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EFFECT OF IMPELLER DESIGN ON HOMOGENEITY, SIZE AND STRENGTH OF PHARMACEUTICAL GRANULES PRODUCED BY HIGH SHEAR WET GRANULATION

Chirangano Mangwandi[1*], Zakaria Mirza[1], Liu JiangTao[1], Yoann Glocheux[1],

Ahmad B. Albadarin[1,2]

[1]Sch. of Chemistry and Chemical Engineering, Queen's University Belfast, Belfast BT9 5AG, Northern Ireland UK

[2]Synthesis & Solid State Pharmaceuticals Center (SSPC),
Department of Chemical and Environmental Science,
University of Limerick, Ireland.

Corresponding author

E-mail: c.mangwandi@qub.ac.uk (C. Mangwandi),

Tel. +44(0)289 097 4378

Fax. +44 (0) 289 097 6524

ABSTRACT

Design of small mixer impellers is not tailored for granulation as they are intended for a wide range of processes. The Kenwood KM070 was employed as a standard apparatus to undertake this investigation. Five different impeller designs with different shapes and surface areas were used. The aim of this research was to evaluate the performances of these impellers to provide guidance on the selection and design for the purposes of granulation. Lactose granules were produced using wet granulation with water as the binder. The efficacy of respective granulates was measured by adding an optically sensitive tracer. This was used to determine variation of active ingredient across random samples of granules from the same size classes. It was found that impeller design influenced the homogeneity of the granules and therefore can affect final product performance. The variation of active ingredient across granule of different sizes was also investigate. The study shows that small granules were more potent when compared to the larger granules.

KEYWORDS

Granules strength; impeller design; homogeneity; high shear granulation; lactose monohydrate

1. INTRODUCTION

Granulation is a size enlargement unit operation in which granular products are produced by sticking together powdery particles with a binder. It has wide applications in several industries for instance pharmaceuticals, detergent industries, fine chemicals and fertiliser industries. Particle agglomeration in wet granulation improves the bulk properties of the formulation by enhancing the flow properties, reducing the dustiness and also the improving the compression properties. Several studies investigated the effect of granulation parameters in the high shear mixer on product attributes and demonstrated that control of process parameters is necessary to obtain product with the desired attributes (Campbell et al., 2011; Johansson and Alderborn, 2001; Mangwandi et al., 2010; Mangwandi et al., 2012; Mangwandi et al., 2013a; Niklasson et al., 2005; Shiraishi et al., 1994). The final product properties are influenced by the process parameters and formulation attributes. In addition to formulation and process variables there are equipment variables which can influence the properties of the granule. Examples of these variables are the type and shape of the vessel, the presence of a chopper (Chitu et al., 2011) and nozzle.

The main source of energy in high shear granulation is power dissipation by impeller rotation. The main task of the impeller is to agitate the powder particles and ensure that they are always in continuous motion and to ensure collision between binder particle and powder particles. The other purpose of the impeller is to ensure proper mixing of the materials being granulated. Previous work done in mixing of fluid systems has shown that the design of the impeller has a significant effect on the flow of the fluid (Jirout and Rieger, 2011; Kacunic et al., 2012; Khare and Niranjan, 2002; Kumaresan and Joshi, 2006).

There are scant papers in literature discussing the effect of impeller design on the granulation process (Campbell et al., 2011; Knight et al., 2001; Niklasson et al., 2005; Schaefer et al., 1993; Smith et al., 2010; Voinovich et al., 1999) . Work done by Schaefer et al. 1993 on the effect of equipment variables on granulation revealed that the impeller blade design affects the shape of the granules formed (Schaefer et al., 1993). Granules that are more spherical were obtained if an impeller with a curved blade was used whilst granulating using a flat blade impeller resulted in formation of irregular shaped granules.

The Kenwood food processer (Kenwood, KM070) which has been used as a lab scale high shear mixture in previous studies (Mangwandi et al., 2013a; Mangwandi et al., 2013b, c) comes with different impellers since it is designed for mixing a range of different materials. Images of the different impeller design are shown in Fig. 1. In the previous studies (Mangwandi et al., 2013a; Mangwandi et al., 2013b, c) only one type of impeller was used, the High Temperature Flexible Beater (HTFB - 14). The aim of this paper is to evaluate the performance of the other impellers in high shear wet granulation in terms of extent of mixing, strength of the granules formed and the size distributions. The extent of mixing will be evaluated using the method used in previous work (Mangwandi et al., 2011; Mangwandi et al., 2014; Mangwandi et al., 2013c).

2. MATERIALS & METHOD

2.1 Materials

Lactose monohydrate powder, supplied by Sigma Aldrich GmbH, was used as the main excipient. Methylene Blue (MB) - high purity biological strain, produced and supplied by Sigma Aldrich, was used as a model active ingredient.

2.2 Binder Preparation and Granulation

All granulation experiments were performed in a Kenwood processor (KM 70). Six granulation experiments were done in triplicates. The granulation conditions used in all the experiments are summarised in Table 1. The purpose of experiments 1 and 2 was to check whether addition of methylene blue (MB) to the granulation liquid had any effect on the granulation properties. The same type of impeller was used in these experiments. Experiments 2 to 6 were used to investigate the effect of impeller type on the batch homogeneity, granule mechanical strength and shape. Methylene blue was added to deionised water to produce a MB solution, with a concentration of 20 ppm.

2.3 Material Characterisation

Data were collected on the powdered samples using a Philips Xpert Pro-Pan-Analytical diffractometer. The instrument used a monochromated Cu Ka lamp radiating at lambda value of 1.5406 Armstrong. The samples were housed in a flat plate sample holder and analysed through a 2θ range of 5 – 40°, using 0.16713° steps over a period of 12 minutes. XRD patterns for alpha lactose powder, granulated lactose with water and granulated lactose with water-methylene blue are shown in Fig. 2. No structural change is noticed in lactose; therefore methylene blue can be used as an inert tracer to monitor lactose granulation in water.

2.4 Granule Drying and Size Analysis

After granulation each batch of granules was transferred to flat aluminium trays with dimensions 236 mm X 297 mm X 59 mm, ensuring that the granules were evenly spread on the tray surface. The granule trays were then transferred to an oven (Binder FD249, Binder GmbH, Germany) pre-set to a temperature of 60 °C and dried for 12 hours. After drying the granules were allowed to cool to room temperature and then stored in sealed bags until further needed.

Retsch sieves (Retsch GmbH, Germany) were used in the size analysis and the aperture sizes used were as follows; 350, 500, 600, 710, 1000, 1180, 1400, 1700, 2000, 2360, 3350, and

4000 μm. The stack of sieves with the granules was placed on an orbital sample shaker, Stuart Orbital Shaker, supplied by Cole-Parmer UK. The speed of the shaker was set to 180 rpm and the sieving duration to 5 min.

The targeted range of granule size in the experiments undertaken was 0.2 to 4 mm which is the typical size range of pharmaceutical granules (Summers and Aulton, 1988). The percentage of granules in this size range was referred to as the product yield (Ψ) and is calculated by the following equation;

$$\Psi = \left(\frac{m_{pro}}{m_{Bat}}\right) \times 100\% \qquad \textit{Eq. 1}$$

where m_{pro} is the mass of granules in the required size range and m_{Bat} is the mass of total granules produced in a batch. Granules in the size range 0.5 to 4 mm were considered to be the product, whilst those below and above this range were considered to be fines and oversize granules respectively.

2.5 Determination of Homogeneity across granules of same size

Ten random samples of approximately 1 g of granules in the required size range were withdrawn from each batch. Colloids were prepared from each of the samples by adding the granules to 50 ml of de-ionised water. The concentration of the methylene blue solution was obtained by measuring the absorbance of the solution at a single wavelength of 664 nm and calculating the concentration from the previously determined calibration equation. The uniformity coefficient was calculated using the following equation (Mangwandi et al., 2011; Mangwandi et al., 2013c; Mangwandi et al., 2015);

$$\kappa = \frac{S}{\hat{c}} \qquad \textit{Eq. 2}$$

where $\hat{c}$ is the mean of the samples and S is the standard deviation of methylene blue concentration in the samples;

$$S = \sqrt{\frac{\sum_i (c_i - \hat{c})^2}{n-1}} \qquad \textit{Eq. 3}$$

In Eq. (3) above, n, is the total number of samples analysed and c_i is the MB concentration in the i^{th} sample.

MB concentration in granules for each particle size of granules was analysed in the same way and the concentration distribution in function of the particles sizes were plotted.

The homogeneity coefficient can then be defined as;

$$\eta = 1 - \kappa \qquad \textit{Eq. 4}$$

where κ is as define in *Eq. 2* and $0 \le \eta \le 1$. A value of homogeneity coefficient of 1 is assigned to a completely homogeneous distribution of the pseudo active ingredient while a low value of η indicates poor distribution.

2.6 Methylene Blue distribution across different size classes

The distribution of the MB across different size of the granules was measured by dissolving a known mass of granules in a known volume of distilled water and measuring the absorbance of the colloid at a wavelength of 664 nm using a spectrophotometer. The concentration (in ppm) of the colloid was calculated using Eq. 5. The concentration of the MB in dry sample (mg/g) was then determined from;

$$c_{MB,\exp}(x_i) = c_{MB} \times \left(\frac{m_{MB}}{m_p}\right) \times \left(\frac{m_s(x_i)}{V}\right) \qquad \textit{Eq. 5}$$

where m_{MB} is the mass of MB added to the batch; m_p is total mass of powder (mass of lactose and MB added; $m_s(x_i)$ mass of sample granules from size class x_i used in measurement; V (in litres) is the volume of dissolution medium.

2.7 Granules Strength Analysis

The strength of granules in the size range 2000 to 2360 μm was determined from diametric compression of the single granules using the method described previously (Mangwandi et al., 2010; Mangwandi et al., 2007). Eq. 6 was used to determine the granule strength from the failure load, F_f, and the granule diameter, D, which is measured as the distance between the fixed platen and the movable platen, when first contact is made between the granule (Hiramatsu and Oka, 1966);

$$\sigma = 2.8 \times \left(\frac{F_f}{\pi D^2}\right) \qquad \textit{Eq. 6}$$

2.8 Shape Analysis

The shape of the granules from different batches was analysed using an Eyecon 3D particle imager (Innopharmalabs, Ireland). The Eyecon device is able to measure particles size from 50-3000 μm. The device applies blue, green, and red light to the analysed objects and several images are generated. Irregular particle shapes are mapped by the software and several measurements are logged. The characteristics of the granule size distribution; d_{10}, d_{50}, d_{90}, d_{max}, d_{min} and, aspect ratio are presented in report form at the end of the measurement. The particle size measurements are taken directly from the image analysis and there is no model applied to the data.

3. RESULTS & DISCUSSION

3.1 Effect of addition of MB

Preliminary results show that addition of MB to the formulation did not significantly affect the granulation process. The granule size distribution and the strength of formulation with and without MB are shown in Fig. 3 and Table 1 respectively. The results are to be expected considering the low level of concentration of the MB used.

3.2 Effect of Impeller Design on Granule size distribution

The impeller design has an impact on the average granule size and the granule size distributions of the batches. The results are presented in Fig. 4 (a). It is noticeable from this Fig. that for all the batches there was a large percentage of granules bigger than 4000 μm. The presence of these large granules could be attributed to the higher liquid to solid ratio used in the experiments. The mass mean diameter of the granules was calculated according to:

$$\bar{d} = \frac{\sum_{i=1}^{n} m_i \bar{x}}{\sum_{i=1}^{n} m_i} \qquad \textit{Eq. 7}$$

where m_i is mass of granules in the interval x_i to x_{i+1} with an average size of $\bar{x}$.

One Way Repeated measures ANOVA statistical analysis, performed using Sigma Plot V. 11 (Systat Software Inc, USA) on the averages from three measurements for each of the 5 experiments showed that the differences in the average values were greater than would be expected by chance; there is a statistically significant difference (P = 0.037). The distribution of the granules between the three categories i.e. fines, product and coarse granules is shown in Fig. 4 (c). The largest fraction of oversized granules is obtained when the impeller ST-17 is employed. Using this impeller produces negligible amount of fines. It seems that this impeller is ineffective in breaking down the oversized particles. The minimum level of oversized granules was obtained when the SPPW-15 impeller was used. The highest fraction of product was obtained when the HTFB-14 impeller was used. It must be pointed out that there is no significant difference between the product fractions for the SSPW-15 and the HFTB-14 impellers. There is no statistically significant difference between the product yield values from the batches produced using the SSPW-15 and the HTFB-14 impellers, which is around 40 %. The use of the impellers SSKB-13 and ST-17 result in formation of a larger fraction of the coarse granules which would necessitate inclusion of a size reduction step to convert the oversize product into usable product.

3.3 Effect on MB content distribution

Fig. 5 shows variation of the MB concentration in the samples of granules taken from different sizes. It is evident from this figure that the finer granules have a higher concentration compared to larger granules. Granules in the size range 1 to 4 mm have almost similar MB concentrations for all the cases. This is not always the case when using drug molecules. Different views have been expressed regarding the drug distribution across granules of different sizes. Differences in solubility and particle size differences between the filler and drug material have been cited as reasons contributing to inhomogeneity (Ojile et al., 1982; Selkirk, 1976). It has also been reported that granulations involving drugs or active ingredients that are finer compared to filler material can result in smaller granules that have higher drug composition compared to the other granules (Egermann and Reiss, 1988). However this could not be used to explain the distribution of MB shown in Fig. 5 because MB was added to the binder solution form during granulation. Previous work has also shown that larger granules have higher binder content compared to the smaller granules (Scott et al., 2000). Therefore one can expect larger granules to have higher composition of MB, since they should contain more binder. It can also be observed from Fig. 5 that the batches produced by HTFB-14 impeller had the least variation in the MB concentration across all sizes whilst that produced by ST-17 exhibited the largest variation.

The homogeneity coefficient based on samples taken from all sizes was determined to compare the efficacy of mixing by the different impellers; the results are presented in Fig. 6. It is apparent from this figure that HTFB-14 had the largest value of homogeneity coefficient implying that better mixing was achieve using this impeller. ST-17 impeller produced batches which showed the greatest inhomogeneity. This is also supported by the observation that the same batch had the highest presence of oversized granules.

3.4 Effect of impeller design on granule homogeneity

The homogeneity of the granules from the 5 experiments were analysed for three difference size ranges; 710-1000 μm, 1000 to 1180 μm and 3350 to 4000 μm in accordance to the method described in section 2.3. The results are presented in Fig. 7 (a). For the granules in the size range 710 to 1000 μm, the concentration of MB is in the range 0.4 to 0.85 ppm. The highest concentration of granules for this case was obtained when using the impeller HFTB-14. The MB concentration of granules in this range was similar for the impellers SSKB-13 and the SSPW-15. Granules obtained using the ST-17 impeller had the least concentration of MB. For the next size class investigated, 1000 to 1180 μm, the concentration of MB ranges from 0.52 to 0.64 ppm. The variability of the MB concentration for this size range across the batches was lower than that for the 710 to 1000 μm size class. The greatest variability in concentration of the MB in the granules across batches was observed for the larger granules (3350 to 4000 μm).

The theoretical average dry concentration of the MB in the granules can be determined from the following equation (Mangwandi et al., 2013c):

$$\bar{c}_{i,theo} = \frac{m_{bin}\tilde{c}_{i,bin}}{m_{bat}} \qquad \textit{Eq. 8}$$

In Eq. (8), m_{bin} is the expected mass of binder in the granule, $\tilde{c}_{i,bin}$ is the MB concentration in the binder, m_{bat} is the mass of the wet batch of granules and V is the volume of deionised water used to dissolve 1g of granules during the test.

Substituting the correct values of the mass of binder used in the granulation experiment (40 g) and the concentration of the MB in the binder solution (20 ppm) and mass of each batch 0.20 kg gives a theoretical average concentration of 4 ppm. It is then clear from Fig. 7(a) that all the granules tested in this study had below average concentration of the MB.

For most of the impellers, granules with different sizes have significantly different concentration of MB; for the SSD-16 and SSPW-15 impellers, the MB concentration decreased with increasing granule size. When the ST-17 impeller is used, granules in the size range 710 - 1000 μm had similar concentration to those in the 3350 μm to 4000 μm range. The granules produced by the impeller HTFB-14 had most similar concentrations of MB. This would give the impression that granulating using an impeller would result in better distribution of the MB across granules of different sizes (see the circle in Fig. 7 (a)). There are previous results in literature describing the binder distribution in high shear granulation and showing that larger granules have higher binder content compared to smaller granules (Osborne et al., 2010; Reynolds et al., 2004; Smith et al., 2010). In another article (Ramachandran et al., 2008), it is reported that granules in the mid-range contain the highest amount of binder compared to the small and large granules. Fig. 7(b) shows the uniformity coefficient of the MB in granules of different sizes produced by different impeller design. The Homogeneity coefficient gives an indication of variability of the MB across each size class. The homogeneity is defined in such a way that a higher value of the coefficient indicates greater variability (less homogeneity) whilst a lower value would indicate better homogeneity (less variability). There is variation in the homogeneity coefficient both across granules made from the same impeller (different sizes) and also variation across granules of the same size but produced by different impeller. No definite correlation could be identified between the impeller type and the homogeneity coefficient. For the SSKB-13, HTFB-14 and SHD impellers the results show that the homogeneity coefficient is lower for the larger granules compared to the smaller granules. This would imply that there is larger variation in the concentration of MB in the samples taken from larger granules. For the other two impellers the highest value of homogeneity coefficient is obtained from samples of granules of intermediate size.

3.5 Effect of Impeller Design on Granule Strength

Statistical analysis of the five groups of strength data (one from each of the impellers) using Kruskal-Wallis One Way ANOVA analysis showed that differences in the median values among the treatment groups was higher than would be expected from chance; there is a statistical significant difference ($P = 0.004$). This implies that the different impellers produced granules of different strength. However, All Pairwise comparison between the five groups of granules showed that strength data from the SPPW-15 impeller was significantly different form the other four impellers; differences between the other groups was less significant. Summary of the ANOVA analysis results is shown in Fig. 8.

The strength distribution curves of granules produced from the different impeller designs are shown in Fig. 9. It is evident from the figure that the granules from the batch produced by impeller SSPW-15 differed significantly from the rest of the batches and this impeller produced the strongest granules. The variation in the strength results was highest when the SSKB-13 impeller was used and the least variation was obtained when the HFTB impeller was used. Fig. 9 (b) also shows that the largest scatter in the strength data was for granules produced by the impeller SSKB-13.

3.6 **Effect of Impeller Design on granule shape**

The images shown in Fig. 10 are of granules in the size range 1000 - 1180 µm produced by the different types of impeller. It can be noticed from the images that the granules have irregular shape and rough surfaces irrespective of the type of the impeller. For this particular size range and other size ranges investigated 710 - 1000 µm; 2000 – 2360 µm and 2800 - 3350 µm, the impeller design does not seem to have an influence on the shape of the structure of the granules formed. Images of the granules are shown in Fig. 11 This is contrary to earlier work (Schaefer et al., 1993) which reported that impeller design has a slight impact on the granule shape.

The shape of the granules was analysed from images, using the aspect ratio as an indicator of sphericity. The closer the value of the aspect ratio to 1 the less elongated the particle; the further the value from 1, the more elongated is the particle. The average shape factors of granules from different size ranges produced by different impeller are presented in Fig. 12.

It is quite clear from Fig. 12 that, for the granule in the size range 710 - 1000 µm, the type of impeller has no influence on the aspect ratio of the granules. The granules in the size ranges 710 - 1000 µm and 1000 - 1180 µm have similar average aspect ratios. The average values of aspect ratio for the granules in the 2360 - 3350 µm range are higher than those of the smaller granules for all five groups of granules. For all impeller designs, the smaller granules are less elongated than the larger granules.

The effect of the impeller design on granule attributes is summarised in Table 2. The impellers are ranked from 5 to 1, 5 being the best based on maximising that particular granule attribute. It shows which of the impellers to choose if the aim is to maximise the listed attribute. For instance, for maximum granule strength, the SSPW-15 is the one to choose. In terms of better product yield there are two candidates, SSPW-15 and HTFB-14, since the product yield from these two do not differ significantly. Overall the HTFB impeller has a highest score compared to the other impellers.

4. CONCLUSIONS

It has been shown that the choice of the impeller has an influence on granule size distribution, the granule mean size, and the strength and extent of mixing during granulation. In terms of homogeneity of the pseudo active ingredient, the HTFB impeller outperformed the other impellers. The impeller type does not seem to have a significant influence on the shape of granules formed. For the size range investigated in this work, granules of the highest strength were produced when impeller SSPW-15 was employed whereas the highest granule mean size was obtained with the ST-17. Whilst the different impeller designs performed differently depending which granule property one is looking at, the HTFB-14 seems to be the one to choose if one is looking for an impeller that gives better mixing, good product yield and reasonable granule strength.

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NOMENCLATURE

$\bar{c}$,	*Concentration of [ppm]*
$\bar{d}$	*Average granules size[mm]*
D	*Granule diameter (mm)*
F	*Force [N]*
m	*mass [g]*
n	*Number of samples analysed [-]*
V	*Volume of dissolution medium [ml]*
S	*Standard deviation of the methylene blue concentration [ppm]*
x	*Arithmetic average size of the granules in the range[mm]*

Greek letters

η	*Homogeneity coefficient [-]*
κ	*Average granules size[mm]*
σ	*Granule strength [Nmm^{-2} or MPa]*
Ψ	*Product yield [%]*

Subscripts

bat	*batch*
bin	*binder*
exp	*Experimental value*
f	*failure*
i	*Sample index*
MB	*Methylene blue*
p	*powder*
pro	*product*
s	*sample*
theo	*Theoretical value*

Abbreviation

API	*Active Pharmaceutical*
HTFB	*High Temperature Flexible Beater*
MB	*Methylene blue*
SDH	*Spiral Dough Hook*
SSKB	*Stainless Steel K Beater*
SSPW	*Stainless Steel Power Whisk*
ST	*Stirring Tool*
XRD	*X Ray Diffraction*

Table 1: Summary of process and granulation parameters.

Experiment No.	Impeller type	Impeller speed (rpm)	Granulation Time (min)	Mass of lactose Powder	Binder	Liquid to solid Ratio
1	HTFB-14	160	4	200	water	0.2
2	HTFB-14	160	4	200	Water + MB	0.2
3	SSKB-13	160	4	200	Water + MB	0.2
4	SSPW-15	160	4	200	Water + MB	0.2
5	SDH-16	160	4	200	Water + MB	0.2
6	ST-17	160	4	200	Water + MB	0.2

Table 2: Comparison of the strength of granules produced from different binders. N.B. Errors indicate Standard error in the mean

Binder	Impeller Type	Granule Strength (MPa)
Water	HTFB-14	0.60 ± 0.06
Water + MB	HTFB-14	0.65 ± 0.08

Table 3: Summary of effect of impeller design on granule attributes.

Impeller type	Product Yield	Homogeneity	Granule Strength	Granule Mean Size
SSKB-13	2	2	2	4
HTFB-14	5	5	3	2
SSPW-15	4	4	5	1
SDH-16	3	3	4	3
ST-17	1	1	1	5

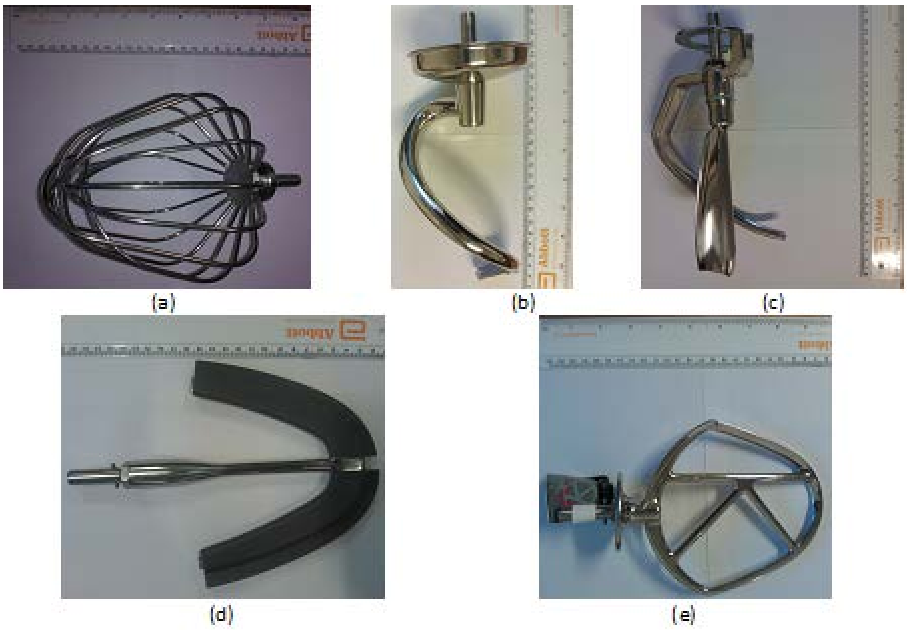


Fig. 1: Images of the different impeller designs used in the granulation experiments (a) Stainless steel power whisk (SSPW-15) b) Spiral Dough Hook (SDH-16) c)Stirring Tool (ST-17) d) High Temperature Flexible Beater (HTFB-14) e) Stainless Steel K Beater (SSKB-13)

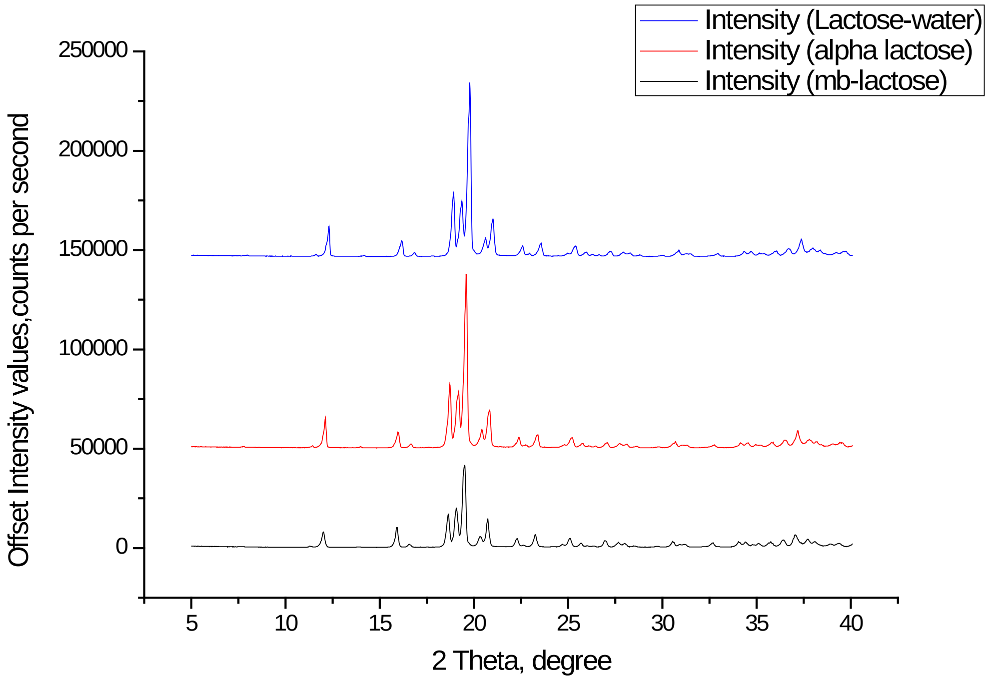


Fig. 2: XRD patterns of samples alpha lactose, granulated lactose from water and water-methylene blue solution.

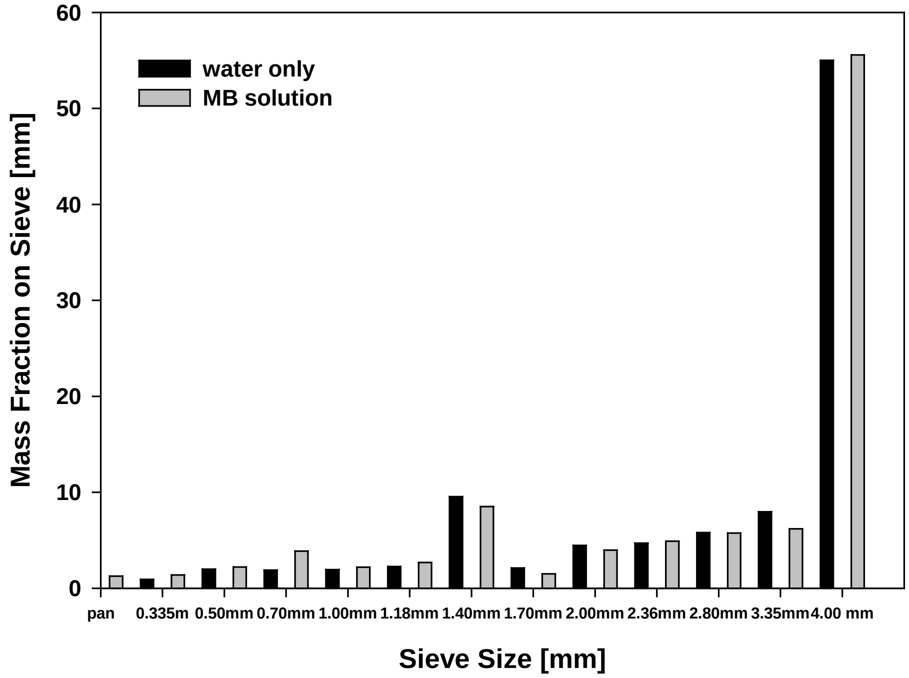
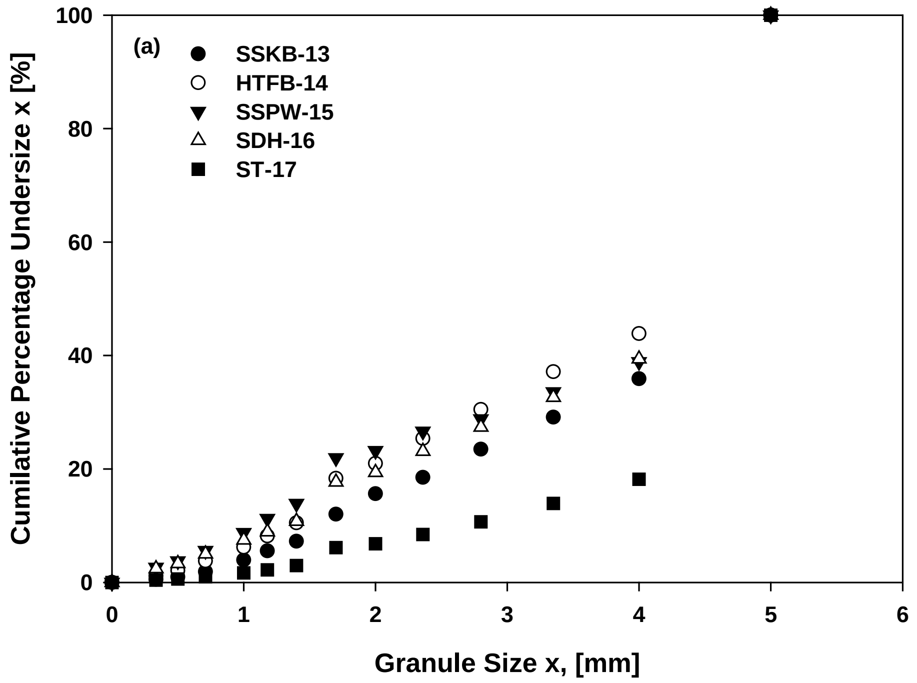
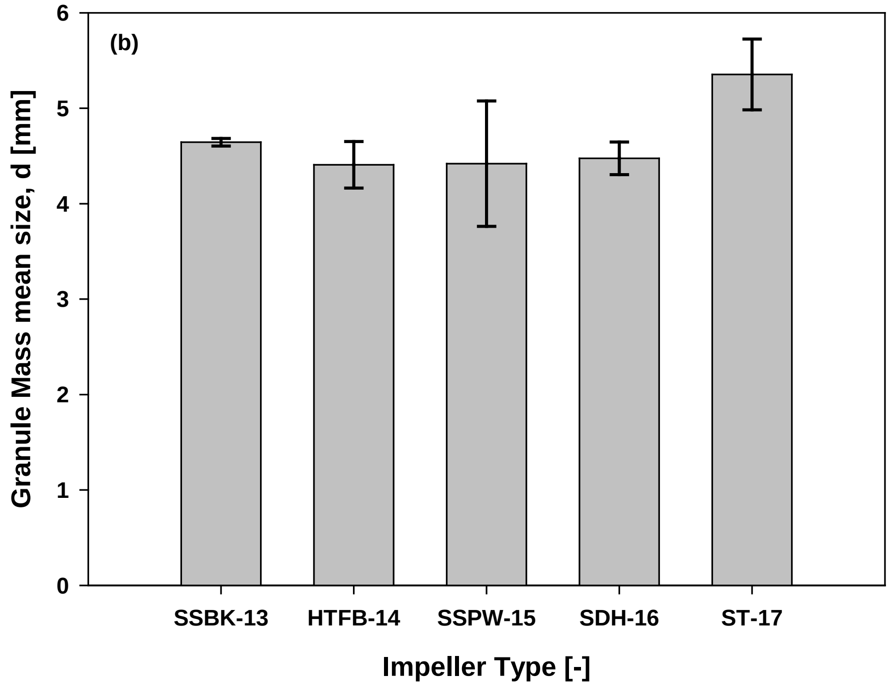


Fig. 3: Comparison of size distributions of batch of granules produced using water and MB solution binders.


(a)
SSKB-13
HTFB-14
SSPW-15
SDH-16
ST-17
Cumilative Percentage Undersize x [%]
Granule Size x, [mm]
0
20
40
60
80
100
0
1
2
3
4
5
6


(b)
Granule Mass mean size, d [mm]
Impeller Type [-]
SSBK-13
HTFB-14
SSPW-15
SDH-16
ST-17
0
1
2
3
4
5
6

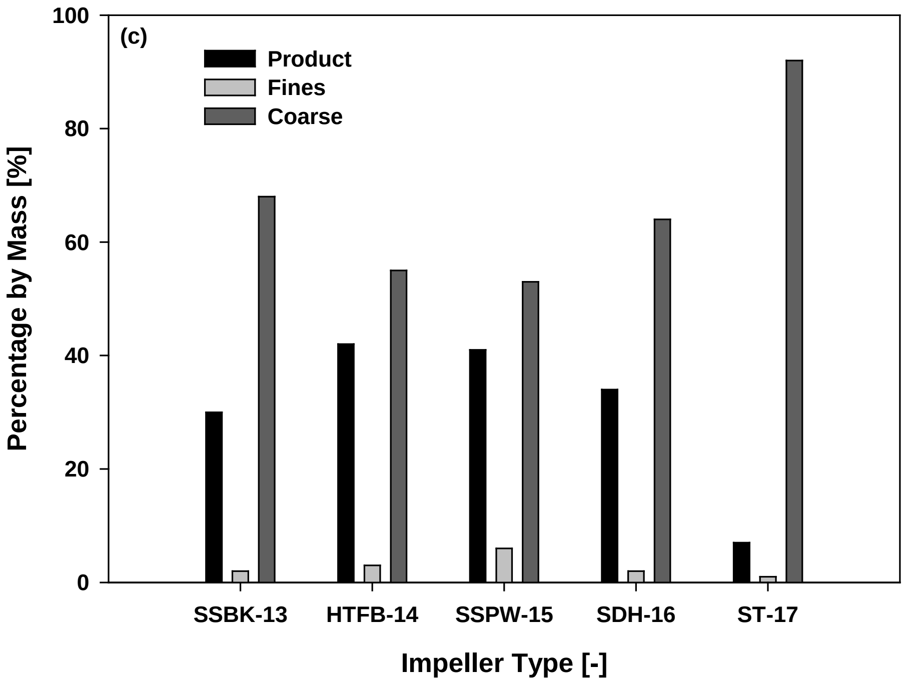


Fig. 4: (a) Typical cumulative granule size distribution plots for experiments 2 to 6. (b) Granule mass mean size as a function of impeller type (c) mass distribution of the granules between fines, product and oversized granules. N.B The plots are average of three replicate experiments.

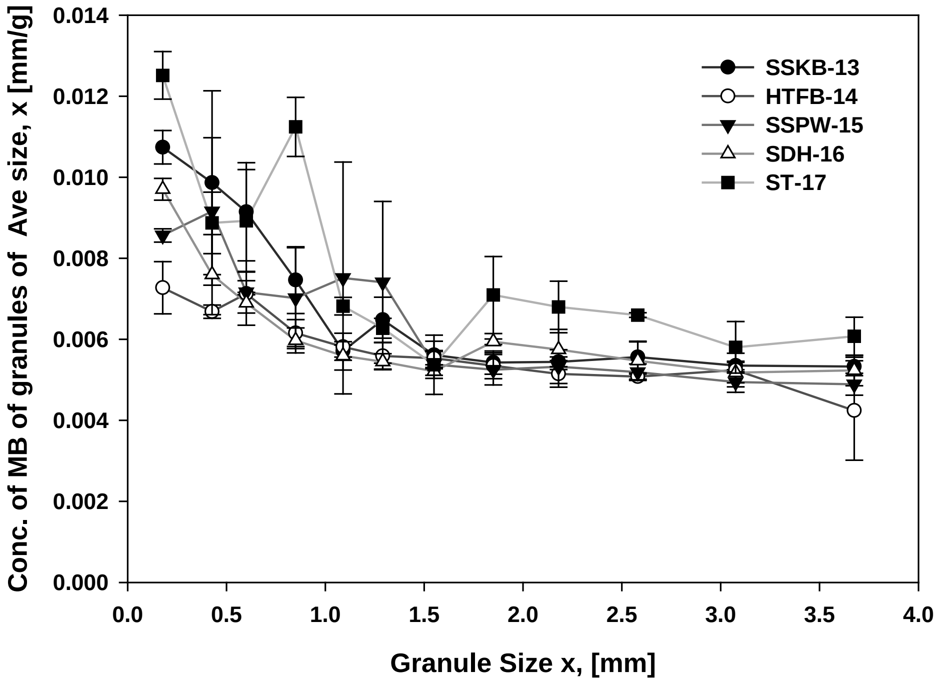


Fig. 5: The variation of MB concentration with size class for batches of granules produced with different impeller designs.

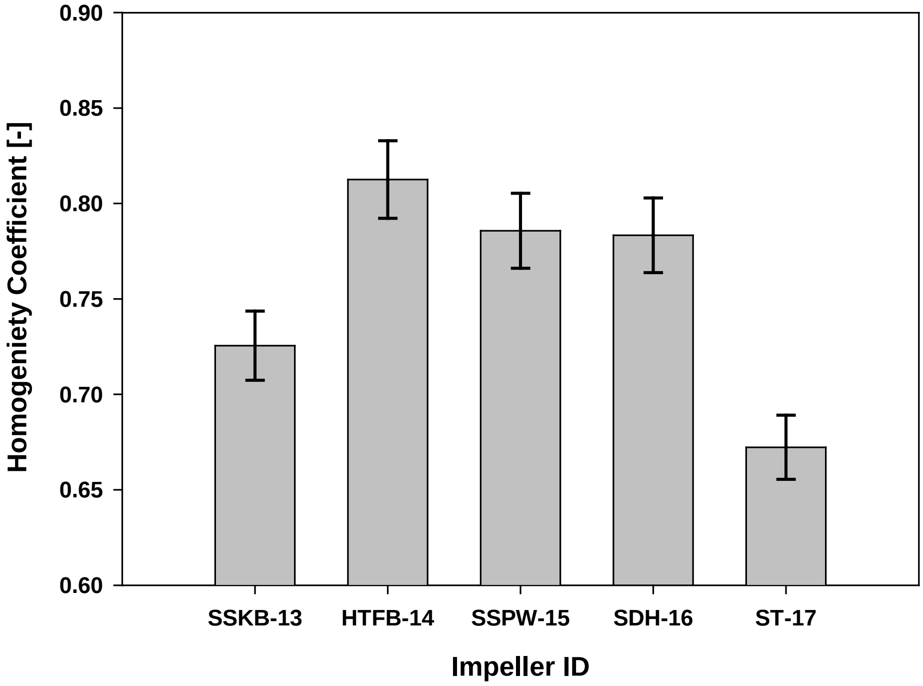


Fig. 6: Variation of homogeneity coefficient across different sizes for batches produced with different impellers.

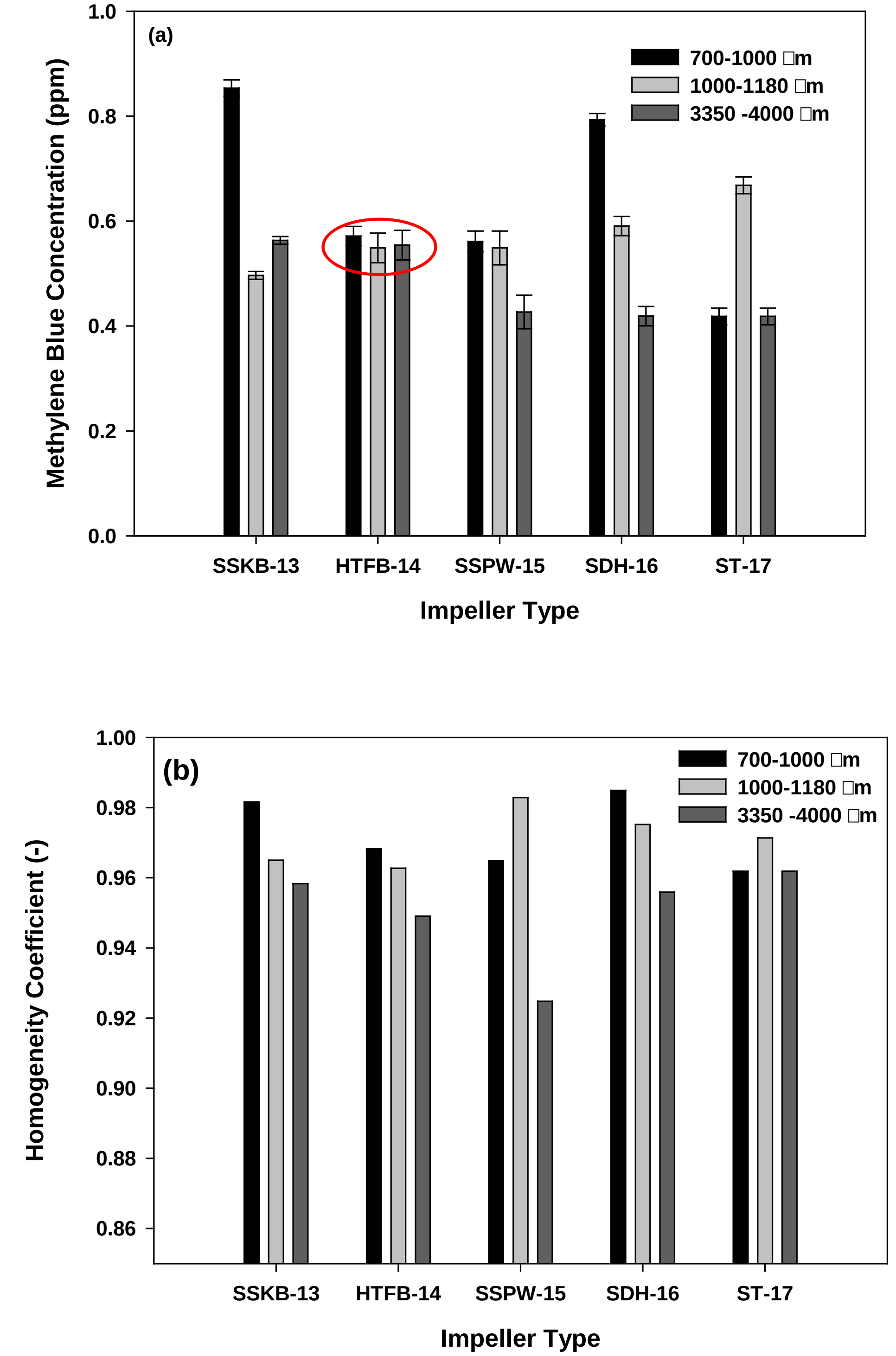


Fig. 7: (a) Methylene blue concentration of granules from different sieve fractions (b) Variation of the granules' homogeneity coefficient with impeller design.

Kruskal-Wallis One Way Analysis of Variance on Ranks Friday, February 22, 2013, 09:59:18

Data source: Data 2 in Notebook1

Group	N	Missing	Median	25%	75%
SSKB-13	25	0	0.686	0.418	0.896
HTFB-14	25	0	0.571	0.344	0.994
SSPW-15	25	0	0.998	0.679	1.563
SDD-16	25	0	0.621	0.350	0.870
ST-17	25	0	0.492	0.321	0.655

H = 15.242 with 4 degrees of freedom. (P = 0.004)

The differences in the median values among the treatment groups are greater than would be expected by chance; there is a statistically significant difference (P = 0.004)

To isolate the group or groups that differ from the others use a multiple comparison procedure.

All Pairwise Multiple Comparison Procedures (Student-Newman-Keuls Method) :

Comparison	Diff of Ranks	q	P<0.05
SSPW-15 vs ST-17	928.000	5.123	Yes
SSPW-15 vs HTFB-14	759.000	5.232	Yes
SSPW-15 vs SDD-16	683.000	6.268	Yes
SSPW-15 vs SSKB-13	620.000	8.506	Yes
SSKB-13 vs ST-17	308.000	2.123	No
SSKB-13 vs HTFB-14	139.000	1.276	Do Not Test
SSKB-13 vs SDD-16	63.000	0.864	Do Not Test
SDD-16 vs ST-17	245.000	2.248	Do Not Test
SDD-16 vs HTFB-14	76.000	1.043	Do Not Test
HTFB-14 vs ST-17	169.000	2.319	Do Not Test

Fig. 8: Statistical analysis of the granule strength data from batches produce with different impellers.

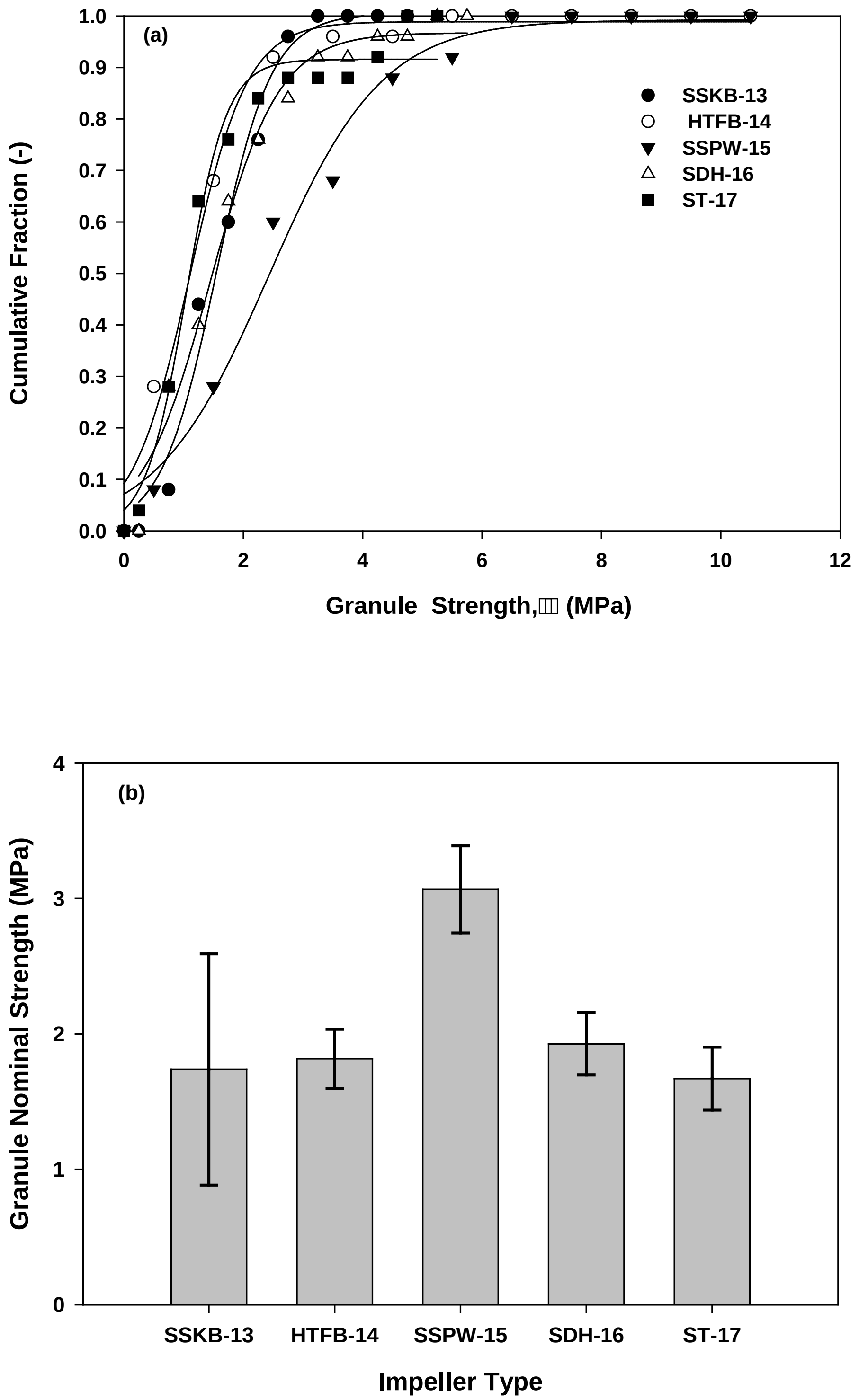


Fig. 9: Effect of impeller type on the strength of the granules.

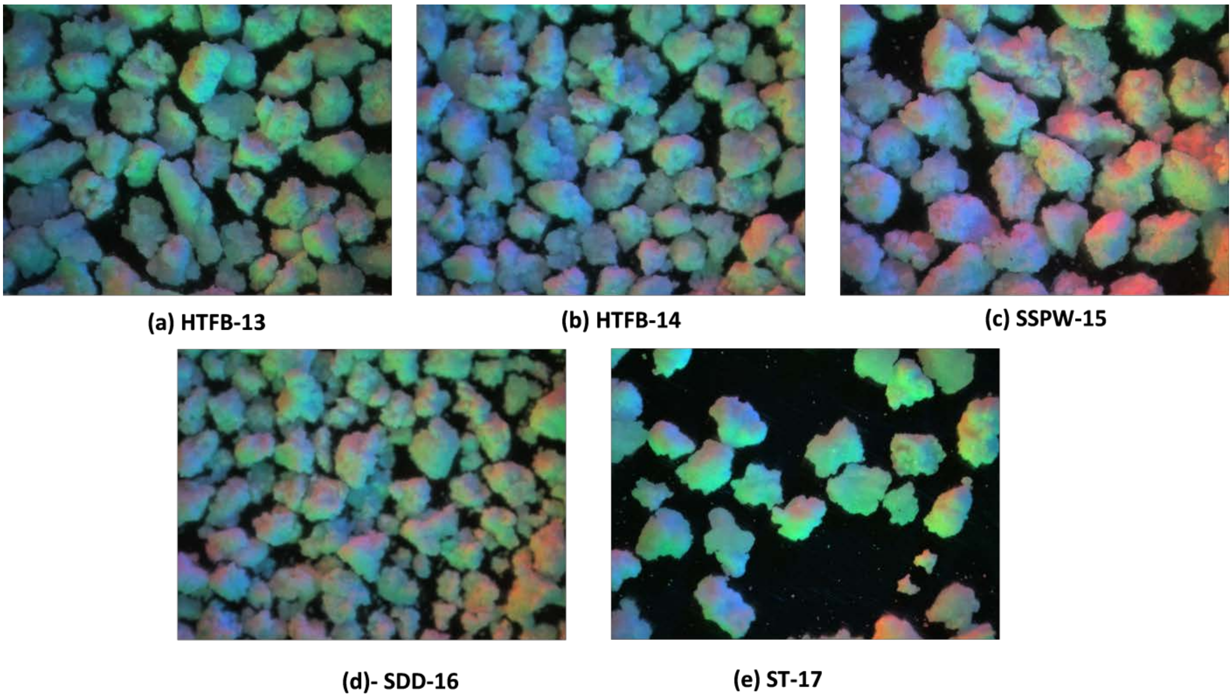


Fig. 10: Images showing the shape and structure of the granules from different batches produced using different impellers.

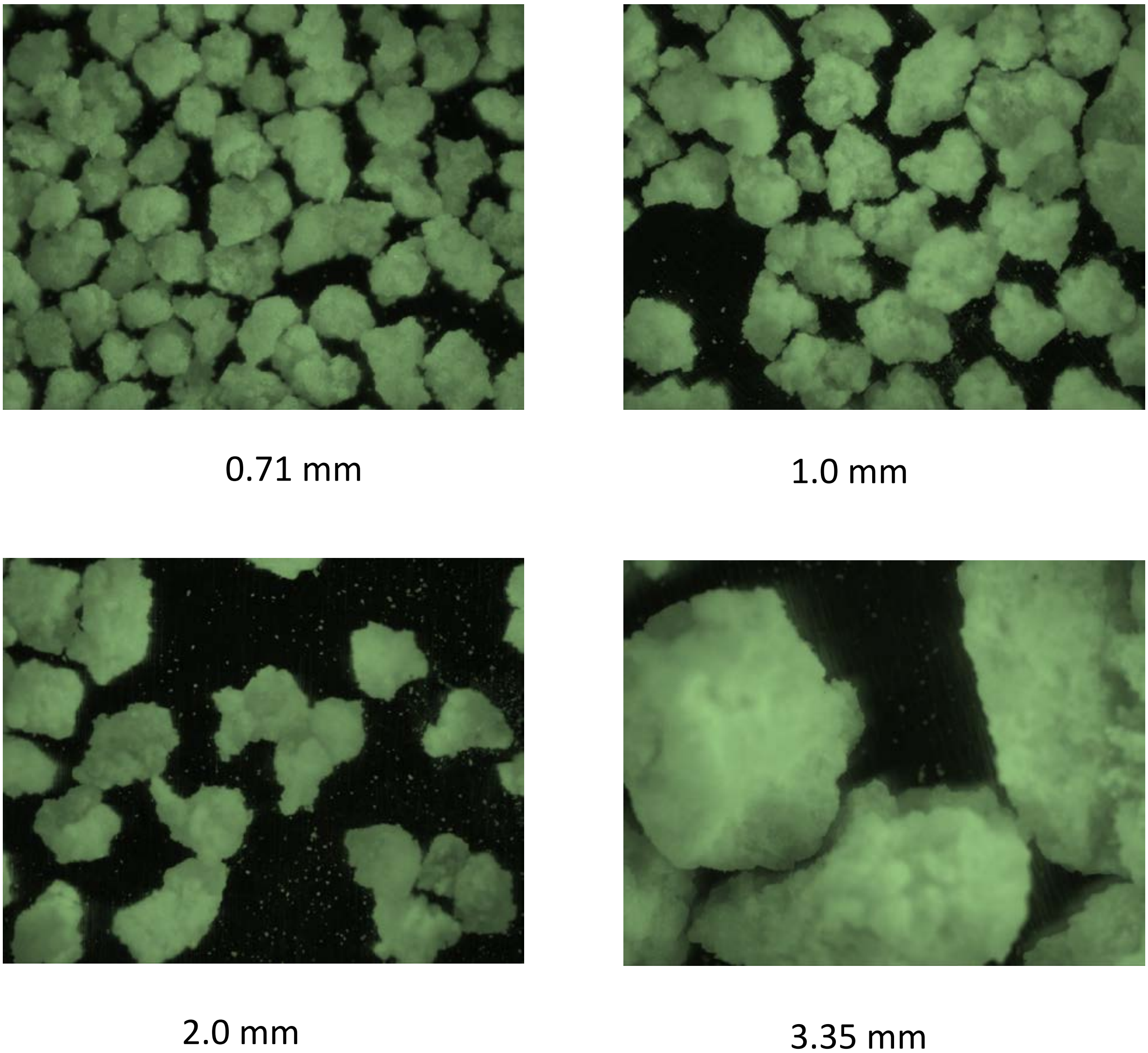


Fig. 11: Images showing the shape and structure of the granules of different sizes from the same batch

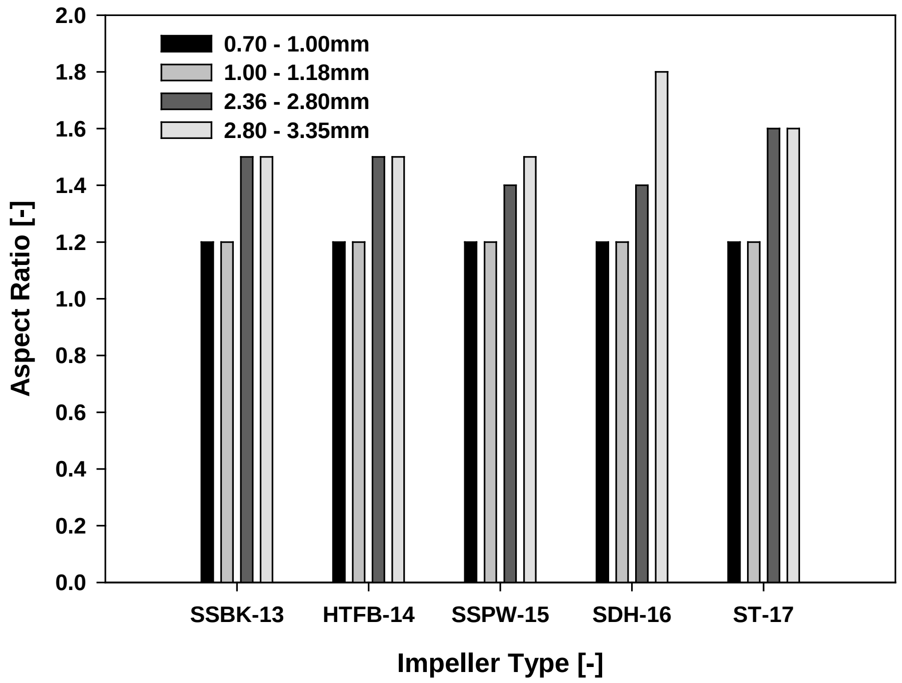


Fig. 12: Effect of impeller design on the aspect ratio of granules of different sizes.