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An Empirical Approach To Mitigate The Risk Of Content Uniformity Variability During The Tablet Compression Of Drug Coated Extended Release Beads

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ABSTRACT

Multiunit bead products are effective extended drug release systems, and the tablet manufacturing of multiunit beads is associated with risks such as content uniformity variabilitydue to beads segregation. The objective of current study is to introduce a new method of blend material transfer to mitigate the beads segregation during compression. The drug coated beads were blended with tablet excipients and compressed to tablets by transferring the homogenous blend to press hopper both by inversionand manual methods. The content uniformity was evaluated using Variance Component Analysis (VCA).The data demonstrated content uniformity variability in the samples obtained with inversion method and acceptable data with manual transfer method. The variability in the content uniformity was presumed due to beads segregation during the material transfer by inversion method. The drug release data of the compressed tablets was consistent to the uncompressed beads concluding no rupture of the film during the tablet compression. Although, the manual material transfer method is primitive and limited to smaller batch size, the method is of a great potential to alleviate the risk of beads segregation and improve the content uniformity. The VCA data analysis provides assurance that future samples from the batch will comply with USP<905>.

Key Words: Beads, Tablets, Content Uniformity, Drug Release, ASTM, Segregation

INTRODUCTION

Multiunit particulate dosage forms have distinct advantages compared to single unit dosage forms in the development of controlled release based solid oral dosage forms[1, 2].Single unit dosage forms such as tablets and capsules comprise the drug within single unit whereas the multiunit dosage forms consist of number of subunits. Although similar drug release profiles can be obtained with both the dosage forms, multiunit dosage forms offer several benefits over the single unit dosage forms including uniform distribution of the active throughout the large surface area of gastrointestinal tract for increased absorption, the particles behave like liquids thereby leaving the stomach within short period of time decreasing the risk of high local drug distribution and dose dumping[3-6].Multiunit particulates are typically administered as compressed tablets or encapsulated into hard gelatin capsules.

The polymer coated drug beads (multiunit particles) are blended with extragranular tableting excipients and then compressed to tablets. The major challenges during compression of coated multiunit particulates are rupture of the polymer film due to compression stress applied during the tablet compression and hence change the release characteristics from the beads[7]. The extent of damage to the polymer film on the beads is highly influenced by the mechanical properties of the polymer film and compression process parameters. The polymer film elasticity and bead core plasticity are critical determining the integrity of the polymer film during the compression by accommodating changes in shape and deformation during tableting[8, 9].

In addition to rupture of polymer film, the variability of content uniformity in the compressed tablets is another major concern during the tablet compression of multiunit particles. Mixing of the multiunit particles with tableting excipients, in powder form, is susceptible for variation in the drug content due to segregation phenomenon.The content uniformity of dosage form is a critical quality attribute and is a prerequisite for maintaining therapeutic drug concentrations and mitigating the drug safety.A number of different mechanisms influenced by process and material characteristics can impact the powder blend for segregation to occur[10].

The content uniformity variability is mainly attributed to insufficient mixing of beads with the tableting excipients during blending process or as a result of beads segregation from the well mixed blend during subsequent blend discharge, handling and transfer to tablet press hopper[11]. Following the uniform blending of the mixture, blend discharge and transfer methods to tablet hopper are critical factors influencingthe segregation. There are two main flow patterns, funnel flow and mass flow, that can develop in a container or tablet press hopper during the discharge of the blend impact the segregation.

A science and risk-based approaches for sampling and testing are critical to assess thecontent uniformity such that the data is useful for determining the homogeneity of the active in the unit dosage from and also to determine the stage of active segregation.The use of nested sampling plans and testing of replicate samples from each location as recommended by American Society for Testing and Materials (ASTM) guidelines are advantageous as they allow the data to be evaluated using statistical approaches such as Variance Component Analysis (VCA) to identify root causes of non-uniformity. This statistical technique divides the total variance into between location and within location and it is interpreted that high between location variances often indicate poor mixing and non-uniformity within the blender, and also can imply non-uniformity or segregation during dosage form manufacture.

In the current study, we have aimed at handling the blend transfer methods from intermediate container to tablet press hopper to avoid the beads segregation and to mitigate the content uniformity issues in the compressed tablets. The extended release (ER) beads that are coated with Verapamil HCl on the inert sugar spheres followed by ethylcellulose coating as extended release film are used in the current study.

MATERIALS AND METHODS

Materials

Inert sugar spheres (20/25 mesh, 710/850 micron) were obtained from Coloron Inc.,India are used as core beads to coat with drug solution. The excipient hypromellose 2910 (Pharmacoat 606) was obtained from Shin Etsu chemical Co, India., and used for seal coat on the inert cores and as a binder in the drug coat solution. The extended release (ER) film materials, the ethylcellulose (Ethocel standard 45 premium) was obtained from Dow chemical company, USA and the pore former in the ER film, hydroxypropyl cellulose (HPC) was supplied by Ashland Specialties, India. The tablet excipients, anhydrous lactosemonohydrate (Impalpable 312)was sourced from Kerry,USA; Crospovidone (Polyplasdone XL)was obtained from International Specialty Products,India; Sodium stearylfumarate was sourced from JRS Pharma, India; Colloidal silicone dioxide (Cab-O-Sil) was from Cabotsanmar Ltd, India. All other chemicals and reagents utilized in the study were of laboratory grade.

Preparation of Extended Release (ER) Beads

The ER beads were prepared by spraying the ER solution on drug and seal coated beads. The qualitative and quantitative composition of ER beads is presented in Table 1.

Table 1: Qualitative and quantitative composition of ER coated beads compressed tablet

Material	Function	mg/Tablet
Verapamil HCl	Active	25
Sugar Spheres (710-850 micron)	Core Beads	100
Hypromellose 2910	Seal coat and Binder	12
Ethylcellulose	ER Coat	15
Hydroxypropyl cellulose	Pore former	5
Lactose Monohydrate	Filler	310
Crospovidone	Disintegrant	25
Sodium Stearyl Sulfate	Lubricant	7
Colloidal Silicon Dioxide	Glidant	1
Total theoretical weight		500

The sugar spheres are coated with seal and drug coat solutions and the seal/drug coated beads are further ER coated with a theoretical drug content of 166.6 mg/gram of beads. The beads are blended with tableting excipients and compressed at a target tablet weight of 500mg.

The preparation process involves, briefly, inert core sugar spheres were first seal coated with aqueous solution of hypromellose 2910 and then the seal coated beads were further drug coated with an aqueous solution of Verapamil HCl and hypromellose 2910 utilizing a Wurster fluid bed (7” Wurster column, Glatt GPCG3). The drug and seal coated beads were characterized for bead size distribution

(PSD) and % assay prior to ER coating.The ER film coated beads were prepared by using the seal/drug coated beads as starting core beads and sprayed with ER solution in a Wurster fluid bed(7" Wurster column, Glatt GPCG3). The ER solution is an alcoholic solution of hydroxypropyl cellulose (HPC), a pore former, and ethyl cellulose (EC), release controlling polymer, at a ratio of 25 :75. The seal, drug coat and ER coat process parameters are presented in the Table 2.

Table 2: The seal /drug, ERcoating process parameters

Seal coat/ Drug coat/ ER coat Process parameters			
Parameter	**Seal Coat**	**Drug Coat**	**ER Coat**
Bowl Charge (kg)	2.2		2.5
Inlet Temperature (^oC)	70	70	65
Product Temperature (^oC)	37	37	35
Air Flow (CFM)	90	95	100
Atomizing air Pressure (PSI)	30	30	30
Spray Rate (g/min)	10	12	8
Partition Height	10	10	10
Exhaust Temperature (^oC)	40	40	40

The sugar spheres (2.2kg) were first seal/drug coated using a Wurster fluid bed and were characterized for drug content (Assay) and bead size distribution. The seal/drug coated beads were further ER coated utilizing Wurster fluid bed

The theoretical drug load of the seal/drug coated, and ER coated beads is 183 mg/ gram and 166.6 mg/ gram of coated beads, respectively. The ER coated beads are characterized for bead size distribution, % assay and % drug release profile.

Characterization of extended release coated beads

HPLC Method for drug estimation

The drug content (% assay) in the seal/drug coated beads, ER beads and in the compressed tablets was estimated using a reverse phase HPLC equipped with a PDA detector. The chromatographic conditions are as follows: The aqueous solvent mixture was prepared by using 0.015 N sodium acetate solution containing about 33 ml of glacial acetic acid per liter. The mobile phase was a filtered and degassed mixture of aqueous solvent mixture, acetonitrile and 2-aminoheptane at a ratio of 70:30:0.5. The column is 4.6mm X 12.5 cm that contains L1 (C18) packing (Spherisorb ODS1 Column). The flow rate is 1.0 ml per minute, injection volume is 10 ul and the maximum absorption is 278nm.

Bead size distribution

The seal/drugcoated beads and ER coated beads were characterized for bead size distribution utilizing mechanical agitation sieving method as defined by USP <786>.

% Assay

The seal/drug coated beads and ER coated beads are evaluated for drug content. Accurately, 100mg equivalent of drug (545mg of drug/seal coated beads and 600 mg of ER beads) were weighed to a 100 ml volumetric flask and approximately 60 ml of mobile phase was added and sonicated for 45 minutes. Then made up the volume with mobile phase to 100 ml and mixed. From the mixture, 10 ml was separated and centrifuged, and 5 ml of supernatant was diluted 100 ml with mobile phase and mixed. The solution was centrifuged, and the drug concentration was estimated using a HPLC.

% Drug Release

The drug release from ER beads was measured using USP apparatus Type 2 dissolution apparatus. The dissolution media was 500ml of 0.1 N HCl. Accurately weighed ER beads equivalent to 25mg of drug (150 mg ER beads) were transferred into dissolution vessel containing 500 ml of 0.1 N HCl warmed to 37^{o}C. The 10ml of sample was collected at regular intervals, 1 hr, 4 hr, 6 hr and 10hr after the start of dissolution study and the drug content was measured using HPLC.

Tablet Compression of ER Beads

Blend Preparation

The qualitative and quantitative composition of ER beads compressed tablet is presented in the Table 1. The batch size was 17.5kg. The ER beads were blended with extra granular tabletexcipients prior to tablet compression. The excipients, lactose, crospovidone, sodium stearyl fumarate and colloidal silicon dioxide, were screened through #18 mesh screen(1mm) to delump any loose aggregates and to ensure better dispersion of materials during blending. Prior to discharge of the blend, 10 samples were collected from different locations in the blender to verify the blend uniformity. The blend was discharged to intermediate container carefully to ensure there is no segregation of beads happened during discharge. Due to the difference in the beads and excipient particle size, there are chances for beads segregation by fluidization segregation mechanism during the discharge of the blend from blender. Therefore, while discharging the blend from the blender the intermediate discharge container was raised close to blender discharge port to limit the drop height and free flow the beads. Three separate samples were collected from discharge intermediate container to verify the blend uniformity in the blend after discharge. A sample quantity equivalent to three times of theoretical dose (1.5gm) was sampled from each location.

Tablet Compression

The discharged blend was utilized for two separate compression studies by varying the blend transfer method from intermediate container to tablet press hopper. In first method, the blend was directly transferred to tablet press hopper from the intermediate discharge container by inversion loading (Method 1)and in the second method, a modified manual method in which the beads blend from the

discharge container was transferred to tablet press hopper by removing the blend layer by layer method by hand scooping (Method 2).Theremoval of the power blend layer by layer scooping method was presumed to mitigate the segregation by avoiding the creation of vortex as the material is always removed from the topmost layer first before removal of deeper materials. The blend in the scoop was transferred to press hopper gently placing the blend in the hopper layer by layer instead of direct pouring.

In both the studies, the bead blend is compressed using rotary tablet press a18 station (HATATablet press) using a round flat faced punches. The tablets are compressed at a target weight of 500mg, a hardness of 10kP and a thickness of 0.200 inches. The tablet press parameters set common to both the batches, and these include press speed (10 rpm), main press pressure(0.75mTons) and feeder speed set point (12%).

Blend Uniformity and Content Uniformity testing

The samples collected from the blender and from the discharge intermediate container were analyzed for drug content to assess the drug uniformity in the final blend and in the discharge intermediate container after discharged from the blender. The sample quantity was transferred to a 200 ml volumetric flask and approximately 100 ml of mobile phase was added and sonicated for 45 minutes. Then made up the volume with mobile phase to 200 ml and mixed. The drug concentration was estimated using a HPLC method discussed above after suitable dilution.

To comprehensively assess the applicability of the manual transfer method for final blend transfer to tablet press to improve the content uniformity of the compressed tablets, an extended assessment testing was performed for the samples collected at different stages of compression. A stratified sampling of the compressed tablets was followed per recommendations of International Society for Pharmaceutical Engineering, specifically, three tablets each from 20 intervals of compression run including start, middle and end of the run. In a total of 60 tablets were tested for drug content.The tablet was crushed to powder and was transferred to a 100 ml volumetric flask and approximately 75 ml of mobile phase was added and sonicated for 45 minutes. The drug concentration was estimated using a HPLC method discussed above after suitable dilution. The data was evaluated by statistical approaches E2709 and E2810 recommended by American Society for Testing and Materials (ASTM). The analyzed data demonstrates a confidence level (90%) and coverage level (95%) that the batch meets USP <905> uniformity criteria.

Composite Sample testing

A composite sample from the compressed tablets from the entire compression run was collected and tested for content uniformity (AV) and % drug release profile.The content uniformity testing was performed as per USP<905> by randomly selecting the 10 tablets and the drug content in the individual tablet was assessed as described above. The acceptance value (AV) was calculated. The % drug release is measured using USP apparatus Type 2 dissolution apparatus as discussed above.

RESULTS AND DISCUSSION

Extended Release (ER) Beads

The seal/drug coated beads were characterized for bead distribution and drug content (% assay). The bead size distribution data and % assay data are presented in Table 3.

Table 3. Physical characteristics of coated beads

Beads characterization	Seal/ Drug Coated Beads	ER Beads
% Assay	99.1	98.8
#16 mesh (1.18 mm) retained (%)	0	0
#18 mesh (1.00 mm) retained (%)	0	1.0
#20 mesh (850 micron) retained (%)	91.0	96.2
#25 mesh 710 micron) retained (%)	9.0	2.8
#30 mesh 600 micron) retained (%)	0	0
Pan retained (%)	0	0

The bead size distribution is measured using analytical sieving method. The #retained on #16mesh and on pan represents the agglomerates and fines, respectively.

The bead distribution data concluded there were no larger agglomerates and fines generated after seal/drug coating as indicated by the 0% beads retained on #16 mesh and on Pan. The seal/drug layered beads have demonstrated an assay value of 99.1% of the total theoretical drug load indicating a good adhesion of drug on the beads. In the current study, HPC polymer with a viscosity of 450 cps was used and the coating process parameters are consistent to previous study with a spray rate of 8 gm/min. The ER beads are characterized for bead distribution and drug content. The data are presented in the Table 2. As seen in the data, the % assay of 98.8 % indicates there was no drug shredding from beads due to beads attrition during the ER coating. Similarly, there were no agglomeration and fines generated during ER coating as indicated by the 0% beads retained on #16 mesh and on Pan. The ER beads were further utilized for tableting at a theoretical dose of 25mg of Verapamil HCl.

Tablet Compression of ER Beads

The major challenge during the tablet compression of ER beads is susceptibility of ER film to rupture due to the compression stress on ER film altering the drug release profile. The ER beads were mixed with tableting excipients prior to tablet compression to ensure there was no damage to polymer film to the beads due to impact of compression force on beads and contact between the pellets. The tableting excipients provide cushioning effect to the beads along with the good tableting properties. The selection and ratio of the excipients is very critical for the tablet compression process as they directly influence the integrity of the ER film and thereby impacting the drug release profile. Also, they have huge impact on the flow ability of the blend, minimization of the segregation and to ensure good tablet properties

such as friability, weight variation and disintegration [12, 13]. Lactose monohydrate was selected as filler in the current study and possess good cushioning effect and protects the ER film from compression damage by adhering on the surface of beads and dissipate compression stress. Also, the size of the excipients was small relative to coated beads thereby exhibits greater flexibility for particle rearrangement during the compression [14]. Crospovidone was selected as an external disintegrant and possess good disintegration property.

Due to a large particle size differences between the beads and tableting excipients exist, there is a risk of segregation during compression process and hence variations in tablet weight and drug content. The ratio of beads to excipients is also an important parameter during the compression process as they directly influence the drug content uniformity, drug release and tablet properties such as tablet mechanical strength, friability and disintegration time[15, 16]. In the current study, the concentration of ER beads was approximately 30% w/w of the blend and was selected to ensure good tablet mechanical strength and to minimize the tablet weight variation and drug content uniformity.

The ER beads and tablet excipient were blended in “V” blender for a complete homogenization of the beads in the blend. To confirm the uniformity in the blend, samples were collected from a total of ten different locations and the drug content was assessed. The drug content data from the samples obtained from blender and intermediate discharge container is presented in Table 4.

Table 4. The drug content data from the samples obtained from the blender and intermediate discharge container

Stage	Sample Location	% Assay
Blender	Left top	98.5
	Left Middle	100.6
	Left bottom	97.8
	Discharge Port	96.8
	Left center Middle	99.2
	Center	102.2
	Right Bottom	95.9
	Right Top	101.5
	Right Middle	99.6
	Right Center Middle	97.4
	Average	99.0
	SD	2.1

	RSD	2.0
Discharge Container	Top	99.5
	Middle	99.1
	Bottom	100.3
	Average	99.6
	SD	0.6

A total of ten samples at different locations in the blender were collected at a sample size of three times to theoretical dose prior to discharging. After the blend was discharged, additional samples were collected from the container at three different locations. All the samples were analyzed for drug content. The sample data was used to demonstrate the blend homogeneity after blending and discharge.

The assay data in the blend samples has demonstrated a good blend uniformity with a mean value of 99.0% (Range: 95.9%-102.2%) anda relative standard deviation of 2.0. Due to the difference in the beads and excipient particle size, there are chances for beads segregation by fluidization segregation mechanism during the discharge of the blend from blender. Therefore, while discharging the blend from the blender the intermediate discharge container was raised close to blender discharge port to limit the drop height and free flow the beads. The blend uniformity after discharge was demonstrated by collecting samples three locations from the discharge container and tested for drug content. The data indicated a mean value of 99.6% with a minimal variability among the samples (Range: 99.1%-100.3%). Since, a homogeneity of the blend and uniform drug content was demonstrated in the blend, the potential variations in the content uniformity of compressed tablets could only be interpreted due to segregation during the compression process including material transfer from discharge container to tablet press hopper.

The blend material transfer from the discharge container to tablet hopper was performed in two different ways. In the first method, the homogenous blend of ER beads and excipients was transferred from the intermediate container by container inversion on top of the tablet press hopper (Method 1). This is typical industry practice to load the materials to the tablet press. In the second method, a manual method was followed for material transfer by hand scooping the blend utilizing layer by layer method (Method 2). In this method, the blend from discharge container was removed by scooping from the topmost layer and presumed to avoid the risk of vortex formation allowing the segregation of beads from the finer particles of the excipients.

The beads blend was compressed utilizing a rotary tablet press using a round flat faced punches. The tabletswere compressed at a press speed of 10 rpm and compression pressure of 0.75mTons. All the tablet compression parameters were maintained similar for both the studies. The compressed tablets were verified for tablet weight, hardness and thickness and were at proximity to the target values of

500mg of tablet weight, 10kp of hardness and 0.200" of thickness. The tablet weights throughout the compression were within the ± 5 % of the target tablet weight.

The data from the 60 tablets from both the studies has demonstrated a mean value of 99.08 % and 99.27% of theoretical drug content for material transfer method 1 (inversion) and method 2 (manual) respectively (Table 5).

Table 5.The content uniformity data obtained from the 20 locations during thecompression and the data analysis by ASTM guidance

Analysis	Parameter	Method 1 (Inversion)		Method 2 (Manual)	
ASTM E2810 Statistics	Overall Mean	99.08		99.27	
	Between location Std Dev	3.07		1.21	
	Within location Std Dev	4.58		2.75	
Variance Components	**Parameter**	**Std Dev**	**% Total**	**Std Dev**	**% Total**
	Between location Std Dev	1.57	10.5	0	0
	Within location Std Dev	4.58	89.5	2.75	100
	Total	4.84	100	2.75	100

The table demonstrates overall mean, the within location standard deviation and between location standard deviation of 20 locations from the variance component analysis. The acceptance criteria table has been obtained from ASTM E2709/E2810

The graphical representation of content uniformity is presented in and Figure 1.The total sample standard deviations for method 1 and method 2 are 4.84 and 2.75, respectively. As per ASTM guidance table, the upper limit of sample standard deviations was 4.737 for the mean assay value of 99.08% and 4.823 for mean assay value of 99.27% for a sample size of 60 units. The upper limits values were taken from the guidance given in the ASTM E2709/E2819 acceptance limit tables for 90% confidence level and 95% coverage.

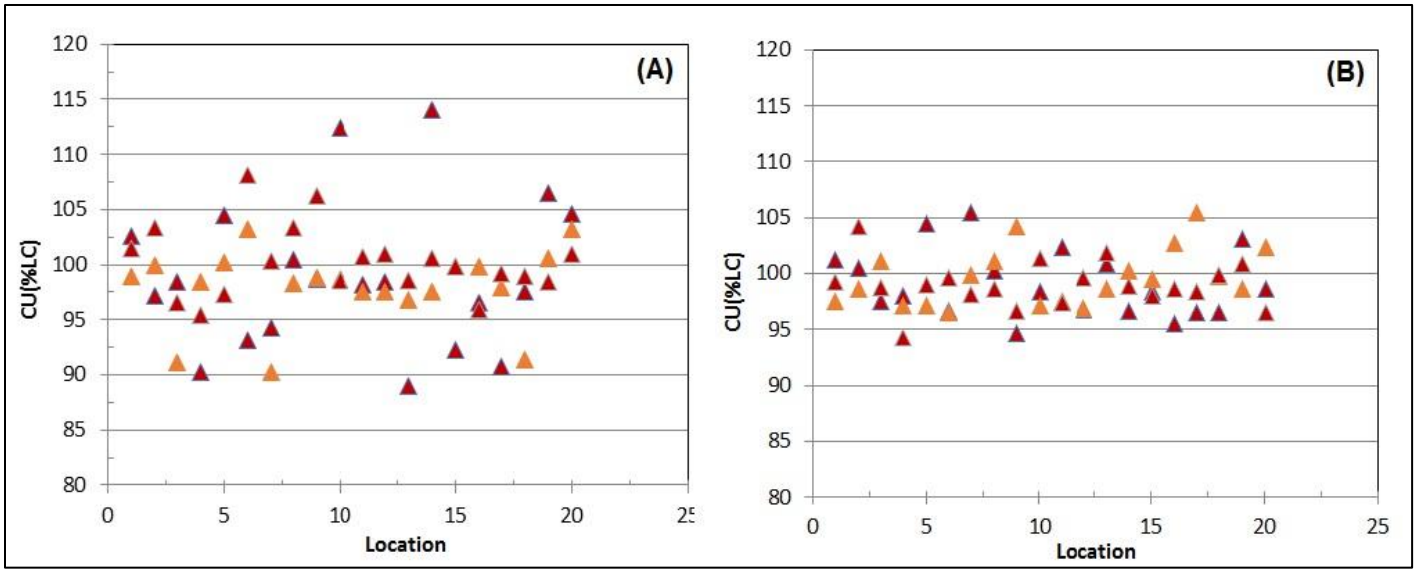

Figure 1: Content uniformity (CU) data from the samples obtained at different stages of compression across 20 locations (A) Samples obtained from Method 1 (Inversion) B) Samples obtained from Method 2 (Manual); LC= Label claim (theoretical dose, 25mg)

Since, the sample standard deviation value of method 2 (manual) was observed to be 2.75 which is lower than the specified upper limit of 4.823, it is stated that with 90% confidence there is at least 95% probability that samples collected from the study meets the uniformity of dosage tests per USP <905>. However, the sample standard deviation value for method 1 samples was found to be 4.84 which is above the specified upper limit of 4.737, it is stated with 90% confidence there is at least at 95% probability that the samples from this study will not meet the uniformity of dosage tests per USP <905>. The variance component analysis also provides the data split the overall variability into between and within location components. As seen in the table 4, the overall variability in the content uniformity was contributed byboth within location (89.5%) and between location (10.5%) for method 2 indicating the variability in the drug content was seen across the batch rather variability was noticed at a particular stage of compression process.

Additionally, the composite samples collected from both the studies were assessed for content uniformity and % drug release. The drug release profile from ER coated beads is presented in Figure 2.

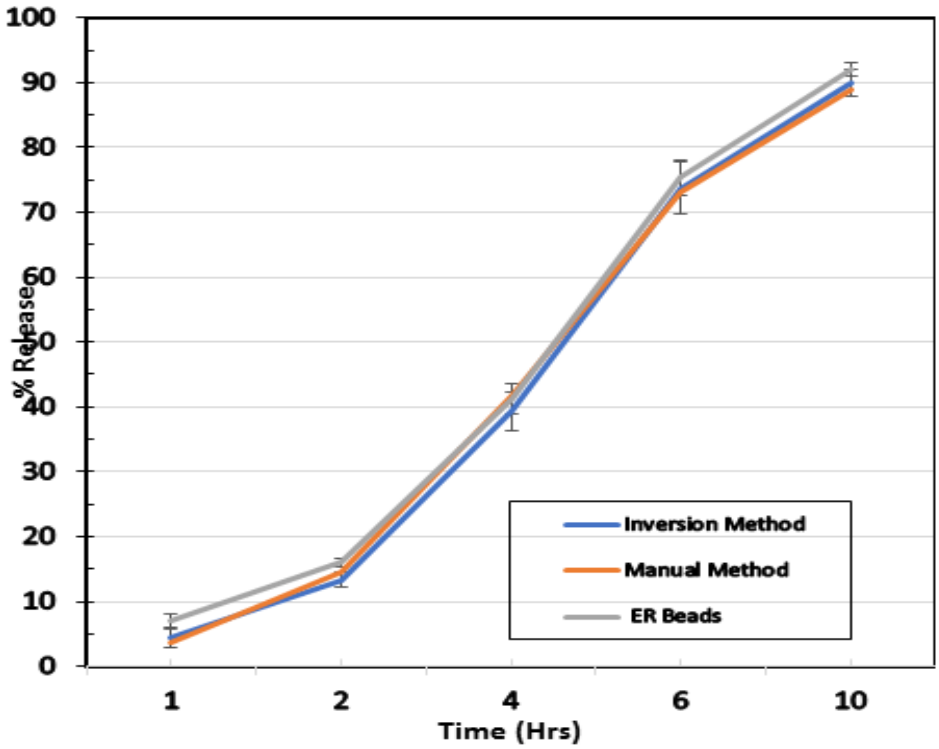

Figure 2. The % drug release profile from the ER beads and from the compressed tablets with the material transfer methods, Inversion method and Manual method. The data is presented as average of 3 ± SD.

The drug release indicates the influence of compression process on the integrity of ER film. The data suggested that the variability in the content uniformity as the AV value was observed to be 15.2 for the samples collected form inversion transfer method. Whereas the AV value for the manually transferred method was 4.6 concluding the applicability of manual transfer method to minimize the segregation of beads and to improve the content uniformity in the tablets. The dissolution data demonstrates the % drug release from both the studies is consistent to uncompressed original ER beads although the release is slightly slower in the first hour and most likely attributed to the disintegration of tablets. Therefore, it is concluded that the ER film is intact during the tablet compression process and the tablet process parameters and tablet excipients are optimal to provide cushioning effect so that the beads will not be ruptured due to the mechanical stress during the compression. The content uniformity variability in the inversion transfer method is presumed most likely due to beads segregation by sifting segregation during the material transfer to the tablet press. Due to the particle size differences in the blend, while transferring the blend, the finer particles tend to sift through the larger particles and as the concentration of fines builds up in the center of the pile, the beads tend to slide to the edges of the pile causing the segregation. The segregation of beads was minimized during the manual method by removing the topmost of the layer blend without the disturbing the blend and avoiding the pile formation during the transfer to tablet press hopper.

Based on the results obtained through the extended testing of the samples obtained from both the inversion and manual transfer methods, it is concluded that the material transfer plays a critical role

contributing to the beads segregation influencing the variability in the content uniformity of the compressed tablets. The material transfer by manual layer by layer method mitigates the beads segregation thereby avoiding the content uniformity variability. Whereas the material transfer by conventional inversion methods favors the beads segregation in a homogenously bended material by sift segregation or fluidization segregation mechanisms.

CONCLUSION

The development of multi-unit particles compressed to tablets is challenging with the major concern of variability in the content uniformity in the compressed tablets. The risk of the content uniformity is caused predominantly by beads segregation during the material transfer to the tablet press hopper. The current study results have demonstrated the applicability of the modified manual layer by layer material transfer method to alleviate the beads segregation and to improve the content uniformity in the tablets. The manual material transfer by layer by layer scooping method mitigates the beads segregation by avoiding the formation of vortex during the scooping of the beads. However, the beads segregation was evident with the high variability in the drug content in the individual tablet when the material was transferred to tablet press hopper by the inversion transfer method. In addition, in the current study, an extended testing recommended by ASTM was applied with the sample collection and testing of 60 tablets collected from 20 different locations and analyzed with the statistical approaches. The analysis provides a confidence level of 90% and a coverage level of 95% that samples collected will meet the USP<905> content uniformity criteria. The compressed tablets were evaluated for % drug release and the data demonstrates the similarity of the drug release from the compressed tablets to uncompressed ER beads indicating the ER film on the beads was not compromised during the tablet compression due to high mechanical stress.Although, the manual material transfer method is primitive and is limited to smaller batch size, the method is of a great potential to alleviate the risk of beads segregation and to improve the content uniformity of the compressed tablets.

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Declaration of interest

The authors declare no potential conflict of interest.

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