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Effect of drug proportion and mixing time on the content uniformity of a low dose drug in a high shear mixer

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The purpose of this study was to investigate the effect of reducing drug proportion and mixing time on the content uniformity of a low dose drug. Buspirone hydrochloride was used as a model drug and was mixed with other ingredients in two different concentrations (0.5% w/w and 5% w/w) in a T. K. Fielder high shear mixer at a high impeller speed (522 rpm) and a high chopper speed (3600 rpm) up to 32 min. Samples were withdrawn from nine locations in the mixer at specific time points using a side-sampling thief probe. The final blends at 32 min were compressed using an instrumented tablet press. Tablets were sampled at the beginning, middle, and end of the compression run. The statistical results indicated that the drug proportion had a significant effect on the content uniformity of the powder blend and the corresponding tablets. For this study, the optimum time to mix the 0.5% w/w formulation was after 8 min while it was only 1 min for the 5% w/w formulation. The RSD of buspirone hydrochloride contents of tablets decreased as the compression run was toward its end. Uniformly mixed blends produced tablets that met the USP XXIV content uniformity requirements.

1. Introduction

Mixing of low dose drugs has recently gained more attention in the pharmaceutical industry. Due to the increasing number of drugs used in a very low dose, the concept of content uniformity upon mixing such low dose drugs becomes very crucial [1]. The FDA has recently distributed new draft guidance for industry concerning the blend uniformity analysis. In the draft guidance, the blend uniformity acceptance criterion was narrowed down from the USP XXIV level between 85.0 and 115.0% of the label claim with the relative standard deviation (RSD) of less than or equal to 6.0% to the level between 90.0 and 110.0% of the label claim with the RSD of less than or equal to 5.0% [2]. Two major problems encountered in mixing low dose drugs include segregation and the inability of the mixer to break down drug agglomerates. The formulator main goal in solid-solid mixing is to obtain uniformly mixed ingredients with no subsequent demixing or segregation. In general, segregregation and demixing occur in the mixing of ingredients having different particle sizes, particle size distributions, densities and shapes [3–5].

Mixture homogeneity is not only affected by the mechanical action of the mixer but also the interaction between drug and diluent particles. A change in drug proportion in formulations influences the interaction between drug and diluent particles. Since diluent selection is not always based on content uniformity considerations, a highly efficient mixer that can mix ingredients of different properties is needed especially when one or two of the ingredients are used in low proportions. High shear mixers are expected to be very efficient for mixing low dose drugs as the high-speed chopper break down drug agglomerates and help in distributing the drug throughout the mixture.

The purpose of this study was to investigate the effect of decreasing the drug proportion on the content uniformity during solid-solid mixing in a high shear mixer and during the compression process by applying both the USP XXIV and the FDA draft guidance for industry acceptance criteria. The purpose was also to evaluate the feasibility of T. K. Fielder high shear mixer in mixing low doses of buspirone hydrochloride in microcrystalline cellulose based formulations.

2. Investigations, results and discussion

2.1. Micromeritic properties

The bulk density of powders depends on the particle size distribution, particle shape, and tendency of particles to adhere to one another. As seen in Table 1, both buspirone hydrochloride (buspirone HCl) and microcrystalline cellulose have similar bulk densities, which decreases the tendency for segregation given that the two materials have similar particle sizes.

For uniform mixing to be achieved, both particle size and particle size distribution of the different ingredients must be controlled to avoid segregation and demixing problems [8–10]. The difference in particle sizes between different ingredients determines the type of mixing. Random mixing is usually formed when the ingredients have similar particle sizes while ordered mixing is formed when one of the ingredients has smaller particle size than the other with subsequent adsorption of the smaller particles on the surface of the large ones [11]. The mean particle size of buspirone HCl as determined by sieve analysis was larger than that recorded by the manufacturer. When the particle size was determined by aerosizer technique, where size of individual particle was measured, a lower mean particle size was obtained which was in good agreement with that recorded by the manufacturer. The results could be attributed to the tendency of buspirone HCl particles to self-ag-

Table 1: Micromeritic properties of the material

Properties	Buspirone HCl	Microcrystalline Cellulose
	Mean (SD)	Mean (SD)
Bulk density (g/cm^3) (n = 3)	0.29 (0.009)	0.30 (0.003)
Tapped density (g/cm^3) (n = 3)	0.48 (0.013)	0.43 (0.004)
Sieve Analysis (n = 3)		
Geometric mean size (μm)	450 (10)	51 (5.5)
Geometric standard deviation	1.67 (0.02)	1.62 (0.01)
Aerosizer technique		
Geometric mean size (μm)	2.22	N/A
Geometric standard deviation	1.99	N/A
Particle shape	Acicular	Acicular

glomerate during sieve analysis that caused the calculated mean particle size to be mistakenly high. Therefore, the mean particle size calculated using the aerosizer technique was considered to be an accurate particle size of buspirone HCl. For microcrystalline cellulose, aggregates were not seen on the sieves and the determined mean particle size was in good agreement with the value recorded by the manufacturer. The difference in particle size between buspirone HCl and microcrystalline cellulose is not expected to cause serious segregation problems especially when the densities of the two materials are similar. Particle shape affects the flow and packing properties of powder as well as the stability of the mixture against segregation [12–14]. Both buspirone hydrochloride and microcrystalline cellulose have acicular particle shape. Since acicular particles tend to prolong the mixing time because of their poor flowability and tendency to bridging, intense mixing is often required to obtain uniform mixing.

2.2. Flowability measurement

Powder flow is a crucial factor for any mixing and compression process. The content uniformity of tablets is highly affected by the flow behavior of the mixture in the feeding hopper. Powder with poor flowability exhibits content uniformity problems due to a non-uniform filling of the dies during compression. The effect of particle shapes on flowability has been reported in the literature [4]. Acicular particles are expected to have flow problems due to their tendency of particles bridging and interlocking. As anticipated, both 0.5% and 5% w/w buspirone formulations failed to pass through the 1-cm opening of the flow instrument. Therefore, it was not feasible to measure the flow rate and angle of repose.

2.3. Effect of drug proportion and mixing time on the content uniformity of powder blends

The relative standard deviation (RSD) was used as a mixing index for this study. Two acceptance criteria from the USP XXIV content uniformity requirements and the FDA draft guidance for industry were applied to evaluate the content uniformity of the mixture. The first criterion (USP XXIV) of acceptable content uniformity required that the drug content lies within the range of 85.0 to 115.0% of the label claim and the RSD value is less than or equal to 6%. The second criterion required that the average drug content lies within the range of 90.0 to 110.0% of the label claim and the RSD value is less than or equal to 5%.

In solid-solid mixing of the two studied formulations as shown in Table 2, it was found that for both formulations, the RSD values decreased with mixing time as shown in Table 3 and Fig. 1. For 5% w/w formulation, the RSD value of less than 6% (3.73%) was achieved after 1 min of mixing. On the other hand, for the 0.5% w/w formulation, the RSD values were above 6% at 1, 2 and 4 min of mixing (10.96%, 8.17% and 6.05% respectively) and the RSD values were lower than 6% (4.49%) after 8 min of mixing. The results could be explained in terms of the number of buspirone HCl particles in the mixture. It has been shown that buspirone hydrochloride particles have a tendency to self-agglomeration; therefore, the main factor to achieve uniform mixing would be the ability of the mixer to break down drug agglomerates and distribute the drug particles throughout the mixture. For the 5% w/w formulation, the larger number of drug agglomerates in the mixture bed increased the probability that these agglomerates are broken down by the chopper. As a result, less time was required to uniformly distribute the drug throughout the mixture. On the other hand, for 0.5% w/w formulation, less number of drug agglomerates exists in the mixture bed with less probability for the drug agglomerates to reach the chopper and break down. Consequently, longer time was required to achieve an acceptable content uniformity.

It can be seen from Table 4 and Fig. 2 that the drug contents of the 5% w/w formulation were within the limit of 85.0 to 115.0% of the label claim after 1 min of mixing (mean = 98.5%, ranging from 93.6 to 104.4%). Drug content uniformity continued to be within the limits throughout the whole mixing process. For the 0.5% w/w formulation, drug contents within the range of 85.0 and 115.0% of the label claim was achieved after 4 min of mixing (mean = 94.2% and ranging from 87.5 to 101.9%). It was also noticed that majority of the drug contents in both formulations were lower than 100% of the label claim. This was due to the loss of mixture scattered by the high speed mixing and adhered to the filter sock of the mixer.

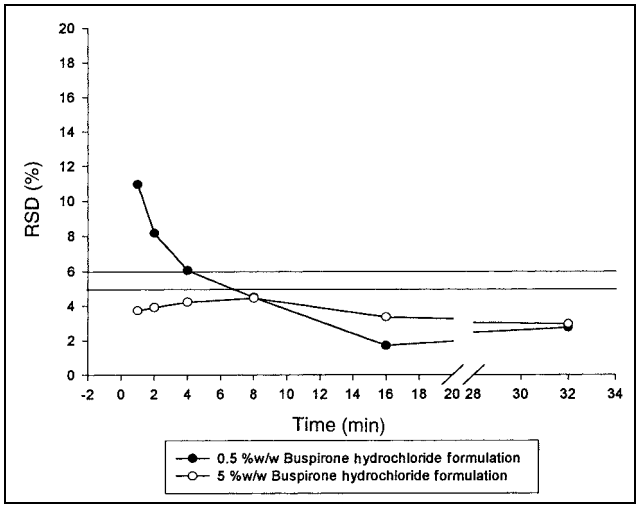

Fig. 1: Effect of drug proportion on the % relative standard deviation of powder blend
6% RSD = USP XXIV acceptance criteria
5% RSD = FDA draft guidance for industry acceptance criteria

Table 2: Tablet formulations

Ingredients	% w/w	
	0.5% w/w buspirone HCl	5% w/w buspirone HCl
Buspirone hydrochloride	0.5	5.0
Microcrystalline cellulose	93.5	88.0
Polyvinylpyrrolidone	5.0	5.0
Sodium starch glycolate	1.0	1.0

Table 3: Effect of drug proportion on mixing uniformity of buspirone hydrochloride powder blends

Time	RSD (%), n = 27	
(min)	0.5% w/w buspirone HCl	5% w/w buspirone HCl
1	10.96	3.73
2	8.17	3.92
4	6.05	4.22
8	4.49	4.45
16	1.70	3.35
32	2.74	2.95

Table 4: Effect of drug proportion on mean, minimum and maximum% label claim of buspirone hydrochloride powder blend

Time	% Label claim, n = 27			
(min)	0.5% w/w buspirone HCl		5% w/w buspirone HCl	
	Mean	Min-Max	Mean	Min-Max
1	90.1*	73.9–107.2	98.5	93.6–104.4
2	89.0*	73.9–98.2	96.8	89.4–101.8
4	94.2	87.5–101.9	94.1	89.4–99.4
8	90.4	85.0–98.4	92.5	87.6–99.5
16	88.8	86.3–90.8	91.2	87.0–97.5
32	90.5	85.4–93.9	91.0	86.5–95.8

* The result is statistically significant from the corresponding result obtained with 5% w/w buspirone hydrochloride formulation at $\alpha = 0.05$

According to the USP XXIV content uniformity requirements, the 5% w/w formulation was uniformly mixed after 1 min, while the 0.5% w/w formulation was uniformly mixed after 8 min. However, according to the FDA draft guidance for industry the 5% w/w formulation was uniformly mixed after 1 min and the mixture remained uniform throughout the 32 min of mixing. For the 0.5% w/w formulation, an acceptable mixture was obtained after 8 min of mixing which was in agreement with the conclusion derived when the USP XXIV-based acceptance criteria were implemented. However, after 16 min of mixing, the drug content was less than the acceptance range for the FDA Draft Guidance for Industry (88.8% compared to 90%). The results suggested that mixture of the drug of a percent as low as 0.5% w/w in the formulation may be acceptable from the content uniformity requirements of the USP XXIV while the same mixture would be rejected based on content uniformity requirements of the FDA draft guidance for industry. Therefore, for 0.5% w/w formulation, care must be taken in monitoring the mixing process especially when the FDA draft guidance for industry is implemented.

Statistical treatment using analysis of variance (ANOVA) was conducted to test the effect of decreasing the drug proportion on the buspirone hydrochloride content uniformity in powder blends as shown in Table 5. A significant difference in buspirone hydrochloride content between the

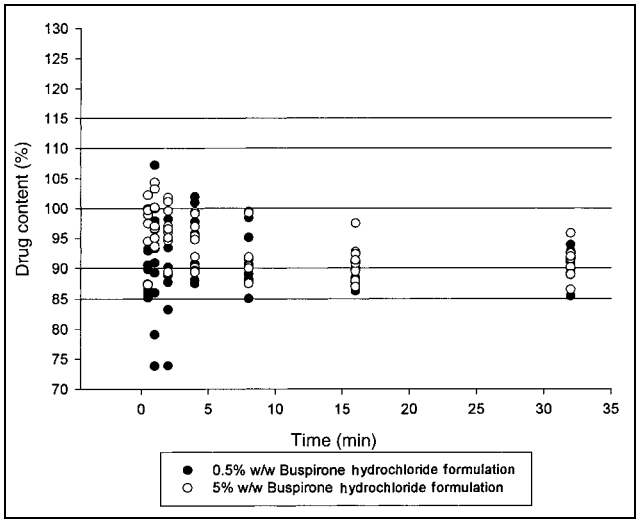

Fig. 2: Effect of mixing time and drug proportion on the % drug content of buspirone hydrochloride powder blend
85–115%: USP XXIV acceptance criteria
90–110%: FDA Draft Guidance for Industry acceptance criteria

Table 5: ANOVA table for the comparison of the effect of drug proportion (0.5% w/w vs. 5% w/w formulations) on buspirone hydrochloride contents in powder blends at different mixing time points

Time points (min)	Parameter	DF	Type III SS	Mean Square	F-value	P-value
1	Drug proportion	1	313.5	313.5	5.65	0.0303*
2	Drug proportion	1	272.0	272.0	8.08	0.0118*
4	Drug proportion	1	0.063	0.063	0.00	0.9597
8	Drug proportion	1	19.5	19.5	1.17	0.2963
16	Drug proportion	1	23.6	23.6	4.08	0.0605
32	Drug proportion	1	1.10	1.10	0.16	0.6919

* Statistically significant at $\alpha = 0.05$

0.5% and the 5% w/w formulations was seen at 1 and 2 min of mixing. After 4 min of mixing, no significant difference in the drug content between the two formulations was found. The results were in agreement with the previous discussion that, for 5% w/w buspirone hydrochloride formulation, more aggregates had high probability to be broken down by the chopper. As a result, less time was required to uniformly distribute the drug than that was required for 0.5% w/w formulation.

2.4. Effect of drug proportion on content uniformity of the finished tablets

The RSD values for the buspirone hydrochloride content in the compressed tablets are shown in Table 6. At the start of the run, a high RSD value for the 0.5% w/w formulation (4.49% compared to 2.74% at the end of the mixing process) was noticed and was attributed to powder handling, bridging and flow problems in the hopper. The poor flow was expected as both buspirone and microcrystalline cellulose have acicular particle shape with tendency to interlocking and bridging. This result was in agreement with the flow test result of the mixture. With the progress of the compression run, the RSD values for the drug content of both formulations decreased from 4.49% to 2.34% for 0.5% w/w formulation and from 2.28% to 0.7% for 5% w/w formulation. This behavior could be attributed to vibrations and occasional tapping of the hopper, which helped in breaking powder bridges and allowed a uniform flow of the powder from the hopper into the dies.

As seen in Tables 6–7 and Fig. 3, both formulations produced tablets that met the USP XXIV requirements for content uniformity throughout the whole compression run as in all cases the RSD values were less than 6% and the drug content in tablets were within the acceptance limit between 85.0 and 115.0% of the theoretical label claim.

Statistical treatment using ANOVA revealed a significant difference between the contents of buspirone hydrochloride between the two formulations in tablets collected at

Table 6: Effect of drug proportion and compression stage on content uniformity of buspirone hydrochloride tablets

Compression Stage	RSD (%), n = 10	
	0.5% w/w buspirone HCl	5% w/w buspirone HCl
Beginning	4.49	2.28
Middle	4.01	0.99
End	2.34	0.70

Table 7: Effect of drug proportion and compression stage on mean, minimum and maximum % label claim of buspirone hydrochloride tablets

Compression stage	% Label claim, n = 27			
	0.5% w/w buspirone HCl		5% w/w buspirone HCl	
	Mean	Min-Max	Mean	Min-Max
Beginning	91.8*	86.7–100.3	88.5	85.9–91.5
Middle	92.8*	89.1–101.1	90.2	89.0–92.2
End	91.2	89.0–95.0	92.1	91.1–93.1

* The result is statistically significant from the corresponding result obtained with 5% w/w buspirone hydrochloride formulation at $\alpha = 0.05$

the beginning and middle of the compression run. No significant difference was observed for tablets collected at the end of the compression run. The results of the statistical analysis are summarized in Table 8.

The RSD values for the drug content of tablets collected toward the end of the compression run were lower than those obtained for buspirone hydrochloride blend at the end of the mixing process (2.34% for tablets vs. 2.74% for powder blend of the 0.5% w/w formulation and 0.7% for tablets vs. 2.95% for powder blend of the 5% w/w formulation). The lowered RSD values for tablets suggested that sampling process by tablet compression gave better content uniformity than sampling process using unit dose thief probe. The results could be explained by the fact that sampling by tablet compression allows samples (tablets) to be withdrawn while the powder is in motion which complies with the first golden rule in sampling [4]. On the other hand, inserting the thief probe into static powder bed may cause segregation and some disturbances especially when the ability of the powder to flow into the opening of the thief probe is limited.

It was concluded that for buspirone hydrochloride, decreasing the drug proportion had a significant effect on the content uniformity of the powder blend during solid-solid mixing process in the high shear mixer, T. K. Fielder PMA25. Reducing drug content also had a significant effect on the content uniformity of the corresponding tablets at the beginning and the middle of the compression run.The high shear mixer used was proven to be highly efficient for mixing 5% w/w buspirone hydrochloride in a microcrystalline cellulose-based formulation as a uniform blend could be obtained after 1 min of mixing using high impeller speed (522 rpm) and high chopper speed (3600 rpm). For lower dose of buspirone hydrochloride at the level of 0.5% w/w, uniform mixing could be achieved after 8 min. Both 0.5% w/w and 5% w/w buspirone hydrochloride formulations could be uniformly mixed in T. K. Fielder PMA25 and compressed into tablets with uniform drug content with no need for preblending or geometric dilution. Care must be taken in monitoring the mixing process for low dose drugs as low as 0.5% w/w especially when the FDA draft guidance for industry is put in to effect.

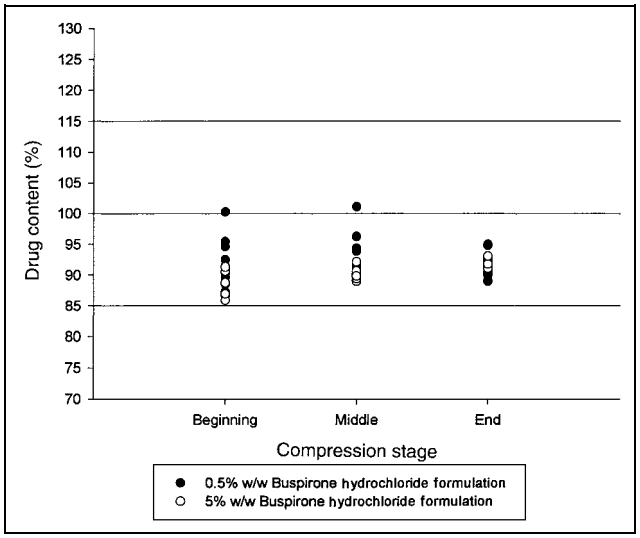

Fig. 3: Effect of drug proportion and compression stage on the % drug content of buspirone hydrochloride tablets

Table 8: ANOVA table for the comparison of the effect of drug proportion (0.5% w/w vs. 5% w/w formulations) on buspirone hydrochloride contents in tablets at different stages of the compression run

Compression Stage	Parameter	DF	Type III SS	Mean Square	F-value	P-value
Beginning	Drug proportion	1	55.4	55.4	5.25	0.0342*
Middle	Drug proportion	1	33.0	33.0	4.52	0.0476*
End	Drug proportion	1	4.9	4.9	1.99	0.1753

* Statistically significant at $\alpha = 0.05$

3. Experimental

3.1. Materials

Buspirone hydrochloride (Orion Corporation Fermion, Espoo, Finland) was used as a model drug. Microcrystalline cellulose, NF (Avicel PH 101; FMC Corp., Philadelphia, PA), polyvinylpyrrolidone, USP (Plasdone K29/32; International Specialty Products, Wayne, NJ), sodium starch glycolate, NF (Explotab; Mendell, Petterson, NY), magnesium stearate, USP (Mallinkrodt, St. Louis, MO), Buspirone HCl USP Reference Standard (USPC, Rockville, MD), potassium phosphate monobasic (Mallinckrodt Baker, Inc., Paris, KY), acetonitrile (Fisher Scientific, Fair Lawn, NJ), hydrochloric acid (Fisher Scientific, Fair Lawn, NJ), propylparaben (Eastman Kodak Company, Rochester, NY). Buspirone hydrochloride was passed through US standard 20-mesh screen and sodium starch glycolate was passed through US standard 30-mesh screen. Other ingredients were used as supplied from the manufacturers.

3.2. Equipment

T. K. Fielder (Nitro-Aeromatic, Inc., Columbia, MD), Optical Microscope System (Mideo system Inc., Huntington beach, CA), CSC Meinzer Sieve Shaker (CSC Scientific Company, Inc., Fairfax, VA), Tapped Density Tester (Vankel Industries, Inc., Amherst, MA), API Aerosizer (Amherst Process Instrument, Inc., Amherst, MA), 0.45 um Membrane Filter (Type HA, Millipore Corp., Milford, MA), L1 Packing Column (3.9 mm × 3090 mm Waters μBondpak C_{18} P/N WAT027324, Waters, Division of Millipore, Milford, MA), Accumet Model 10 pH Meter (Fisher Scientific, Fair Lawn, NJ), Hitachi L-6000 Pump (Hitachi, Ltd., Tokyo, Japan), Hitachi L-7200 Autosampler (Hitachi, Ltd., Tokyo, Japan), Waters 486 Absorbance Detector (Waters, Division of millipore, Milford, MA), Instrumented Manesty Model D3B Rotary Tablet Machine (Manesty Machine Ltd., Liverpool, England), Turbula Unit Type T2C Mixer, (Willy A. Bachofen AG, Maschinenfabrik, Basle, Switzerland), Pharma Test Powder Flow Instrument (Sitco, Bound Brook, New Jersey).

3.3. Methods

3.3.1. Micromeritic properties

3.3.1.1. Bulk density

The bulk density was determined by carefully pouring 25 g of the sample into a 100-ml graduated cylinder. The volume of the sample was recorded to the nearest 0.5 ml and the bulk density was calculated as the actual weight of the sample divided by the occupied volume. The tapped density was then determined by subjecting the graduated cylinder with the same sample to 1000 taps from the height of approximately 2 cm using tapped density tester. It was pre-determined that 1000 taps were sufficient to obtain constant occupied volume of the samples. The tapped density was calculated by dividing the sample weight by the tapped volume. The bulk and tapped densities were determined in triplicate for each sample.

3.3.1.2. Particle size distribution

Geometric mean particle size and the size distribution were obtained from sieve analysis that was performed using a nest of US standard sieves (20 to 325 mesh corresponding to 74 to 840 μm) with the CSC sieve shaker. Approximately 100-g sample was weighed and added onto the pre-weighed nest of sieves. The sample was shaken at a moderate frequency (setting #5) for 10 min. The sieves were again weighed and the fractions under the sieve size were recorded. The cumulative percent frequency undersize of each fraction was calculated and used to construct the log-probability plot. From the plot, 50% probability gave the geometric mean size and the ratio of 84% to 50% probability or the ratio of 50% to 16% probability gave geometric standard deviation or size distribution. The geometric mean particle size and the standard deviation were determined in triplicate for both buspirone hydrochloride and microcrystalline cellulose. To compare with the result obtained from sieve analysis, geometric mean particle size and size distribution were also determined using the API Aerosizer. The instrument consists of dispersion system, sensor unit, vacuum pump, data acquisition and data analysis system. A minimum sample weight of 5 mg is placed into the sample cup. The sample was dispersed and particles are accelerated by air stream where different size particles move with different velocities. The time needed for the particles to cross two laser beams was recorded and used to measure the particle sizes.

3.3.1.3. Particle shape

In this study, the particle shape was observed through the optical microscope system that is capable of capturing image under the microscope. Micromeritic properties of buspirone HCl and microcrystalline cellulose used in the study are summarized in Table 1.

3.3.2. Flowability measurement

Powder blends were carefully added to the funnel of the powder flow instrument. Any excess materials were wiped off into the channel surrounding upper part of the funnel. The instrument was programmed to allow the powder to pass through a 1-cm nozzle at the bottom of the funnel into a collecting dish on a calibrated balance. The time needed for the powder to flow was measured as the powder intersects a light beam and the weight obtained together with the flow time are used to measure the flow rate. The instrument also measured the angle of repose by recording the height of the powder heap (h), taking the diameter of the heap as the diameter of the collecting dish (d), and calculating the value using the following equation:

$$\mathrm{Tan}\,\theta = 2\,\mathrm{h}/\mathrm{d} \qquad (1)$$

where θ is the angle of repose.

3.3.3. Mixing experiment

The materials were accurately weighed in accordance to the formulations shown in Table 2. Calculations were made to load the mixer between 40 and 50% v/v of its capacity (total of about 3 kg of materials per batch were studied). The materials were loaded into the T. K. Fielder high shear mixer in the following order: microcrystalline cellulose, polyvinylpyrrolidone, buspirone hydrochloride and sodium starch glycolate. The materials were mixed in the high shear mixer at high impeller speed (522 rpm) and high chopper speed (3600 rpm). The mixer was divided into three sections, each with three sampling locations. Sampling locations were chosen in such a manner that assures representative sampling as shown in Fig. 4. Location 1, 4 and 7 represent the center of the powder blend, location 2, 5 and 8 represent the powder blend behind the impeller blade and location 3, 6 and 9 represent the powder blend in front of the impeller blade. Samples were taken from nine different locations at time points of 1, 2, 4, 8, 16 and 32 min of the mixing process. A 1-ml unit side-sampling thief probe was used for sampling and care was taken so as not to disturb the powder bed. The capacity of the sampler was chosen to remove mixture samples that weigh approximately one to not more than three unit dosages. Each sample was accurately weighed and analyzed for drug content using HPLC system with a modified USPXXIV method [6].

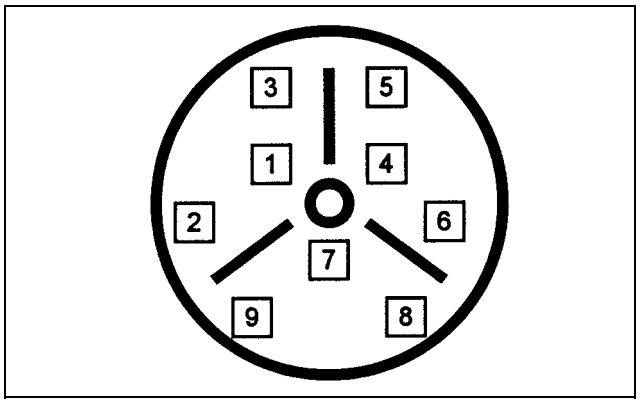

Fig. 4: Schematic top view of the high shear mixer. The numbers indicate the locations where the samples have been drawn

3.3.4. Tablet manufacturing

Final mixtures, after 32 min of mixing, were accurately weighed to 500-g batch size and mixed with 1%w/w magnesium stearate in a Turbula mixer for 3 min. The final blends were compressed into standard round concave tablets of 300 mg weight using 3/8" punches in an instrumented tablet press with compression forces of approximately 3000 lb. Two of the sixteen stations of the tablet press were used to compress the tablets at a speed of 15 revolutions/min. Approximately 200 tablets were collected at the beginning, middle and the end of the compression run. The beginning of the compression run was considered when the necessary parameters such as tablet weight (300 mg) and compression force (3000 lb) were established (approximately 5 min after the start of the compression run). The middle of the compression run was considered at 15 min after the necessary parameters were established. The end of the compression run was considered when the mixture was nearly emptied from the hopper (approximately 35 min after start of the compression run).

3.3.5. Sample analysis

All the samples were analyzed for buspirone hydrochloride concentration using the USP XXIV HPLC analytical method [6]. However, due to the difference between the studied dose (1.5 mg for 0.5% w/w buspirone hydrochloride formulation and 15 mg for 5% w/w formulation) and the lowest commercially available dose (5 mg), the sample preparation procedures were modified in order to be able to detect and quantify lower concentrations of the drug. For blend samples, each sample was accurately weighed and transferred into separate 100-ml volumetric flasks containing 1 N HCl. On the other hand, tablets were first crushed in porcelain mortars and quantitatively transferred into the volumetric flasks. The volumetric flasks were then sonicated for 5 min and shaken by mechanical means for 30 min. Purified water was then added to volume. The content was filtered through 0.45 μm membrane filters. The chromatographic system consisted of an L1 packing column and mobile phase (potassium phosphate buffer pH 7.5 : acetronitrile, 60 : 40). The mobile phase flow rate was 2 ml/min. A 25 μl of each sample was injected into the HPLC system and eluted for 15 min and absorbances were measured at a wavelength of 254 nm. Propylparaben was used as an internal standard and in a system suitability check. Approximate retention time for propylparaben and buspirone hydrochloride were 5.5 and 9.5 min, respectively. A standard curve was constructed from five replicated injections of different concentrations over a range of 0.25–200 μg/ml. The results were calculated for% label claim and relative standard deviation. The relative standard deviation (RSD) of the buspirone hydrochloride content was plotted against mixing time to indicate the extent of mixing uniformity.

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