Influence of Type and Content of Guar Gum as A Disintegrant and Production Technique on Attributes of Immediate Release Tablets

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ABSTRACT

The objective of this study is to select between native and treated guar gum as tablet disintegrant and to explore the possible influences of disintegrant content and production method on different tablet attributes using promethazine-HCl as a model drug. Tablet batches were formulated according to 2^3 full factorial design in which each of the selected factors was investigated at two possible levels for their individual and combined influences on tablets properties. Native and treated gum were considered for guar gum type, guar content was examined at 2 and 8% w/w whereas dry and wet granulation were selected as levels for tablets production method. Guar gum content was demonstrated to affect weight variation, thickness variation and friability properties of different tablet batches (p ranged 0.012-0.038). Guar gum type was also established to influence weight and thickness variation as well as disintegration and drug dissolution properties (p ranged 0.025-0.039). Influences of production method on weight variation, thickness variation, friability, disintegration and drug dissolution properties were found to be considerable (p< 0.05, for all effects). None of the investigated factors has measured a significant effect on tablet hardness property (p ranged 0.4511- 0.9214 for the effects of all factors). Compared to native guar gum, treated guar gum was found to be more efficient as a tablet disintegrant (p= 0.039). Formulations including 2 or 8% w/w treated guar gum and processed by dry granulation were found to yield tablets with average short disintegration time (5.0 ± 0.9 min) and enhanced dissolution efficiency (0.805 ± 0.005).

Keywords: Guar gum; Treated guar gum; Tablets' properties; Dry granulation; Wet granulation.

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Received 27 July 2014, Accepted 13 August 2014
INTRODUCTION

The effects of formulation and manufacturing method on tablet disintegration and dissolution are well-known\(^1\)-\(^4\). In making tablets by wet granulation it has been a common practice to add the disintegrating agent both before the formation of granules (intrgranularly) and in the final granules (extra granularly). Since the intragranular disintegrant undergoes both wetting and drying during the granulation process, it may not be as effective, in equivalent load, as the disintegrant used in tablets made by direct compression and slugging. This has been a problem in some formulations with corn starch and has caused formulators to search for disintegrating agents which are equally effective regardless of the method of tablet production. One of the advantages of some of the newer tablet disintegrant is that the method of manufacture has less effect on functionality. Guar gum, a polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, is commonly used in cosmetics, food products, and pharmaceutical formulations. It is used in oral solid-dosage forms as a binder and/or disintegrant, moreover, it is utilized as suspending, thickening, and stabilizing agent in some topical products. In addition, guar gum has been numerous reported as a drug controlled-release carrier and has also been examined for use in colonic drug delivery\(^5\). Chemical and physical treatment of guar gum are reported to provide a low molecular weight gum with improved physical, chemical and mechanical properties for many pharmaceutical applications\(^6\)-\(^7\). Although numerous researches dealing with pharmaceutical application of guar gum have been reported, the influences of formulation and processing variables on disintegration efficiency of guar gum has received less attention among formulation scientists. The objective of this study is to select between native and treated guar gum as tablet disintegrant and to investigate the possible effects that disintegrant loading level and manufacturing method (wet and dry granulation) might have on characteristics of immediate release tablets using promethazine HCl as a model drug.

MATERIALS AND METHODS

Guar gum (Batch No. 39B2B2) was a pharmaceutical grade product of Nanjing Co, (China); Treated guar gum, was obtained by thermal processing of guar gum; Promethazine hydrochloride reference standard was British Pharmacopeial chemical reference standard grade (Batch No. 2316); Promethazine hydrochloride raw material (Batch No. 140136, Dandong Yichuang Pharmaceutical Co., China) and microcrystalline cellulose (Avicel\(^\text{®}\) PH-101, JRS pharma, Germany) were pharmaceutical grade, obtained as gift samples from Amipharma laboratories- Sudan and were used as received; Lactose monohydrate (Batch No. F08Z/0508/2405/31) was a
pharmaceutical grade product of S d fine – chem. Limited, Mumbai, India; Talc (Batch No. 160509) and Magnesium stearate were pharmaceutical grade products of Avis Chemical Co. India and Alfa Acer, a Johnson Matthey company, respectively. Other materials were either analytical or pharmaceutical grade obtained from different commercial sources.

**Preparation of thermally treated guar gum**

The method reported by Bradley, et al. for thermal treatment of guar gum was followed where for each run, solution of guar gum was prepared by wetting a known weight of guar with a small amount of absolute ethanol (0.5 ml ethanol per 100 mg guar) to prevent aggregation during the dispersion process. The guar solutions was then dispersed in a mixed phosphate buffer (KH$_2$PO$_4$, Na$_2$HPO$_4$) of pH 6.0 containing 0.2M NaCl using a magnetic stirrer for mixing, then heated for a pre-determined temperature and time for each run. The resultant content was then dried in hot air oven.

**Experimental design**

Design and composition of formulation runs within this research were conducted following 2$^3$ full factorial screening design (Table 1) where three factors, namely, disintegrant type, disintegrant amount and tablet production method were investigated at two different levels to determine their possible effects on the physical performance of produced tablets through 8 experimental runs. Native and treated guar gum were considered for disintegrant type with content levels of 2% or 8% w/w whereas dry and wet granulation were selected as levels for the production method (Table 1).

**Table 1: Experimental design and composition of different promethazine HCl tablet formulations**

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Drug/tablet</th>
<th>Lactose (% w/w)</th>
<th>Avicel (% w/w)</th>
<th>GG (% w/w)</th>
<th>GG Type*</th>
<th>Mg st. (% w/w)</th>
<th>Production Method**</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25 mg</td>
<td>80.5%</td>
<td>4%</td>
<td>2%</td>
<td>NGG</td>
<td>1%</td>
<td>DG</td>
</tr>
<tr>
<td>F2</td>
<td>25 ~</td>
<td>74.5%</td>
<td>4%</td>
<td>8%</td>
<td>NGG</td>
<td>1%</td>
<td>DG</td>
</tr>
<tr>
<td>F3</td>
<td>25 ~</td>
<td>80.5%</td>
<td>4%</td>
<td>2%</td>
<td>NGG</td>
<td>1%</td>
<td>WG</td>
</tr>
<tr>
<td>F4</td>
<td>25 ~</td>
<td>74.5%</td>
<td>4%</td>
<td>8%</td>
<td>NGG</td>
<td>1%</td>
<td>WG</td>
</tr>
<tr>
<td>F5</td>
<td>25 ~</td>
<td>80.5%</td>
<td>4%</td>
<td>2%</td>
<td>TGG</td>
<td>1%</td>
<td>DG</td>
</tr>
<tr>
<td>F6</td>
<td>25 ~</td>
<td>74.5%</td>
<td>4%</td>
<td>8%</td>
<td>TGG</td>
<td>1%</td>
<td>DG</td>
</tr>
<tr>
<td>F7</td>
<td>25 ~</td>
<td>80.5%</td>
<td>4%</td>
<td>2%</td>
<td>TGG</td>
<td>1%</td>
<td>WG</td>
</tr>
<tr>
<td>F8</td>
<td>25 ~</td>
<td>74.5%</td>
<td>4%</td>
<td>8%</td>
<td>TGG</td>
<td>1%</td>
<td>WG</td>
</tr>
</tbody>
</table>

*GG stands for guar gum; NGG and TGG stand for native and treated guar gum, respectively.

* DG and WG stand for direct and wet granulation techniques, respectively.

**Production of tablets in the screening design**

The design comprises utilization of both dry and wet granulation techniques, each for production of four batches.
Dry granulation method
For batches manufactured by dry granulation method (F1, F2, F5 and F6), ingredients equivalent to 400 tablets for each batch (Table 1) were weighed (Electronic balance ABS 120-4, Germany), excluding Mg stearate, and thoroughly mixed using mortar and pestle for 10 minutes. The blend was then compressed into large slugs using single punch tablet machine equipped with size 14mm flat punch (Cadmach machinery Co. India). Obtained slugs were granulated using a Erweka granulator (GmbH, Germany) and the yield passed through #20 mesh screen. Lubricant (Mg stearate) was added to the obtained granules with gentle blending for 5 minutes and the resulting material was then compressed using a single punch tableting machine equipped with size 9mm flat punch to produce tablets with average weight of 200 mg and contain 25mg of the model drug per tablet. Tablets were then examined for their physicochemical performance.

Wet granulation method
For batches F3, F4, F7 and F8, the tablets were prepared by first mixing one-half of the amount of the disintegrant (native or treated guar gum) with the drug and the filler (lactose), which were previously sifted through a 500 µm sieve and mixed for 5 minutes. Suitable amount of freshly prepared aqueous solution of 10% w/w Microcrystalline cellulose (Avicel® PH-101) was added, as granulating solution, to the powder blend while mixing to form wet mass which passed through a #16 mesh screen and tray-dried in a drying oven (Memert, Germany) for 14 hours at 55°C. To the dried granules which were re-sized through a #20 mesh screen, the remaining half of the disintegrant was sifted through the 500µm sieve and mixed for three minutes followed by addition of lubricant (sifted through the 500µm sieve) and mixing for extra 1 minute. Lubricated granules blend were finally compressed on a single punch tableting machine equipped with size 9mm flat punch to produce tablets with average weight of 200.3 mg and contain 25mg of the model drug per tablet. Tablets were then evaluated for their physicochemical performance.

Evaluation of tablets
Randomly selected tablets from all batches were subjected to variety of pharmacoeial tests to distinguish their physicochemical characteristics (USP33-NF28)

Tablet weight and thickness variation
Prepared tablet batches were subjected to the official weight variation test where 20 randomly selected tablets from each batch were individually weighed and the average tablet weight was calculated. Deviation % (percent coefficient of variation, % CV) of each tablet weight from the average tablet weight was then determined and compared with the compendia specifications. Another sample of 10 randomly selected tablets from each batch were each measured for thickness
using micrometer. Average tablet thickness and deviation of tablets from average thickness were then determined and compared to pharmacopoeial specifications.

**Tablet hardness**

Ten randomly selected tablets from each batch were tested using electric hardness tester (Erweka, Germany) that measures the diametrical crushing strength required to break the tablet in kg/cm².

**Tablet friability**

For each batch, sample of 20 tablets were weighed and tested in friabilator (Erweka, TA, Germany) rotating at speed of 25 rpm for 4 min. After dust removal, tablets were re-weighed and friability percentage was calculated using the ratio (as percent) of the difference in the total tablets weight before and after the test to the total weight of tablets before the test.

**Tablet disintegration**

Disintegration testing was performed according to disintegration monograph for uncoated tablets of USP33-NF28. Purified water at 37 ± 2 °C was used as the test media. For each batch, 6 randomly selected tablets were placed into each of the six tubes of the disintegration test apparatus (Erweka, Germany). The apparatus was operated and the time for the last tablet to disintegrate was recorded as the disintegration time and notable observations were also traced.

**Drug Dissolution**

Six randomly selected tablets for each batch were subjected to pharmacopoeial drug dissolution testing (USP33-NF28). Dissolution was performed in 900 ml of 0.01N HCl at 37±0.5°C using USP apparatus 1 (baskets) set at 100 rpm. After 45 minutes aliquot samples from dissolution apparatus were withdrawn, filtered, suitability diluted and analyzed spectrophotometrically for promethazine-HCl at UV λ_max of 249 nm. Amount of drug dissolved in each sample was then determined by comparison to absorbance of solution of known concentration of reference standard promethazine-HCl dissolved in the same medium. Dissolution efficiency at 45 minutes was then computed for all tablet batches.

**Statistical data analysis**

Values for different tablet properties were presented as mean value ± standard deviation whereas coefficient of variation term was used to assess tablet weight and thickness variation among different tablet batches. Inferential statistics relying on regression and one way analysis of variance (ANOVA) in addition to the descriptive determination coefficient (r²) were used to analyze different responses and to determine depth of contribution of factors on different tablet properties. Pearsons' correlation coefficient (r) was used to grade the correlation between disintegration and dissolution profiles of investigated tablet batches. Analysis was aided by the software package
STATISTICA® (version 8, Statsoft Inc., 2007) and in all cases, probability p ≤ 0.05 was considered as a cutoff point for statistical significance.

RESULTS AND DISCUSSION

Table 1 summarizes formulation and processing components for different tablet formulation batches in the screening design whereas measured properties of tablets investigated within all batches are shown in Table 2. Individual and combined influences of factors in the $2^3$ screening design on tablet properties. Based on data presented in Table 3 that concerning effect estimate of guar gum type, guar gum amount and tablet production method on properties of produced tablets, it appears that different factors affect tablet characteristics in disparate manner and accordingly, discussion will be based on the effects on properties rather than the influences of individual factors.

**Table 2: Properties of different tablet batches. Values were presented as mean ± SD.**

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Weight Variation$^a$</th>
<th>Thickness Variation$^a$</th>
<th>Friability, (%)</th>
<th>Hardness (kg/cm$^2$)</th>
<th>Disg Time$^b$ (min)</th>
<th>DE$_{45\text{min}}$$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.3%</td>
<td>0.8%</td>
<td>0.27±0.11</td>
<td>5.9±0.6</td>
<td>12.5±1.5</td>
<td>0.69±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>1.6%</td>
<td>0.7%</td>
<td>0.48±0.07</td>
<td>5.4±0.5</td>
<td>20.8±3.6</td>
<td>0.65±0.02</td>
</tr>
<tr>
<td>F3</td>
<td>1.1%</td>
<td>0.6%</td>
<td>0.40±0.05</td>
<td>5.8±0.5</td>
<td>40.2±6.4</td>
<td>0.59±0.03</td>
</tr>
<tr>
<td>F4</td>
<td>1.3%</td>
<td>0.5%</td>
<td>0.45±0.04</td>
<td>5.8±0.5</td>
<td>78.2±12.6</td>
<td>0.50±0.01</td>
</tr>
<tr>
<td>F5</td>
<td>1.2%</td>
<td>0.7%</td>
<td>0.41±0.08</td>
<td>5.4±0.4</td>
<td>4.1±0.9</td>
<td>0.81±0.04</td>
</tr>
<tr>
<td>F6</td>
<td>1.5%</td>
<td>0.5%</td>
<td>0.41±0.07</td>
<td>5.9±0.5</td>
<td>5.8±1.2</td>
<td>0.80±0.01</td>
</tr>
<tr>
<td>F7</td>
<td>1.0%</td>
<td>0.5%</td>
<td>0.41±0.09</td>
<td>5.5±0.6</td>
<td>9.1±0.5</td>
<td>0.77±0.05</td>
</tr>
<tr>
<td>F8</td>
<td>1.1%</td>
<td>0.4%</td>
<td>0.51±0.01</td>
<td>5.6±0.5</td>
<td>11.9±1.0</td>
<td>0.75±0.03</td>
</tr>
</tbody>
</table>

$^a$ Presented as percentage coefficient of variation (cv%); $^b$ Disintegration time; $^c$ Stands for dissolution efficiency of different tablet formulations at 45min.

**Effects on tablet weight and thickness**

Displayed values for tablet weight and thickness among different runs ranged 199.6—201.7mg and 2.87—2.98mm, respectively, whereas calculated values for coefficients of variation corresponding to tablet weight and thickness were varied between 0.4 and 1.6%, indicating that both properties were in the acceptable range of compendia specifications for tablets. It is apparent from Table 3 that production method, guar gum content and guar gum type have considerable effects on tablet weight and thickness variations (p< 0.05 for the three factors, Table 3). Moreover, whilst the three factors showed influences of comparable magnitude on thickness variation (0.0013-0.0018), magnitude of the influences of guar gum content and production method on weight variation (0.0023 and 0.0028, respectively) appear to be higher than that associated with the influence of guar gum type (0.0013).
Table 3: Standardized estimated effects of factors on properties of different tablet batches.

<table>
<thead>
<tr>
<th>Factors setting</th>
<th>Weight variation</th>
<th>Thickness variation</th>
<th>Friability</th>
<th>Hardness</th>
<th>Disg T&lt;sup&gt;c&lt;/sup&gt;</th>
<th>DE&lt;sub&gt;45&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Guar gum content</td>
<td>0.0023*</td>
<td>-0.0013*</td>
<td>0.0009*</td>
<td>0.0225</td>
<td>12.70</td>
<td>-0.0350</td>
</tr>
<tr>
<td>(2) Guar gum type</td>
<td>-0.0013*</td>
<td>-0.0013*</td>
<td>0.0003</td>
<td>-0.0625</td>
<td>-30.20*</td>
<td>0.1750*</td>
</tr>
<tr>
<td>(3) Production method</td>
<td>-0.0028*</td>
<td>-0.0018*</td>
<td>0.0005*</td>
<td>-0.0075</td>
<td>24.05*</td>
<td>-</td>
</tr>
<tr>
<td>1 by 2</td>
<td></td>
<td>-0.0003</td>
<td>-0.0004</td>
<td>0.3075*</td>
<td></td>
<td>0.0850*</td>
</tr>
<tr>
<td>1 by 3</td>
<td>-0.0008</td>
<td>0.0003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 by 3</td>
<td></td>
<td></td>
<td>-18.5</td>
<td>0.0400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r&lt;sup&gt;2b&lt;/sup&gt;</td>
<td>0.988</td>
<td>0.981</td>
<td>0.989</td>
<td>0.948</td>
<td>0.901</td>
<td>0.979</td>
</tr>
</tbody>
</table>

<sup>a</sup>1by2, 1by3, 2by3 and 1by2by3 stand for pooled setting of respective factors; <sup>b</sup>Determination coefficient for fitted model; <sup>c</sup>Disintegration time; * Indicates significant effects at p< 0.05.

Effects on tablets’ friability and hardness

Displayed range for values of tablet hardness and friability among different formulations were 5.4-5.94 kg/cm<sup>2</sup> and 0.27-0.51%, respectively (Table 2). In spite of the fact that displayed tablet friability of formulation F8 is approximately twice that revealed by F1, all tablet batches were found to be within the acceptable USP limits for friability and hardness properties (USP33-NF28). As individual factors, guar gum content and production method were shown to influence tablet friability (p= 0.014 and 0.042 for both factors, respectively). In addition, the pooled influence of the three investigated factors on tablet friability was found to be considerable (p= 0.026) whereas the pooled influence of guar gum content and type demonstrated to be substantial on tablet hardness (p= 0.045) (Table 3). Though production method revealed a neglected effect on tablet hardness (p= 0.9214), it measured a profound influence on tablet friability (p= 0.0421) next to the guar gum content (Table 3). Moreover, guar gum type, as individual factor, showed no (or a little) influence on both tablet properties (p> 0.05 for factor influence on both properties). As compared to tablet friability, hardness appears to be less affected by individual influences of the investigated factors, under any factors setting. Generally, tablet friability is a property that mostly related to the binder system utilized and since guar gum is reported to have a binder usage in tablet technology<sup>(9,10)</sup>, it might not be surprising then that the amount of guar gum has greatly influenced this property regardless of its type. Figure 1 substantiates that application of guar gum in small amount might be associated with desired small values of tablet friability which could be attributed to the poor compressibility and/or deformation properties of guar gum when used in large amount, especially if a non treated type is applied. These findings are in agree with a relevant published work<sup>11</sup>.
Figure 1: Marginal mean ± SD of friability for different tablet batches as a response of using native or treated guar gum each investigated at 2 and 8% content levels.

Influences on tablets’ disintegration and dissolution profiles:

Disclosed values of disintegration time and dissolution efficiency (DE) for different tablet formulations are ranged 4.1—78.2 min and 0.50—0.81, respectively (Table 2). It is notable that drug release data were transformed in terms of dissolution efficiency (DE) because drug dissolution data incorporated an integral mode (area under dissolution curve) are better for correlation with disintegration. The concept has been considered and widely used to evaluate and compare drug release profiles of solid dosage forms\textsuperscript{12, 13}. As USP official monograph for promethazine-HCl immediate release tablets is devoid of tablet disintegration specification, it might be worthless to categorize these formulations in terms of best disintegration profile. Yet, the smaller the disintegration time, the more likely that a formulation will fulfil the dissolution acceptance specifications. USP33-NF28 specification necessitates that 75% of loaded promethazine-HCl is to dissolve within 45 min. Simple transformation revealed that 75% release is equivalent to DE of 0.44 and, therefore, to fulfil the dissolution requirement, tablet formulation has to attain DE ≥ 0.44 at 45 min. In spite of the wide range for the measured DE, all tablet formulations have fulfilled the acceptance criteria for drug dissolution where none has exhibited a DE value less than 0.44 (Table 2). It is apparent from Table 2 that formulations processed by dry granulation method (F1, F2, F5 and F6) attain shorter average disintegration time (10.8 ± 6.6 min) and more enhanced average drug dissolution efficiency (0.74 ± 0.07) as compared to respective formulations containing the same amount and type of guar gum which accomplished average disintegration time and drug dissolution efficiency of 34.9 ± 27.8 min and 0.65 ± 0.11,
respectively. Moreover, formulations including 2 or 8% w/w TGG (F5-F8) achieve lesser disintegration time and improved DE when compared to NGG containing ones, especially when produced by dry granulation method (F5 and F6). It might be also obvious that increase in content of native and/or treated guar gum from 2 to 8% w/w has result in a delay in disintegration time which is accompanied by a little decrease in drug dissolution efficiency characteristics of respective tablet batches (Table 2). The effect estimate of the three factors on disintegration and dissolution profiles (Table 3) support that the influences of guar gum type and production method on disintegration (p= 0.039 and 0.045) and drug dissolution properties (p= 0.002 and 0.017, respectively) are statistically considerable. In other words, observed influences of guar gum content on tablet disintegration and drug dissolution properties lack the required statistical support for consideration (p= 0.234 and 0.110 for the effects on both properties, respectively). The improved disintegration and dissolution properties observed with batches produced by dry granulation method could be explained in term of the incorporation mode of the disintegrant which is reported to affect its functionality\(^{14}\) and, consequently, the reduced efficiency of disintegrant with tablet batches processed by wet granulation technique could possibly be attributed to the combined effects that wetting and subsequent drying might have on intragranular disintegrant during the granulation process. Objectives of treating guar gum include enhancement of water uptake, reduction of gel strength and improvement of deformation behaviours of the polymer. Bearing in mind that the efficiency of a disintegrant depends on how fast the polymer uptakes fluids and to what extent it swells, treated guar gum, therefore, is expected to provide more efficient tablet disintegration than the native gum, as the results imply. These findings are in accordance with the results obtained by Sharma, et al.\(^{15}\). It is believed that for immediate release products containing a highly soluble drug, as the case with this study, disintegration might be the time-limiting step for dissolution and a good correlation between disintegration and dissolution data could possibly be accomplished\(^{16}\). Thus, achieved DE\(_{45\text{min}}\) of different tablet batches were plotted against the respective disintegration times in an attempt to find a correlation between disintegration and drug dissolution profiles of these tablet batches (Figure. 2). Though the plot supports that drug dissolution might be a function of disintegration in these tablet batches, displayed correlation coefficient (r= -0.9360 at p= 0.0001) indicates that the inverse relation between the two properties is not a simple univariate where other variables deem to have an effect on dissolution, at least under the experimental conditions of this study.
CONCLUSIONS

Guar gum content demonstrated to affect weight variation, thickness variation and friability properties of different tablet batches whereas guar gum type also established to influence weight and thickness variation as well as disintegration and drug dissolution properties. Influences of production method on weight variation, thickness variation, friability, disintegration and drug dissolution properties appear to be considerable. None of the investigated factor seems to influence tablet hardness property. As a tablet disintegrant, treated guar gum demonstrated to be more efficient than the native one.

ACKNOWLEDGMENT

Authors would like to acknowledge Amipharma Laboratories for Pharmaceuticals (Sudan), for the materials donation. Technical assistance provided by Tahir M. Tahir (Head technician at Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum) during the experimental part of this study is highly admitted.

Conflict of Interest

Authors certify that there is no conflict of interest regarding the material discussed in the manuscript.

REFERENCES


