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Research paper

An investigation into the impact of key process variables on the uniformity of powder blends containing a low-dose drug in a gentle-wing high shear mixer

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ABSTRACT

Manufacture of low-dose tablet products has always the uniformity challenge. The objective of this work was to investigate the influence of key process variables of a gentle-wing high shear mixer on the uniformity of 1.0% w/w albuterol sulphate/microcrystalline cellulose blend. Albuterol sulphate and excipients were mixed at various impeller and chopper speeds from 0.5 to 30 min. Triplicate samples were taken from nine different positions in the mixer bowl and the albuterol content was analyzed spectrophotometrically. Long mixing time (15 min) was necessary to achieve proper blend uniformity at low speeds of impeller and chopper. Otherwise, when the high chopper speed was applied, demixing occurred after 8 min with low impeller speed and after 6 min with high impeller speed. Furthermore, ANOVA analysis indicated the significant effect ($P \leq 0.05$) of impeller speed and mixing time on the uniformity of the powder blends. Finally, dry mixing of low-dose based formulations in a gentle-wing high shear mixer; improving the dispersion of drug particles and formation of stable interactive mixture upon suitable selection of process variables. This study make the process variables of gentle-wing mixer a better candidate for further investigation and optimization using quality by design approach.

1. Introduction

In the last few decades, the formulation of low-dose tablet products has been increasingly developed [1]. From a formulation prospective, the British Pharmacopeia (BP) defined low-dose formulation as those formulations "containing less than 2 mg or 2% drug loading (w/w) of active pharmaceutical ingredients (API) [2,3]. According to the previous definitions, low-dose formulation has a relatively huge ratio of excipients to drug substance, which represent many obstacles during formulation and process development. Consequently, the manufacturing of low dose tablet formulations could be a challenging task due to (1) difficulty in obtaining proper content uniformity i.e. the level of uniformity in the quantity of the drug substance in each unit, which is the most quality attributes to produce effective and safe dosage unit; (2) low potency due to loss of drug during manufacturing process and (3) potential lack of stability due to the higher ratio of excipients to active substance and thus a probable loss of compatibility [4–6].

The direct compression is the straightforward method for tablet manufacturing. Generally, the main steps of direct compression method consist of mixing and tableting, which has advantages like simple process validation, stability, cost effective process and relatively rapid dissolution [7]. However, at lower drug doses, achievement of proper content uniformity might be decreased [8,9]. Accordingly, direct compression of low dose tablet formulations needs a particular care. Powder mixing is the critical step before tableting, which produces a uniform blend to be compressed into tablets [10,11]. A direct compression-manufacturing platform displays clear challenges for product content uniformity, as well as for achieving and conserving a uniform blend. Thus, this platform needs a crucial approach for excipients selection, powder mixing, and in-process control [11]. Without delicate estimation, failures are highly potential, particularly in manufacturing of low-dose drug product [12].

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To overcome the problems of content uniformity and provide dosage units within the acceptance criteria the wet granulation process is generally utilized [13,14]. In the pharmaceutical industry, wet granulation method is the most common granulation process and extensively utilized in production of tablets [15]. Wet granulation is a superior method for production of oral solid dosage forms with high-dose drugs of poor compressibility and poor flow properties, as well as for dosage units containing extremely potent, low-dose drugs [16,17]. In addition, wet granulation encompasses a wide range of technologies and equipment including high shear granulators with an impeller and chopper blade, blenders with a liquid dispersion bar and fluid beds with top or bottom spray [13]. Recently, high-shear granulators are widely applied in the pharmaceutical industry [18]. In these type of granulators, powders are added either previously mixed or they can be mixed in the granulator before wet granulation [19]. Although the mechanical agitation during the wet granulation step itself may enhance the uniformity of the active substance in the granulation, the uniformity of the drug substance in the powder blend before wet granulation remains very critical [20].

The mixing step may be simple, including mixing of the drug with all or most of the excipients in a convenient blender like V-blender. However, removal of the pre-blending step may minimize any potential loss of drug during mixing or during the transfer of powder blend to the granulator bowl [21]. Thus, blending of drug and excipients in high shear mixer bowl before granulation step is preferred. However, the process parameters during powder mixing in the high shear mixer-granulator need to be investigated [20].

From the aforementioned literature point of view, it could be concluded that whether the low dose drug formulation is made into tablets by direct compression or by granulation, the investigation of the uniformity of drug content in the powder mix is of paramount importance [22,23]. Up To date in the literature, only Kornchankul et al., 2000, have carefully studied the influence of process variables (impeller speed, chopper speed and mixing time) of conventional high shear mixer with three-blade impeller on mixing uniformity of buspirone HCl powder blends. They found that the process variables of high shear mixer have a significant impact on uniformity of the powder blend [24].

Gentle-wing high shear mixer-granulator is a new mixing technology in which the conventional three-blade impeller substituted with a novel two-blade impeller with elongated wings as shown in Fig. 1 [19,25]. Consequently, segregation problem that caused by high dynamic forces of classical high shear mixers are minimized as the gentle-wing's regularly distribute the energy of mixing at lower speeds and a higher torque through the mixer bowl as well as the product [21,25]. However, the influence of process variables on powder blend uniformity through dry mixing stage using gentle-wing mixer/granulator has not yet been studied.

Thus, the aim of this study was to investigate the influence of process variables like impeller speed, chopper speed and mixing time of a gentle-wing high shear mixer on uniformity of powder blend containing a low-dose drug during the dry mixing step. The second aim was determination of the optimum process conditions required to provide acceptable content uniformity for low-dose tablet formulations. In the present study, micronized albuterol sulphate has been chosen as a low-dose model drug.

2. Materials and methods

2.1. Materials

Micronized albuterol sulphate, USP, was obtained as gift from Riyadh Pharmaceutical Company, (Riyadh, Saudi Arabia). Microcrystalline cellulose (Avicel PH 101®) and croscarmellose sodium (Ac-Di-Sol®) were kindly donated from FMC biopolymer (Cork, Ireland). Povidone (Kollidon 30®) was purchased from BASF Co. (Ludwigshafen, Germany), and magnesium stearate was purchased from Riedel-de Haen (Seelze, Germany). Hydrochloric acid (37%) was purchased from Fisher Scientific, (Fair Lawn, NJ. USA).

2.2. Methods

2.2.1. Particle size analysis

Laser light scattering method was carried to measure the particle size of albuterol sulphate and microcrystalline cellulose using Mastersizer 2000, with a Scirocco dry disperser (Malvern Instruments Ltd., UK). Samples (5–6 g) were air dispersed at an inlet air pressure of 3 bars and a feed-rate of 10%. Obscuration preserved between 0.6 and 6%.

2.2.2. Experimental design

According to the preliminary experiments and the previously reported by Kornchankul et al., 2000 [24], a two speed increments of both impeller and chopper were chosen for the study; low impeller speed (100 rpm), high impeller speed (300), low chopper speed (1000 rpm), and high chopper speed (3000 rpm). With respect to the levels of impeller and chopper speeds, four experimental trials were designated. The full matrix of experiments is shown in Table 1. Mixing time was selected in order to recognize insufficient to extensive mixing (zero −30 min of mixing). The zero time point represents a baseline and no mixing condition. The response variable of study was the content uniformity of the powder blend sampled from various locations at different time points for each mixing experiment.

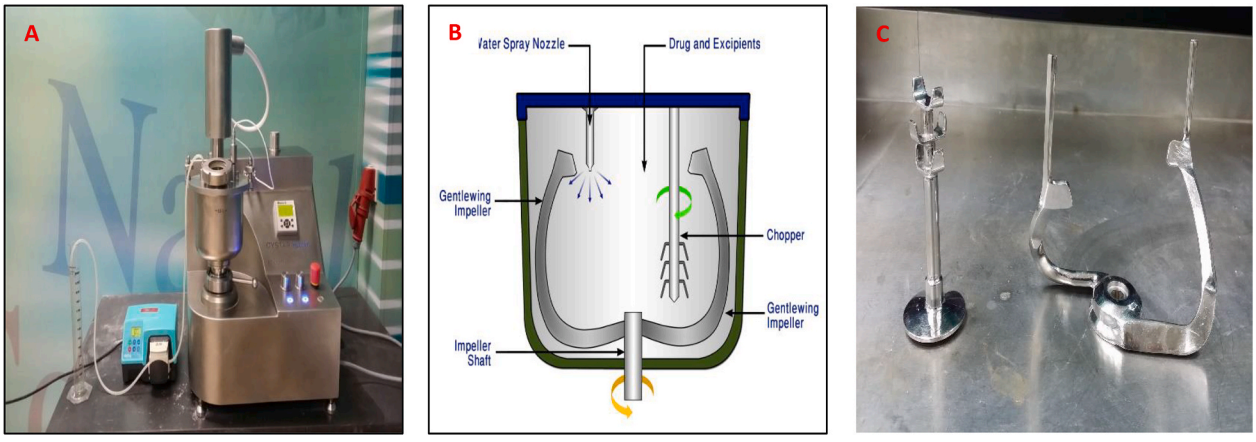

Fig. 1. (A) A 2-L laboratory scale gentle-wing high shear mixer (B) Schematic diagram for laboratory scale gentle-wing high shear mixer (C) Gentle-wing impeller and chopper (25).

Table 1
Matrix design for investigation of process variables of gentle-wing high shear mixer.

Experiments	Mixing conditions	Mixing time	Sample locations*
1	Low impeller – Low chopper (100 rpm) (1000 rpm)	0.5, 1, 2, 4, 6, 8, 10, 15, 30	1, 2, 3, 4, 5, 6, 7, 8, 9
2	High impeller – Low chopper (300 rpm) (1000 rpm)	0.5, 1, 2, 4, 6, 8, 10, 15, 30	1, 2, 3, 4, 5, 6, 7, 8, 9
3	Low impeller – High chopper (100 rpm) (3000 rpm)	0.5, 1, 2, 4, 6, 8, 10, 15, 30	1, 2, 3, 4, 5, 6, 7, 8, 9
4	High impeller – High chopper (100 rpm) (1000 rpm)	0.5, 1, 2, 4, 6, 8, 10, 15, 30	1, 2, 3, 4, 5, 6, 7, 8, 9

2.2.3. Preparation of sample blends

Table 2 showed the composition of formulation used in this study. The drug as well as excipients were carefully weighed using an electronic analytical balance with an accuracy of 1: 10.000 and transferred into the mixer bowl (Huttlin mycromix, BOSCH Packaging Technology, Schopfheim, Germany). The materials were added to the mixer bowl in the following order: microcrystalline cellulose, polyvinylpyrrolidone, albuterol sulphate, and croscarmellose sodium that correspond to approximately a 50% vessel filling level. The materials were blended in the mixer according to the design points shown in Table 1. For each trial, the ingredients were blended at the fixed impeller (100 or 300 rpm) and chopper speeds (1000 or 3000 rpm) for 0.5,1, 2, 4, 6, 8, 10, 15, and 30 min. At the end of the mixing period, the blend was sampled at nine distinct locations from three parts of the mixer, each part represents one-third of the mixer bowl. According to Fig. 2, location 1, 4, and 7 represent the center of the blend. Locations 2, 5, and 6 represent the blend behind the impeller blade. Locations 3, 8, and 9 represent the blend in front of the impeller blade. A 1 ml unit side-sampling thief probe (Sampling systems Ltd., Coleshill, UK) was utilized for sampling and care was taken so as not to disturb the powder bed. The samples were carefully extracted from 3 layers of the powder blend, 3 samples from top (about 3–4 mm from the surface of the powder bed), 3 from middle (about 7.5 cm) and 3 from bottom (about 15 cm). To avoid any form of bias in the results; the protocol of sampling was kept the same for all experiments. The extracted samples were stored in glass vial and analyzed for the drug content using the method mentioned in section 2.2.4.

2.2.4. Sample analysis

Albuterol sulphate in the extracted samples was analyzed according to method reported in British Pharmacopeia [26]. Each extracted sample was carefully weighed and transferred into separate volumetric flasks containing 0.1 N HCI. After that, the volumetric flasks were sonicated for 15 min and shaken using water bath shaker for 30 min. Volume of 25 ml was then completed using 0.1 N HCI. The content was filtered through 0.45 μm membrane filters; the produced clear solution was then analyzed using UV spectrophotometer (Shimadzu, UV-1800, Japan) at λ_{max} of 276 nm. A standard curve was constructed using pure albuterol sulphate diluted to eight known concentrations (10–80 μg/ml). Triplicate measurements were carried out to prove accurate analysis of albuterol sulphate.

Table 2
The composition of formulation used in the dry mixing study.

Ingredients	%w/w	Weight (g)
Albuterol sulphate, USP	1	3
Microcrystalline cellulose (Avicel PH 101®)	93	279
Croscarmellose sodium (Ac-Di-Sol®)	1	3
Polyvinypyrrolidone (Kolidon 30®)	5	15
Total	100	300

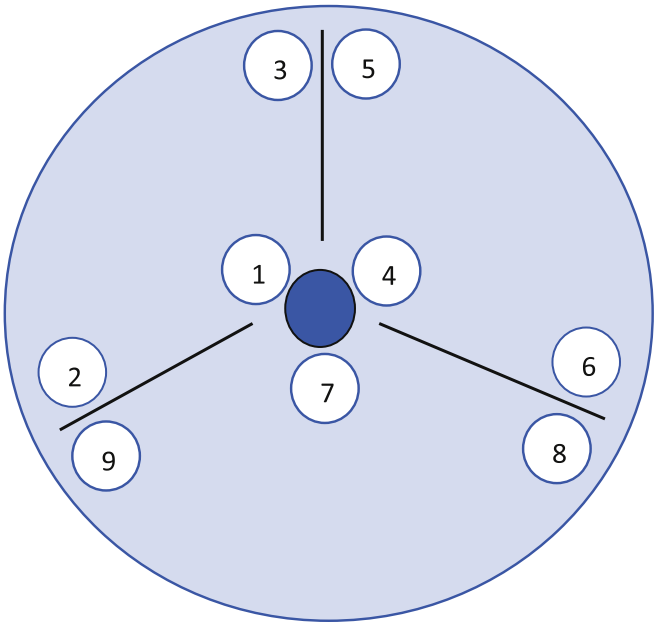

Fig. 2. Schematic view from the top of the bowl of gentle-wing high shear mixer. The numbers show the locations where the samples have been extracted (location radius is approximately 1.5 cm).

2.2.5. Validation of analytical method

The UV-spectrophotometric analytical method was validated for its analytical performance characteristics including accuracy and precision. The accuracy of the analytical method was determined by application of the proposed analytical method to samples of the drug and excipients to which 80, 100 and 120% of the normal levels expected in the samples had been added. The accuracy was calculated as the percentage of the drug recovered from the formulation matrix.

The precision of the analytical method was measured in terms of reproducibility, intermediated precision and repeatability. Reproducibility was determined by analyzing the sample in different laboratories. The intra and inter day precision was investigated by analyzing the sample on the same day and on different days at different time interval, respectively. Repeatability was carried out by analyzing sample ten times, at 100% of test concentration within the same day. The precision was calculated as the relative standard deviation (RSD) for different measurements.

2.2.6. Uniformity analysis

Relative Standard Deviation (RSD) is the most usual uniformity index utilized in the pharmaceutical industry. To indicate the extent of mixing uniformity; the RSD of albuterol sulphate content was plotted against mixing time. The comparison of those curves shows qualitative approach to indicate the impact of specific mixer on blend uniformity [27,28]. According to the previous study, the level between 90.0 and 110.0% of the label claim with RSD $\leq$5% was taken as a standard for the current study [21].

2.2.7. Preparation of tablets

Powder blend with stable and acceptable uniformity was accurately weighed and mixed with 1% m/m magnesium stearate in 3D Turbula mixer (type S27, Erweka, Apparatebau, Germany) for 2 min. The lubricated blend was compressed using RoTap rotary tablet press (Kg pharma, Berlin, Germany) into 100 mg tablets at compression force of 10 KN using 7 mm standard flat tooling. The produced tablets were randomly sampled at the beginning, middles and toward the end of the compression run. The beginning of the compression run was considered when tablet weight and compression force were established (5 min after start of compression run). The middle of the compression run was

considered at 10 min after establishing the compression conditions. The end of the compression run was considered when the blend was approximately emptied from the hopper of the tablet machine (10 min after the middle run tablets were collected). The produced tablets were collected and stored for analysis of drug content using the method described in section 2.2.4.

2.2.8. Statistical analysis

All obtained results were statistical analyzed using GraphPad Prism 5.01 software package (GraphPad Inc., California, USA). The results were analyzed using analysis of variance (ANOVA) with a post-hock Tukey test. The statistical significance level was set at $P \leq 0.05$.

3. Results and discussion

3.1. Particle size investigation of ingredients

Albuterol sulphate and microcrystalline cellulose showed a mean particles size of 16.24 ± 0.023 and 59.12 ± 0.031 μm, respectively. Due to micrometer size of albuterol sulphate, their particles demonstrated strong tendency to form agglomerates with large size distribution. Thus, the breakdown of albuterol sulphate agglomerates is the rate-limiting step of mixing process of powder blend [6,29].

3.2. Validation of analytical method

The UV-spectrophotometric analytical method for the analysis of albuterol sulphate was validated to be convenient for the use in determination of albuterol content. The mean percentage of recovery was found to be 100.6% and RSD of 0.4%. The proposed analytical method showed good reproducibility, intermediated precision and repeatability. The RSD values were 1.4% (The assay in different laboratories), 0.5% (intra-day) and 0.9% (inter-day) indicating high precision of the method.

3.3. Effect of impeller and chopper speeds on mixing uniformity of the albuterol sulphate blend

Figs. 3 and 4 showed the effect of impeller and chopper speeds on the uniformity of 1.0% w/w albuterol sulphate blend with regard to mixing time. At low impeller (100 rpm) and low chopper (1000 rpm) speeds, a RSD of less than 5.0% was achieved after 15 and 30 min of mixing as shown in Fig. 3. This indicating that the forces produced by the low

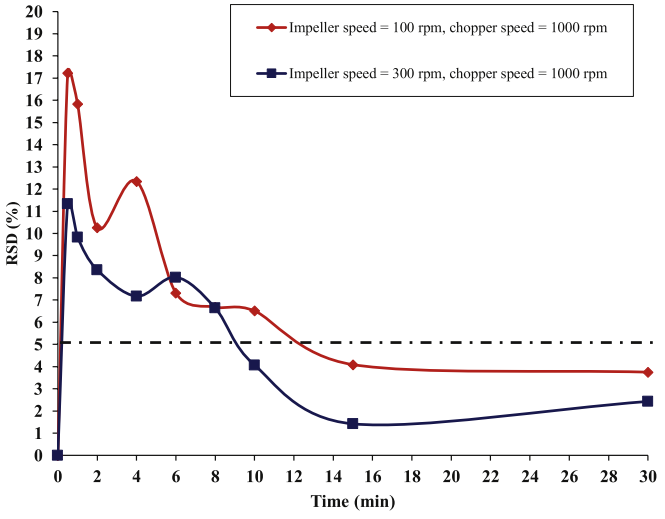

Fig. 3. Effect of impeller speed and mixing time on mixing uniformity of 1% w/w albuterol sulphate blend at low chopper speed.

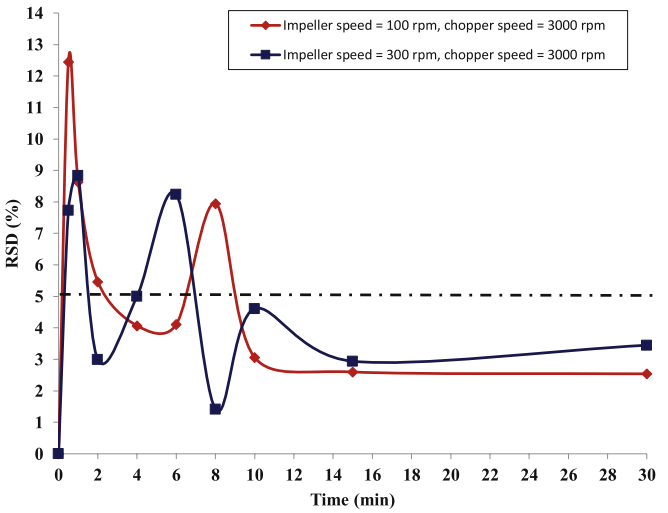

Fig. 4. Effect of impeller speed and mixing time on mixing uniformity of 1% w/w albuterol sulphate blend at high chopper speed.

speeds of impeller and chopper were insufficient to overcome the particle surface energies to bring about mixing uniformity at initial mixing time prior to 15 min of mixing [24]. Thus, long mixing time (15 min) was necessary to achieve proper blend uniformity when low speeds of impeller and chopper were applied. In case of high impeller and low chopper speeds of 300 and 1000 rpm, respectively a RSD of less than 5.0% was attained after 10 min of mixing. In this case equilibrium between de-mixing (segregation) and mixing was achieved as well as improvement in the state of mixing with increasing impeller speeds, which lead to improvements in the overall uniformity of the powder blend [30]. Furthermore, with increasing impeller speeds the extent of de-mixing decreases, as percolation of minor components reduced with increasing the rotation rates. This might be attributed to exposing powder blend to a higher centrifugal force in comparison to the gravitational force that reduces the percolation of minor ingredients [30].

On the other hand, with low impeller and high chopper speeds of 100 and 3000 rpm, respectively a RSD of less than 5.0% was achieved after 4, 6 and 10 min of mixing as depicted in Fig. 4. In addition, a RSD of less than 5.0% was achieved after 2 and 8 min of mixing with high impeller (300 rpm) and high chopper (3000 rpm) speeds as shown in Fig. 4. These results suggested that, when the high chopper speed was applied, a decrease in the RSD with an increase in mixing time was followed by an increase in the RSD after 8 min of mixing with low impeller speed and after 6 min of mixing with high impeller speed as demonstrated in Fig. 4. The increase in the RSD could be attributed to the de-mixing caused by an interrupted flow of the powder bed and formation of electrostatic charges on the particle surface due to high-speed chopper [24]. Moreover, during the extreme mixing, the difference between components particle size may have contributed to the preferential particle movement due to the centrifugal force moving large particles to the outer perimeter of the mixer bowl. For high shear mixer, it was reported that, the smaller particles settled to the bottom, while the larger particles drifted to the surface of the powder bed. This is attributed to the commonly known phenomenon called sieving segregation or inter-particle percolation or Brazilian nut effect, where small particles fill inter-particle spaces generated in shear region, forcing less mobile large particles to rise [30–32]. Additionally, de-agglomeration of albuterol sulphate agglomerates due to high speed of chopper may also have participate to the sudden increase in variation of albuterol sulphate content followed by relatively steady in albuterol sulphate content. It was reported that the rate of de-agglomeration depends on the speed of the mixer during random mixing [33]. After a transient alteration from random to ordered mixing, the rate of de-agglomeration was not impacted by a change in mixer speed [33]. Overall, as shown in Figs. 3 and 4, the RSD

values of all mixing situations were lower than 5.0% after 15 min of mixing indicating that after all drug agglomerates were fragmented; the RSD values were relatively unchanged as mixing time increased.

3.4. Effect of impeller speed, chopper speed and mixing time on content uniformity of albuterol sulphate

The drug content of powder blend was found to be within the limit (90–110%) of theoretical claim after long mixing time (30 min) as shown in Figs. 5–8. At low speeds of impeller and chopper, the uniformity of drug content was attained after 15 and 30 min of mixing with values of (Average = 96.9%, Range = 98.9–102.2%) and (Average = 99.05%, Range = 92.3–104.4%) of theoretical claim respectively as shown in Fig. 5. The same result was observed with low impeller and high chopper speeds since the proper content uniformity was produced after 15 (Average = 98.2%, Range = 94–106.3%) and 30 (Average = 98%, Range = 95.6–101.4%) minutes as shown in Fig. 6. With high impeller and low chopper the uniformity of drug content was achieved at shorter time of mixing, at 2 (Average = 96.5%, Range = 91.8–109.2%), 4 (Average = 93.6%, Range = 92.1–99.9%), 8 (Average = 97.7%, Range = 92.6–110.5%), 15 (Average = 98.3%, Range = 95–99.6%) and 30 min (Average = 99.2%, Range = 95.8–100.4%) as shown in Fig. 6. In addition, with high impeller and chopper speeds the content uniformity was achieved after 2 (Average = 99.02%, Range = 95.3–104.4%), 4 (Average = 99%, Range = 99.8–106%), 8 (Average = 100.6%, Range = 94. 4–104.8%), 10 (Average = 98.4%, Range = 91.8–104.7%), 15 (Average = 97.8%, Range = 93.3–103.5%) and 30 (Average = 98.7%, Range = 98.3–102.3%) minutes of mixing as shown in Fig. 8.

As shown in Table 3, the statistical analysis indicated that the impeller speed and mixing time had significant ($P \leq 0.05$) effects on content uniformity of albuterol sulphate. In addition, ANOVA analysis of data of comparable sampling locations showed that there was not a statistically significant difference between the mean albuterol sulphate content for the studied mixing times (results of ANOVA is too long and not shown). This results demonstrating that the gentle-wing mixer has a high mixing efficiency and provides a proper content uniformity for low dose drug formulations during the dry mixing step. Furthermore, the locations in each section of the mixer bowl were comparable to locations in the other section of the mixer bowl.

Based on the previous results, to achieve stable and acceptable content uniformity with low RSD, the powder blend of albuterol sulphate should be mixed in gentle-wing mixer with high impeller and high chopper speeds for 8 min to overcome the de-mixing stage that occurred after 4 and 6 min of mixing due to the agglomeration of albuterol

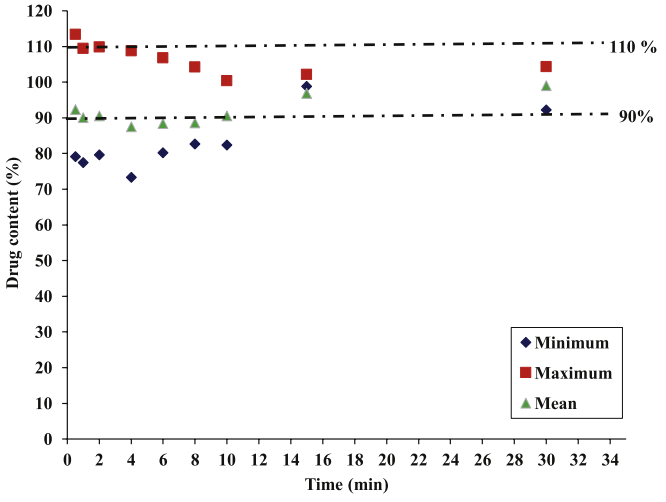

Fig. 5. Effect of mixing time on percentage drug content of 1% w/w albuterol sulphate blend at low impeller and low chopper speed.

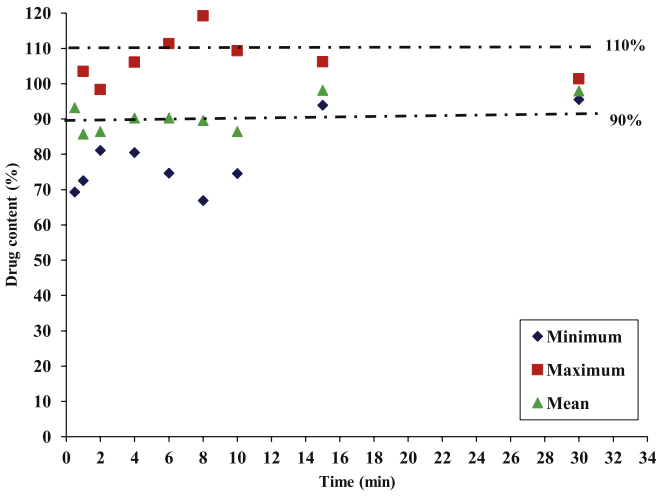

Fig. 6. Effect of mixing time on percentage drug content of the 1% w/w albuterol sulphate blend at low impeller and high chopper speed.

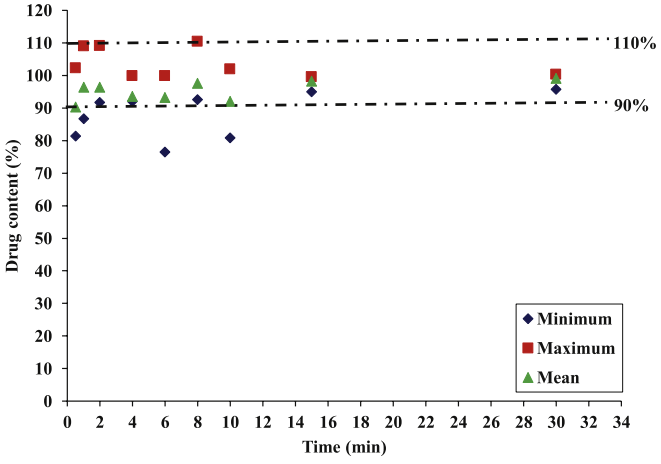

Fig. 7. Effect of mixing time on percentage drug content of the 1% w/w albuterol sulphate blend at high impeller and low chopper speed.

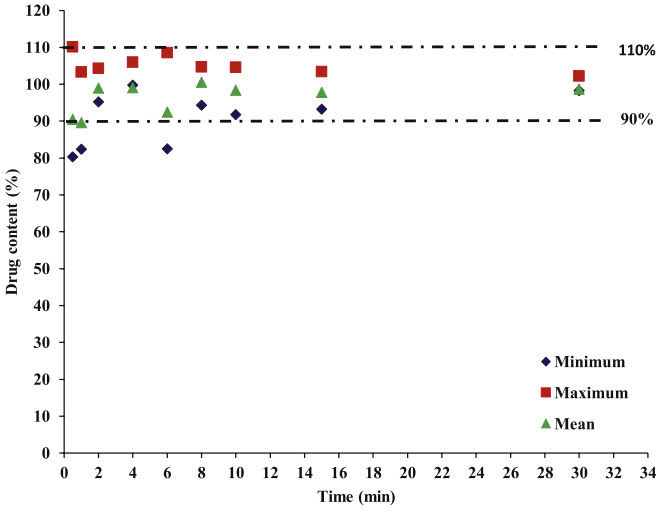

Fig. 8. The effect of mixing time on percentage drug content of the 1% w/w albuterol sulphate blend at high impeller and high chopper speed.

Table 3
Effect of impeller speed, chopper speed, and mixing time on mixing uniformity of 1 %w/w albuterol sulphate blends.

Variables	DF	SS	MS	F-value	P-value
X_1	4	170.63	0.96	23.12	<0.0001*
X_2	4	3.72	0.96	4.56	0.339
X_3	4	167.53	0.96	21.65	<0.0001*

X_1 = impeller speed; X_2 = Chopper speed; X_3 = Mixing time.
DF = Degree of Freedom; SS = Sum of Squares; MS = Mean Square.
* Statistically significant at $P \leq 0.05$ using ANOVA test.

Table 4
Influence of blend uniformity on content uniformity of prepared tablets at high impeller speed (300 rpm), high chopper speed (3000 rpm) and mixing time of 8 min.

Compression stage	Mean (%)	Min-max (%)	RSD (%)
End of mixing	100.6	94.4–104.8	1.42
Beginning of compression	99.4	94.2–103.4	2.36
Middle of compression	98.7	93.4–103.6	2.75
End of compression	102.3	98.1–101.7	1.23

sulphate. As previously mentioned, during dry mixing step and after 8 min there is a transient change from random mixing to ordered mixing. Once the ordered mixing has been attained, the de-agglomeration of the drug reach to steady state and not influenced by alteration in the mixer speed.

3.5. Influence of blend uniformity on content uniformity of prepared tablets

The powder blend prepared at high impeller speed and high chopper speed for 8 min was selected to be compressed into tablets as this condition provide stable and acceptable uniformity as previously discussed. As shown in Table 4 the drug content of prepared tablets was within the limit of 90–110% of the theoretical label claim and the RSD values were less than 5.0% through beginning, middle and end of tableting process. Specifically, the tablets collected at the beginning of compression run displayed a high RSD (2.36%) compared to RSD (1.42%) of powder blend at end of mixing. This could be attributed to segregation and damage to the structure of the blend during discharge or potential interaction between drug and the stainless steel hopper of tablet machine due to electrostatic charge or flow problems [21,34]. Besides, at the end of compression run the RSD of collected tablet was decreased from 2.36% to 1.23%. This might be attributed to improve the flow of powder blend due to shaking and intermittent tapping of the hopper, which help in breaking powder bridges and allowed a better powder flow from the hopper into tablet dies [21]. Furthermore, the RSD of tablets collected at the end of the compression run was lower than RSD of powder blend at the end of the mixing (1.23% for tablets vs. 1.42% for powder blend). This could be attributed by the fact that, insert the thief probe into static powder bed causes segregation and some disturbances specifically when the potential of the powder to flow into the opening of the thief probe is reduced [35]. This indicated that, the content uniformity of blend samples collected before compression into tablets are not suitable measure of content uniformity of finished products [36]. Thus, sampling process during tableting demonstrate superior content uniformity than the sampling by a unit dose thief probe.

4. Conclusions

Gentle-wing high shear mixer could be considered as an efficient mixer for dry mixing of low-dose based formulations. Therefore, formulation containing low dose drug could be uniformly mixed in gentle-wing high-shear mixer and directly compressed into tablets with acceptable content uniformity with no need for geometric dilution. The content uniformity of powder blend could be improved with accurate selection of key process variables. Thus, the processing variables should be controlled and optimized to avoid the de-mixing phenomenon. This conclusion make the process variables of gentle-wing high shear mixer a better candidate for further investigation and optimization using quality by design approach.

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Declaration of interest

The authors report no declarations of interest.

CRediT authorship contribution statement

Mohamed H. Fayed: Writing - original draft, Formal analysis, Conceptualization, Funding acquisition. **Sayed I. Abdel-Rahman:** Writing - original draft, Writing - review & editing, Formal analysis, Funding acquisition, Conceptualization. **Fars K. Alanazi:** Writing - original draft, Writing - review & editing, Formal analysis, Conceptualization, Funding acquisition. **Mahrous O. Ahmed:** Writing - original draft, Writing - review & editing, Formal analysis. **Hesham M. Tawfeek:** Writing - original draft, Writing - review & editing, Formal analysis, Conceptualization, Funding acquisition.

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