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RESEARCH PAPER

Evaluation of Xylitab 200, a New Filler/Binder for Direct Compression, Using Factorial Design

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ABSTRACT

The influence of a number of tablet factors were used to evaluate Xylitab 200®, a new filler/binder for direct compression, following a factorial design. The factors include types of filler/binder, drug, disintegrant, and amount of compression force. In the extended design, two storage conditions were selected. Factors found to have strong influence on tablet qualities from time after manufacturing to storage were drug solubility, amount of compression force, and storage condition. Comparison between tablets manufactured with the new filler/binder and those prepared with a known good filler/binder have shown that the latter is better than the former.

INTRODUCTION

Pharmaceutical technology, which involves among other things the designing of formulations (i.e., tablets) has made use of the various experimental designs (1–3) as opposed to the "one factor at a time" method (4). The design process involves developing a formulation such that many tablet quality requirements are met not only at the time of preparation but also during the whole shelf life. The ingredient of interest is a new filler/binder suitable for direct compression, Xylitab 200®. To evaluate Xylitab 200, this is compared to a known good filler/binder, Ludipress® (5–7) in the preparation of tablets using direct compression. And for this purpose, a factorial design experiment (8) was carried out. The design developed consists of factors considered pharmaceutically important components for a solid dosage formulation. The general aim of this work is to find which effects and interactions have significant influence on the response (tablet quality). A more specific aim is to determine how Xylitab 200 compares to Ludipress.

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MATERIALS AND METHODS

Materials

Xylitab 200 (Pugh & Co., Belgium) composed of 98% Xylitol, USP/NF, FCC and 2% sodium carboxymethylcellulose FCC (9)
Ludipress (BASF, Germany) containing 93% lactose monohydrate USP/NF, 3.5%, povidone, USP, BP (Kollidon 30®, BASF, Germany) and 3.5% povidone, cross linked (Kollidon CL®, BASF, Germany) (10)
Aspirin, USP (Asagran®, Monsanto, Belgium)
Phenazone, Ph.Eur. (BUFA, The Netherlands)
Sodium starch glycolate, NF (Explotab®, E. Mendell, USA)
Casein, cross linked (Esma Spreng®, W. Schlüter, Germany)
Povidone, cross linked (Kollidon CL, BASF, Germany)
Magnesium stearate, Ph.Belg. VI (Federa, Belgium)
Acetic acid p.a., DAB (E. Merck, Germany)
Sodium acetate trihydrate p.a., DAB (E. Merck, Germany)
Sodium chloride p.a., DAB (E. Merck, Germany)
Milli-Q water (Millipore, USA)

Methods

Formulations were chosen at random, weighed (Mettler PC 4400, Switzerland), and mixed (Turbula Mixer, Switzerland) without lubricant for 5 min. Lubricant was always added separately and mixed for 1 min (Table 1). The formulations were compressed on a single-punch tableting machine fitted with flat punches 12 mm in diameter (Ateliers Courtoy, Belgium) with compression force measured by a piezoelectric cell (Kistler, Switzerland) attached to a recorder (Hitachi, Japan). The tablet average weight, standard deviation (*SD*) and coefficient of variation (*CV%*) were obtained from 20 individually weighed tablets. Crushing strength (mean of 10 tablets) was measured using Schleuniger 2E hardness tester (Schleuniger, Switzerland). Friability was calculated as percentage weight loss from 10 tablets before and after 20 rotations per minute (rpm) for 5 min using an Erweka AR400 instrument, Erweka, Germany. Tablet disintegration time (data were mean of 6 tablets) was measured according to the European Pharmacopoeia (11) with the Erweka ZT3 apparatus (Erweka, Germany) in Milli-Q water at 37°C without disks. Dissolution on aspirin tablets was according to the USP XXI monograph (12). For phenazone-containing tablets, determination was done at 37°C, 50 rpm in 1 liter of Milli-Q water at 285 nm and analyzed at 2-min intervals (Uvikon 860 Spectrophotometer, Switzerland) and stored (INS Computer System, Belgium). The paddle method (12) was used and results obtained represent the mean of 3 tablets. From each formulation, tablets were divided into two sets and exposed to either of the two selected storage conditions: Belgian summer room temperature or a simulated Asiatic condition of

Table 1

Units and Codes

Factor	Level[a]	Level and Ingredient	Amount
A (filler/binder)	–	Xylitab 200 (added with povidone, cross linked)[b]	48%
	+	Ludipress	48%
B (drug)	–	Phenazone	50%
	+	Aspirin	50%
C (disintegrant)	–	Sodium starch glycolate	2%
	+	Casein, cross linked	2%
D (compression force)	–	1.5 kN	
	+	3.0 kN	
E (storage condition)	–	Belgian summer condition (room temperature)	
	+	Simulated asiatic condition (25°C/75% RH)	
Lubricant		Magnesium stearate	1%

[a]Negative sign (–) denotes low level; positive sign (+) denotes high level.
[b]Preformulation was carried out to be sure that a tablet could be manufactured with the chosen ingredients. It was observed that all formulations had acceptable disintegration time except when Xylitab 200 was combined with aspirin. Xylitab 200 has no disintegrant in its product formulation as compared to Ludipress (see Materials and Methods), so it was decided to add povidone, cross linked, to all formulations containing Xylitab 200.

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25°C/75% RH. Tablets stored under the Belgian summer condition were placed in closed containers and stored in an ordinary room. For the simulated Asiatic condition, tablets were placed in open containers and stored inside an exsiccator with saturated salt solution of NaCl (75 ± 5 RH) (13) under a controlled temperature of 25 ± 1°C. The respective sets of tablets were tested after 12 weeks.

Design and Calculation

A 2^4 factorial design (8) was used for the initial data (i.e., results obtained before storage). For results obtained after storage, an extended design of 2^5 was used. The theory and practice of factorial analysis are widely discussed by Box et al. (4) and Bolton (8). Calculation and analysis on effects were done according to Yates' algorithm (4). To determine significant effects and interactions, analysis of variance (ANOVA) (14) or the plotting of effects and interactions on a normal probability paper (4) was used, whichever was most appropriate. This study was conducted without replicates.

RESULTS AND DISCUSSION

In order to know whether a factor actually affects the measured response (result) or whether the value obtained is simply due to experimental error (15), significant effects were determined.

Crushing Strength

The significant effects of the factors on the response crushing strength (hardness) were determined using ANOVA wherein the influence of the higher-order interactions were considered negligible (14). Main effects *B* (drug) and *D* (compression force), and interaction *BD* (drug × compression force) were found significant. According to the Yates algorithm (4), effects of *B* and *D* mean that, on average, there will be an increase in response, and this is approximately so irrespective of the tested levels of other factors. The interaction *BD* evidently arises from the difference in sensitivity of the drug to the change in compression force from 1.5 kN (low level) to 3.0 kN (high level) which on average will increase the response. Pharmaceutically, the crushing strength of the tablets was found to be directly influenced by the drug and amount of compression force. The absence of aspirin (high-level drug) or 3.0 kN (high-level compression force) resulted in crushing strengths less than half the limit (Table 2), gradually increasing in the presence of either factors, with the highest columns containing both (Fig. 1). In the extended design, storage condition was found to play an important influence in the response (Fig. 2). There was a general decrease in response of tablets after storage, more pronounced with the tablets stored at 25°C/75% RH (high-level storage condition). The same observation was also noted in studies by Bos et al. (16,17). Four formulations stored at 25°C/75% RH became very soft and thus were not tested for crushing strength [Fig. 2: l(e), d(e), b(e), and bd(e)]. These formulations have two ingredients in common: Xylitab 200, which easily dissolves in an aqueous medium (18); and sodium starch glycolate, whose mechanism of action as a disintegrant involves rapid adsorption of water as a predisposition to tablet swelling (19). The hydrophilic nature of these ingredients was believed to be the cause of tablet softening. When dealing with formulations which contain water-sensitive ingredients, extra precaution should be

Table 2

Tablet Specifications

Response	Limit
Crushing strength (newton)	≥ 60.0
Friability (%)	< 1.0
Weight variation (%)	< 0.5
Disintegration time (sec)	≤ 300.0
Dissolution rate (min)	≤ 30.0

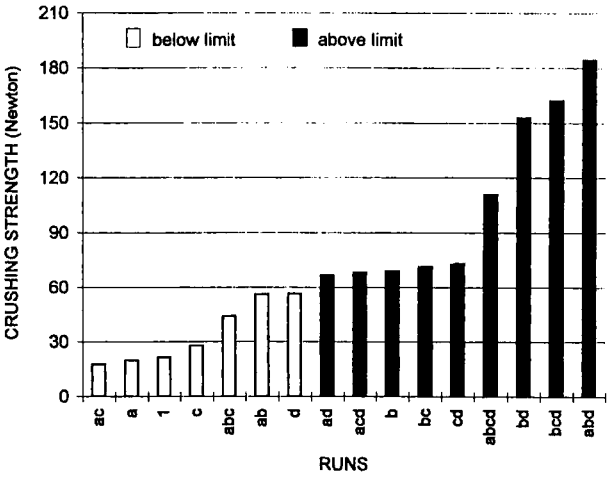

Figure 1. Influence of significant effects and interaction on crushing strength before storage.

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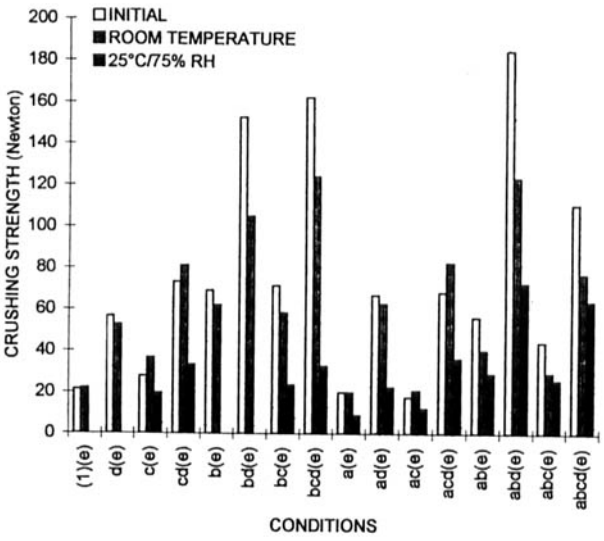

Figure 2. Influence of factor *E* (storage condition) on crushing strength.

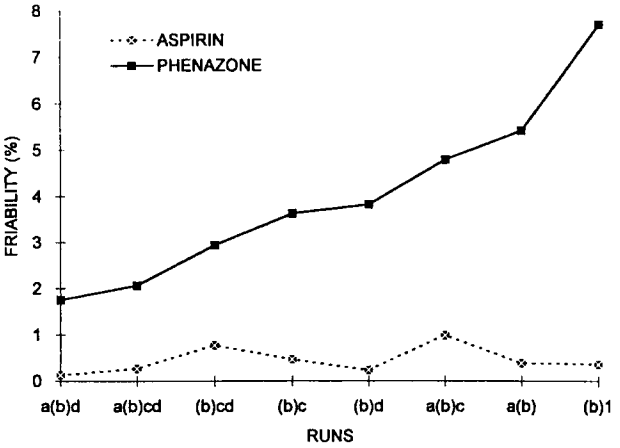

Figure 3. Influence of factor *B* (drug) on friability.

taken if intended for marketing in areas with high humidity. Xylitab 200 in general was more sensitive to high humidity than Ludipress. Being a water-soluble filler/binder (18), the entrance of moisture into the tablet greatly diminished its crushing strength. Ludipress was affected but not as dramatically compared to Xylitab 200 (Fig. 2: columns (1)(e)–bcd(e) contain Xylitab 200; a(e)–abcd(e) have Ludipress).

Friability

The ANOVA (14) method identified similar main effects and interaction as significant with crushing strength. However according to the Yates algorithm (4), main effects *B* and *D* will, on average, decrease the response while interaction *BD* suggests an increase, which in tablet property denotes: low friability with factors *B* and *D*, and a higher friability with interaction *BD*. Sufficiently hard tablets have the ability to resist abrasion and shock, as was observed in the tablets containing aspirin (high-level drug) or when compressed at 3.0 kN (high-level compression force). All aspirin-containing tablets passed the criterion (Table 2), irrespective of the other factors, while phenazone-containing tablets had too high friability (Fig. 3).

Weight Variation

With one of the higher-order interactions substantially large, significant effects and interactions were determined by plotting on normal probability paper (4). Five points which did not reasonably fit the drawn line—effects *A* (filler/binder), *C* (disintegrant); and interactions *AB* (filler/binder × drug), *BD* (drug × compression force), and *ABCD* (filler/binder × drug × disintegrant × compression force)—thus are significant (data not shown). The effects of *A* and *C* will decrease the response while interactions *AB*, *BD*, and *ABCD* will, on average, increase weight variation. Pharmaceutically, the sensitivity of the filler/binder to drug differentiates Xylitab 200 from Ludipress such that in the presence of aspirin (high-level drug), Xylitab 200 generally gave lesser weight variations as compared to Ludipress. The opposite was observed in the presence of phenazone (low-level drug); Ludipress had less responses than Xylitab 200. After storage, the tablets which were described earlier as very soft (storage condition 25°C/75% RH) were carefully weighed, and results have shown that there was a substantial increase in the weight of these tablets.

Disintegration Time

With *BCD* (a higher-order interaction) substantially large, normal probability paper (4) was used and 10 points were found not to fit the line. The points which, on average, will increase the disintegration time of the tablet are *B* (drug), *D* (compression force), *BD* (drug × compression force), and *BC* (drug × disintegrant); the same set were noted earlier to influence crushing strength, except *BC*. While main effects *A* and *C*, and interactions *AB, AC, AD, BCD* will, on average, decrease the response. However, a low value of disinte-

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gration time will not necessarily mean a good tablet. Results have shown that majority of the tablets found to be within the criterion have casein, cross linked, as disintegrant of choice. Xylitab 200-containing tablets have longer disintegration time than those made with Ludipress. Due to specific behavior of respective formulations after storage, only a general assessment was made, and the same results were observed by Bos, et al. in their formulations after storage. The tablets which were very soft were not tested for disintegration [Fig. 4: columns l(e), b(e), d(e), bd(e)]. The majority of the tablets stored under room temperature (low-level storage) were noted to have an increase in response, while those placed under the 25°C/75% RH were noted to have an increase in response and those placed under the 25°C/75% RH (high-level storage) had decreased responses except in two formulations: columns bc(e) and bcd(e). This is believed to be due to the blocking of disintegrating action of casein, cross linked [insoluble and acts by capillary action (23)], by the water adsorbed during storage. Xylitab 200 faired poorly in all aspects as compared to Ludipress.

Dissolution Rate

Generally, different equations are available to evaluate the release rate profiles (23–25); however, it was not possible to use one equation that could best describe all the different responses obtained. Thus it was decided to determine the time it takes to dissolve at least 80% of the drug from the dosage form into the medium. The main effects *B* (drug) and *D* (compression force) were found significant using ANOVA (14), which on average increases the response. The presence of aspirin (high-level drug) has more influence than 3.0 kN (high level compression force) in obtaining longer dissolution rate. All tablets containing aspirin [insoluble drug (20)] had at least 80% of the drug dissolved in more than 30 min as compared to phenazone [soluble drug (22)]. Tablets found to have good dissolution rates were also the ones that have good disintegration times. The majority of Xylitab 200-containing tablets had longer dissolution rates than Ludipress. After storage, main effects *B* (drug), *E* (storage condition), and interaction, *AB, AE, ABE* were found significant. All significant effects will, on average, increase the response except *E*, which, on average, will decrease the dissolution rate of the tablet. The soft tablets were not tested [Fig. 5: columns l(e), b(e), d(e), bd(e)], while the absence of data for bc(e) and bcd(e) under 25°C/75% RH was due to the very slow but steady release of the drug to the medium (less than 80% was released in 3 hr).

CONCLUSION

The factorial design identified drug solubility, amount of compression force, and storage condition as the factors that strongly influence tablet qualities from time of manufacture to storage. To a lesser extent, the type of filler/binder and disintegrant affected the tablets, especially after storage. Since significant higher-order interactions were observed, the influence of the factors among these has to be taken into account in the development of tablet formulations in pharmacy. Which factors will interact with each other is rather difficult to predict; thus fractionalization [fractional factorial design (4)] seems unsuitable for these experiments. The water-

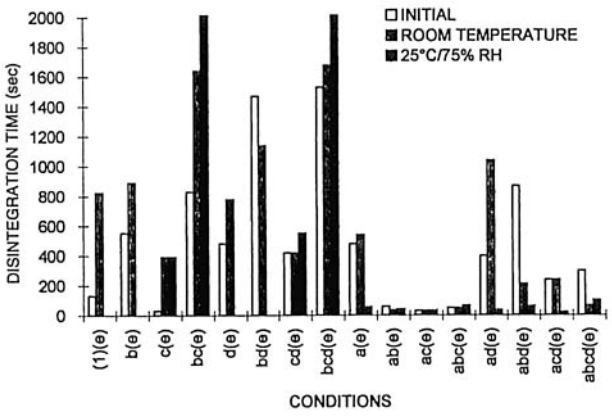

Figure 4. Influence of factor *E* (storage condition) on disintegration time.

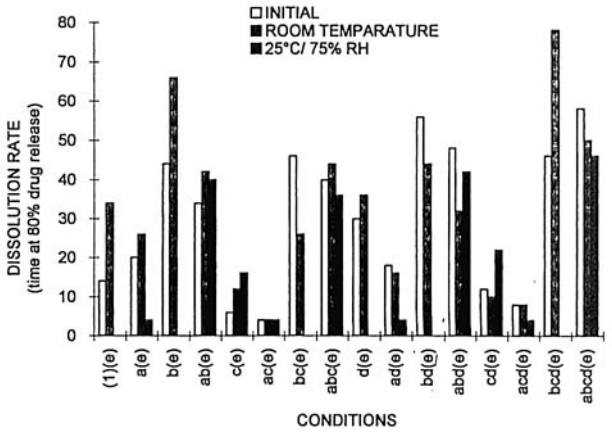

Figure 5. Influence of factor *E* (storage condition) on dissolution rate.

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soluble ingredients enhance softening of the tablet in the presence of high humidity. Xylitab 200-containing tablets in the presence of other soluble ingredients should not be exposed to high humidity unless packed in tightly closed, appropriate containers. Ludipress as the filler/binder of choice gives better quality tablets than Xylitab 200.

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