.0	14.5	25.0
B	1.7	43.0	16.3	25.0
C	2.2	43.0	16.9	25.0
D	2.8	43.0	18.9	25.0
Treatment 2: **fixed concentration - fixed carrier with compensation standardisation**				
E	1.3	43.0	14.4	21.0
F	1.5	43.0	15.4	25.0
G	2.0	43.0	15.8	33.0
H	2.5	43.0	16.9	42.0
Treatment 3 **fixed volume - fixed carrier standardisation**				
I	1.3	32.0	15.0	25.0
J	1.5	37.5	14.2	25.0
K	2.0	50.0	12.2	25.0
L	2.5	62.5	10.2	25.0
Treatment 4 **fixed volume - fixed liquid to carrier ratio standardisation**				
M	1.3	32.0	16.4	27.3
N	1.5	37.5	15.3	25.5
O	2.0	50.0	14.7	24.5
P	2.5	62.5	13.5	22.5

2.4.3 Fixed volume standardisation

2.4.3.1 Treatment 3) Fixed carrier

Similarly to the treatment 1, the concentrate is added to a fixed amount of carrier. The amount of additional liquids was fixed. As the amount of concentrate was fixed due to it, the fixed volume standardisation, the amount of liquids only changed due to the differences in the concentration of native extract in the concentrate. No compensation for dry mass has been done with the carrier. The variable amounts of the resulting granulates need to be addressed

by adding different amounts of the major constituent (the filler) of the formulation (in our case; it was lactose).

2.4.3.2   Treatment 4) Fixed liquid to carrier ratio

As it was thought, the amount of liquid per carrier would have a huge influence in the granulation size, a treatment was set up to fix the ratio of liquid to carrier. In addition, the amount of carrier was set so that the resulting amount of granulate was fixed and a compensation in a later step was not necessary.

The composition of the formulation is described in detail in Table 2. Fig. 1 shows a chart of the calculated liquid per carrier ratio in relation to the dry mass of the tincture as a result of concentration and adding a more amount of liquid. The treatments are described above.

Figure 1. The ratio of liquid per carrier calculated in relation to the dry mass
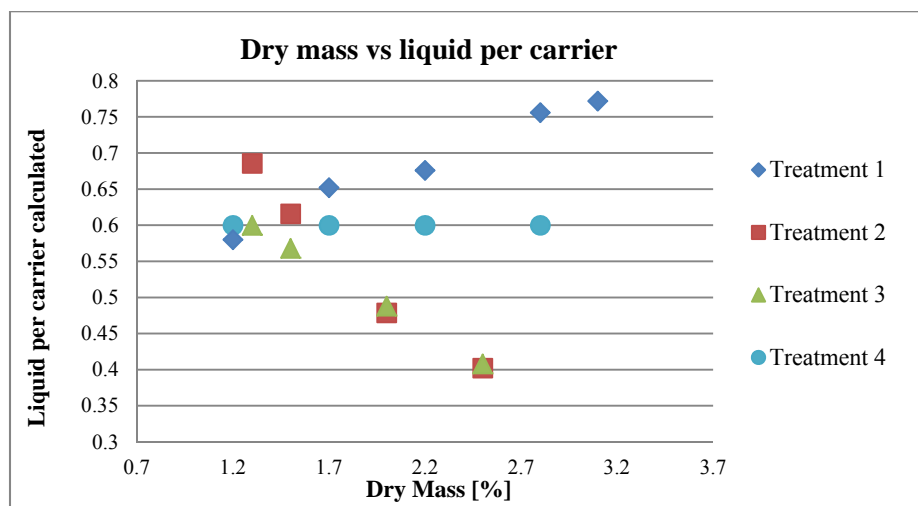

3.   Results and Discussion

3.1   Influence of the Liquid per MCC on the Compaction properties and disintegration time

During the experiments, it was able to observe that the amount of the total liquids per carrier had an influence in the physical character of the granulate. High volumes of liquids in comparison with the amount of carrier led to "wet massing granules" (Fig. 2a) whereas little water only showed more "dry" granules (Fig. 2b). This behaviour could be quantified by measuring the resulting MPSD (Fig. 3). In this figure the ratio of liquid to carrier was plotted against MPSD results resulting in a sigmoidal shape.

It can be described that there is a kind of plateau at 150 µm which at about point 0.6 starts to increase to about points 1 when there is a transition into a second plateau at about 500 µm.

Figure 2. (a) Granulate containing a higher liquid amount in the formulation. **(b)** Granulate containing a lower liquid amount in the formulation

a)   b)
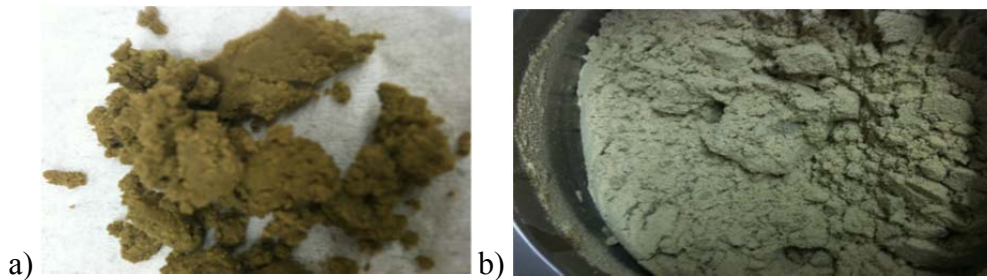
Since the granulation at the lower liquid per carrier has not taken place, it can be considered that the lower plateau can be related to the particle size of the carrier which was not well granulated. In contrast the upper plateau obviously depends on the sieve size of the sieved granulate with a given sieve size of 500 µm. Increasing the liquid amount per carrier in the formulation increased significantly (p-value = 0.001) the granule size. Evolution of mean granule size during liquid addition was mentioned from Benali et al. [9].

**Figure 3.** Mean granule size depending on the liquid amount
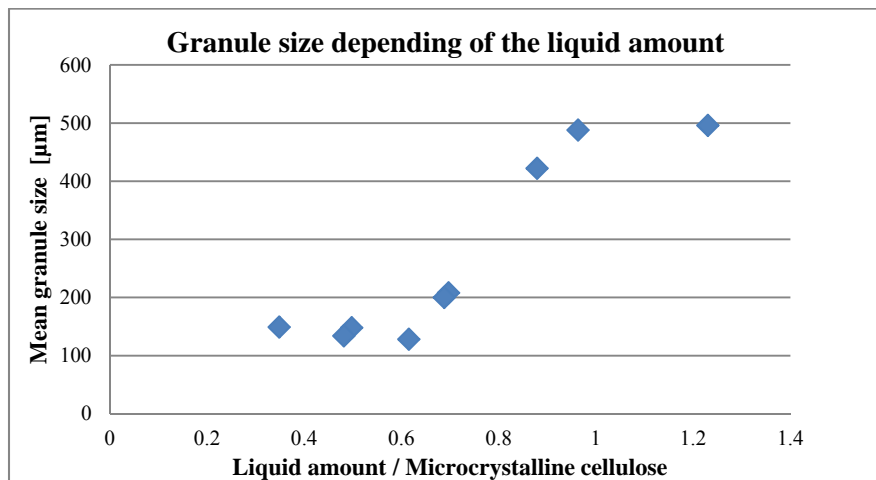
Furthermore, mean granule size diameter showed also an influence on the maximum breaking strength of the tablets (Fig. 4a). Increasing the mean granule size caused a decrease of maximum attainable breaking strength of the tablets. The significance correlation of the data was calculated (correlation coefficient (r) and the p-value (α)). The data were accepted as significant correlation, if the significance level is below α = 0.05. A significant correlation of MPSD to the maximum attainable breaking strength has been found (p-value= 0.002, r = -0.884).

Increasing the mean granule size of the granules, the diagram suggested that the disintegration time of the tablets was prolonged (Fig. 4b). However, it was only showing a significant correlation between MPSD and disintegration time, if the experiments 2 (Table 1) from the calculation is excluded (p-value= 0.002, r = 0.899). The disintegration value of sample 2 seemed to be a little odd, since it had the same amount of liquid as sample 1 and 3 and the amount of MCC is almost in the middle of both of them. While both show disintegration

times of 107 and 88 seconds, sample 2 showed disintegration times of 155 seconds. Including the experiment 2 in the calculation, the significance diminished (p-value= 0.125, r = 0.550).

Figure 4. (a) Maximum breaking strength of the tablets compared to different mean particle size. **(b)** Disintegration time of the tablets compared to different mean particle size.

a)

b)
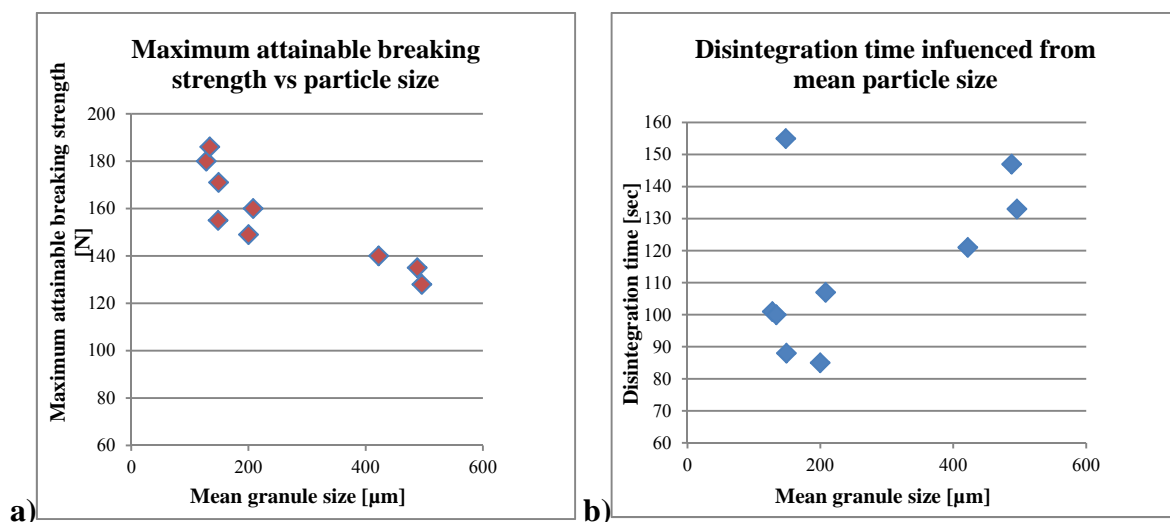
MPSD seems to be in the present study the main factors which influenced the compression properties (and maybe the disintegration time) of the tablets. The effect of granule size upon disintegration time and capping in compressing tablets was investigated from Forlano et al. [10]. From those experiments, we can demonstrate that the liquid amount per carrier which was the key factor for the next step of the development of tablet formulation.

Increasing the liquid amount in the formulation required the increasing of the amount of the carrier in order to obtain the same granule size. In order to achieve fast disintegration time and maximum compaction properties during development of the tablets, small granule size (100-200 μm) were preferred. Therefore in the granulation process, the liquid amount per carrier should be accomplished below a liquid to carrier ratio of 0.7 (Fig. 3) for the required properties of the tablets.

3.2 Standardisation strategies

Standardisation strategies for the extraction process and reduction of the liquid amount of herbal extracts are very important in order to reduce the variability of the drug content in the dry mass on Echinacea maceration. It was desired to start with standardisation as early as possible. Therefore, the mode and date of harvesting [11], the geological properties of the fields and the parts of the plant could be determined. However, despite the attempts to control all of these factors, some environmental conditions such as weather, sun shine, duration, etc. cannot be controlled. Hence there are still unavoidable variations from batch to batch which is reflected by the variable amount of ethanolic / aqueous soluble substances. These components forming the "native extract" can be determined as the amount of dry mass in the tincture. The chemical composition of the Echinacea extract is complex, and it seems that the most pharmacologicaly active compounds are the alkylamides, phenylpropanoids and

polysaccharides [12]. Due to its complexity it is impossible (at least impracticable) to assess the effect of each component on the tableting properties. They have to be handled as total.

3.2.1 Effect of dry mass of the tincture on granule size (MPSD) at different treatment strategies

MPSD of granulates are shown in Fig. 5. It was expected that the changes in the dry mass of the tincture would lead to changes in the granule size according to its liquid per carrier value as seen in Fig. 1. Thus, increased the liquid amounts in proportion to carrier in the formulation increased the MPSD in granulate (treatments 1 and 2). This phenomena was described also from Ohno et al.[13] that increasing the water amount and the kneading time increases the particle diameter. On the other hand in the treatment 3 the MPSD slightly increased, although the calculated liquid per carrier decreased. In this treatment, it seems that there was another factor which influenced the MPSD. It could be that the dry mass in treatment 3 probably superimposes the reduction of the MPSD. In addition, the liquid per carrier value was below 0.7. Therefore, the influence of the liquid per carrier was considered present, but very low.

Figure 5. Mean granule size to dry mass of tincture
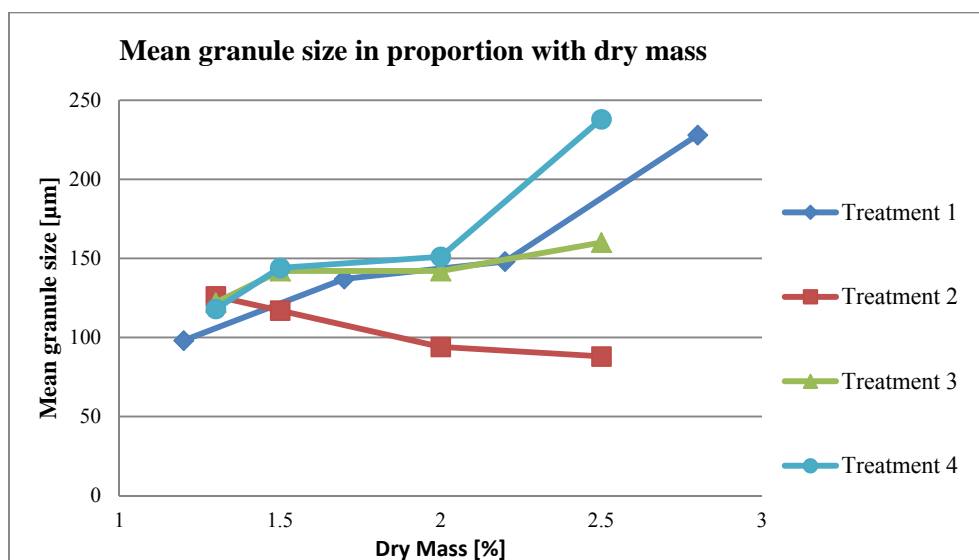
In the treatment 4 (Fig. 5) all the samples have the same liquid per carrier ratio. Interestingly the MPSD is increasing with increasing dry mass. As the major difference is the amount of the native extract per granules, it could be concluded that the dry mass content of the tincture would enhance the resulting granule size. As a result we see that in treatment 3 there was almost no change, but even a slight increase in the MPSD as described above.

3.2.2 Effect of dry mass of the tincture on compaction properties at different treatment strategies

To measure the maximum breaking strength of the tablets, the compaction force was increased continuously (but not necessarily linear) until the highest amount of breaking strength was reached. The reasons for this could be explained by the fact that higher

compression forces induced "capping" during the tableting process or that the porosity of the tablet was too low for further compaction.

The maximum attainable breaking strength of the tablet recorded from the formulation was presented in the Fig 6.

Figure 6. Maximum attainable breaking strength depending on dry mass of tincture
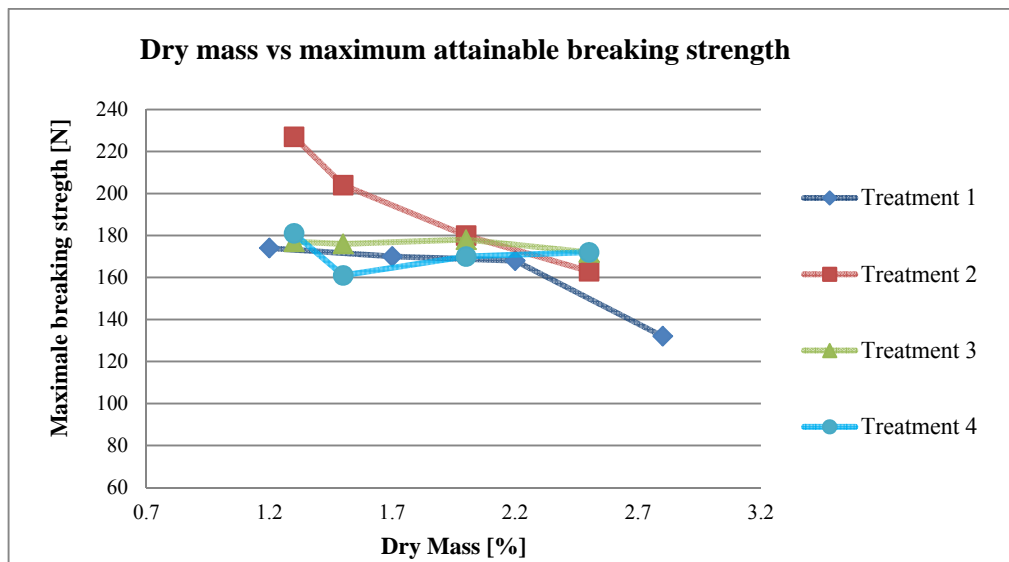
It can be seen that in Figure 6 the effect of the mean granule size was not pronounced such as in Fig. 4a. The effect of the dry mass was observed in the treatment 1 as a reduction of the maximum attainable breaking strength at point 2.8. However, this point was outside of the range of the other treatments. Therefore, it cannot be used for comparisons of the treatments. There was no effect of the dry mass in the treatment 3 and 4 on the maximum attainable the breaking strength. However, in the treatment 2 additional extragranular MCC seems to show effects on the compaction properties. The extragranular MCC was added in the formulation to compensate the variabilities of the dry mass related to the Echinacea tincture. This additional MCC could increase the compaction properties of the granulate [13].

It cannot be avoided that the different amount of dry mass would lead to different amount of granulates. We have used three different approaches to solve this issue. First of all, we could compensate the loss or the excess with the filling material of the tablet (in our case lactose). This postponed the compensation step to a later processing step. Mixing different batches could be difficult (treatment 1 and 3). Secondly, we could use the carrier as compensation material and add the missing amount to the dried granulate after the milling step (treatment 2). Thirdly, we could calculate the amount of carrier according to the amount of dry mass in the tincture, respectively with the amount of dry mass in the concentrate (treatment 4). Since the amount of "free" MCC has been changed in treatment 2 in higher proportions, it showed the highest variations in maximum attainable breaking strength. If the goal was a reduction of variations on the tableting properties coming from the variation of the tincture, compensation with additional MCC might be not a good idea, as it induced additional variations.

### 3.2.3 Effect of dry mass of the tincture on disintegration time at different treatment strategies

In Fig. 7, the disintegration time of the different treatments was described. There was an overall effect of dry mass on disintegration time (p= 0.01) and on treatment (p<0.05) analysed from ANOVA.

The effect of the higher amount of dry mass in disintegration time was observed more to treatment 1 (p-value= 0.029, r= 0.916). Treatment 2 showed a faster disintegration time, caused from the additional of the extra granular MCC. Influence of the dry mass and additional MCC was significantly correlated (p-value= 0.004, r= 0.996). In the treatment 3 and 4 the effects on the higher amount, showed no significant correlation in the disintegration time, treatment 3 (p-value= 0.072, r= 0.928), treatment 4 (p-value= 0.058, r= 0.942).

Higher amount of the dry mass influenced negatively the disintegration time of the Echinacea tablets. In the literature, the effect of the herbal dry extracts is described to usually increase tablet hardness and to prolong disintegration time [14] due to their hygroscopic nature. In addition, additional MCC [15] in the tablet can produce water uptake, swelling and quick rupture of the compact. In other hand, additional "free" MCC as a compensation material could reduce the disintegration time, but could be also a source for variabilities of the disintegration time similar as the one described above.

In the first experiments we could demonstrate that the amount of liquid to the amount of carrier has a strong influence on the mean granule size diameter. In addition, this was accompanied by lower compaction properties and (maybe) increased disintegration time.

Figure 7. Disintegration time of different treatments influenced from the dry mass of tincture
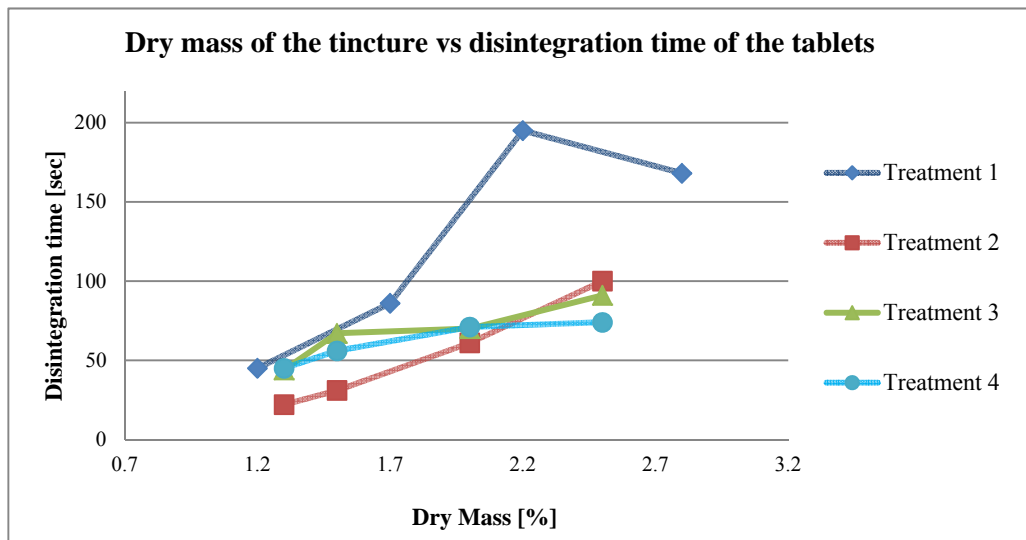
In terms of strategies, which should erase the effects of the natural variation in dry mass, four different strategies have been presented. Two strategies demonstrating a fixed concentration standardisation and two strategies with a fixed volume standardisation concentrate. In each group the concentrate is added to a fixed amount of carrier and one with some "useful" compensatory modifications.

Here, the mean granule size diameter of the granulate can taken as a parameter to determine the character of the granulates and the granulation process. Depending on the used amount of the liquid per carrier it shows a sigmoidal shaped curve with two plateaus.

In the context of the development, it is recommended to work either in the lower or upper plateau in order to reduce the variability.

In addition, the standardization of the concentrates and the granulation are important. With different concentrations of the dry mass, the liquid per carrier ratio, the total amount of granulate, the quality and quantity of the excipient for compensation, the resulting mean granule size diameter can change. Together with the already changing amount of dry mass, these factors can influence compression properties and disintegration time of the tablets massively.

Standardisations are also increasingly prone to errors. The more parameters need to be standardized and the more parameters need to be considered, the more susceptible is the system. Therefore, an easy and less complicated standardization should be preferred.

In the present study, it can be easily, a simple standardisation (treatment 3) performed quite well in terms of eliminating the variation. In a range of dry mass 1.3-2.5 %, it showed the lowest differences in the mean granule size diameter; small differences in maximum breaking strength and together with treatment 4 the lowest differences in disintegration time.

4. Conclusion

To summarize, it can be observed that in terms of a Quality by Design approach standardization should be emphasised. The standardization of concentration and granulation has a strong influence on how a present variation may affect the final result. Basic test models, can give a first impression, how a system can work, however, playing through the various treatment models only can show, whether these attempts work in reality.

References and Notes

1. Wang, S. Y.; Jiao, H., Scavenging capacity of berry crops on superoxide radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen. *J Agric Food Chem* **2000,** *48*, 5677-5684.
2. Raghavendra, H.; Yogesh, H.; Gopalakrishna, B.; Chandrashekhar, V.; Kumar Sathish, B.; Kumar, V., AN OVERVIEWOF HERBAL MEDICINE. *Int. J. Ph.Sci.* **2009,** *1*, 1-20.
3. Okunlola, A.; Babatunde, A. A.; Oluwatoyin, A. O., Evaluation of Pharmaceutical and Microbial Qualities of Some Herbal Medicinal Products in South Western Nigeria. *Trop. J. Pharm. Research* **2007,** *6*, 661-670.
4. Runha, F. P.; Cordeiro, D. S.; Pereira, C. A. M.; Vilegas, J.; Oliveira, W. P., Production of Dry Extracts of Medicinal Brazilian Plants by Spouted Bed Process: Development of the Process and Evaluation of Thermal Degradation During the Drying Operation. *Food and Bioproducts Processing* **2001,** *79*, 160-168.
5. Palma, S.; Lujan, C.; Llabot, J. M.; Barboza, G.; Manzo, R. H.; Allemandi, D. A., Design of Peumus boldus tablets by direct compression using a novel dry plant extract. *International Journal of Pharmaceutics* **2002,** *233*, 191-198.
6. Autralian Government, A., Guidance on equivalente of herbal extract in complementary medicine. In Ageing, D. o. H. a., Ed. Therapeutic Goods Administration, 2011; Vol. 1.0, pp 1-16.
7. Brinkeborn, R. M.; Shah, D. V.; Degenring, F. H., Echinaforce and other Echinacea fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine* **1999,** *6*, 1-6.
8. Gajdziok, J.; Bernatoniene, J.; Muselik, J.; Masteikova, R.; Dvorackova, K.; Petkeviciute, Z.; Lazauskas, R.; Kalveniene, Z.; Bernatoniene, R., The evaluation of formulations for the preparation of new formula pellets. *Pharm Dev Technol* **2011,** *16*, 520-528.
9. Benali, M.; Gerbaud, V.; Hemati, M., Effect of operating conditions and physico–chemical properties on the wet granulation kinetics in high shear mixer. *Powder Technology* **2009,** *190*, 160-169.
10. Forlano, A. J.; Chavkin, L., The effect of granule size upon disintegration time and capping in compressed tablets. *Journal of the American Pharmaceutical Association* **1960,** *49*, 67-69.
11. Bauer, R.; Netsch, M.; Kreuter, M., Echinacea purpurea. In http://www.askic.co.jp, 1996.
12. Bauer, R.; Wagner, H., Echinacea species as potential immunostimulatory drugs. *Economic and medicinal plant research* **1991,** *5*, 253-321.
13. Ohno, I.; Hasegawa, S.; Yada, S.; Kusai, A.; Moribe, K.; Yamamoto, K., Importance of evaluating the consolidation of granules manufactured by high shear mixer. *Int J Pharm* **2007,** *338*, 79-86.
14. Schiller, M.; Heydt, H. V. D.; Marz, F.; Schmidt, P. C., Enhanced processing properties and stability of film-coated tablets prepared from roller-compacted and ion-exchanged Eschscholtzia californica Cham. dry extracts. *STP Pharma Sciences* **2003,** *13*, 111-118.
15. Palma, S.; Lujan, C.; Llabot, J. M.; Barboza, G.; Manzo, R. H.; Allemandi, D. A., Design of Peumus boldus tablets by direct compression using a novel dry plant extract. *Int J Pharm* **2002,** *233*, 191-198.