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Research

Impact of compaction and re-compaction on granule properties in dry granulation process

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ABSTRACT:
Dry granulation is defined as a process whereby powder of different physical properties are combined to form denser, bigger, permanent masses with the aid of some tangible or intangible external agents. In dry-granulation roller pressure is the driving force. Careful selection of quantitative composition of functional ingredients has big role to play in the scalability of the manufacturing process, when drug load as high as 66.67%w/w. Metformin hydrochloride has inherent issue of flowability and compressibility. At high drug load gives little space for other functional inactive ingredients; hence it becomes more critical to choose efficient highly compressible diluent of at equal quantitative ratio with dry binder. Better compressible diluents along with dry binder also add flexibility and helps re- cycling of granules for better results. Physical property of selected individual ingredients and mixture of ingredients has direct impaction on compressibility of granules, solid fraction, density and particle size distribution of compressed granules. Current dry granulation study with composition of Lactose anhydrous and Silicified Microcrystalline Cellulose along with 2% w/w hydroxy propyl cellulose gives flexibility of recycling to high drug load Metformin hydrochloride granules, this helps to improve its tabletability.

KEYWORDS: Dry granulation, High drug load, recycling, tabletability.

INTRODUCTION:

Metformin hydrochloride is the first choice of medication for Diabetes mellitus. Its plasma elimination half life is 6.2 hours and available in generic form in both immediate release and extended release dosage form. The highest adult dose is varying from 500 mg to 2000 mg per day [1]. Due to higher dose of Metformin hydrochloride, formulating immediate release tablet dosage form with lower quantities of diluents is really challenging [2]. To meet this huge demand for high dose IR Metformin hydrochloride pharmaceutical industry looks for a robust reproducible manufacturing process for its generic tablets, which can be reproduced in commercial scale. IR formulation with high drug load mostly fails in the processing hence it is necessary to give attention at the initial stage of development. This can be achieved by a) Modifying physical property of the model API by careful qualitative selection of functional ingredients at the initial stage of composition finalization b) Developing a low risk process, with proper risk mitigation strategy. Metformin hydrochloride in pure form has inherent issue of developing lumps on storage, challenges in flowability and compressibility [3]. Hence in high drug load formulation this above property of API drives the manufacturing process into gray area where the processability challenges are more. To overcome challenges associated with higher drug load formulation it is essential to forecast the initial risk and to have solution or risk mitigation strategy for this at the beginning. The most common risk for high drug load formulation are flow issue, non-uniform die filling, compatibility, tabletability and compressibility issue [4]. Higher particle size of API with D (0.9) greater than 200µm can considered as worst case for the current study where agglomeration tendency of Metformin hydrochloride increases the trouble further. To have better working design space it is essential to understand the physical property of Metformin hydrochloride and have risk mitigation strategy for its issue. Diluents are evaluated at a ratio of 1:1(% w/w) in a mixture where impact of binder also evaluated for single cycle and recycling of the compacted granules at an optimum roller pressure [5]. The impact of roller pressure on granule's physical property studied at a wider range of roller pressure starting from 30 bar to 100 bar keeping other roller compaction parameters constant [6]. Recycling of compacted granules is an option overcome challenges such as compatibility, tabletability and compressibility associated with Metformin

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hydrochloride [7].

MATERIALS AND METHODS

Materials

For the experiment raw material such as API- Metformin Hydrochloride used from LAURUS Labs, India, Microcrystalline cellulose (Grade- Avicel pH 102) as diluent and Hydroxy propyl methyl cellulose (Methocel E3LV) as dry binder used from DuPont Pharma, a extra fine grade of Hydroxy propyl cellulose (Klucel EXF HPC) used from Ashland and Lactose anhydrous (Super Tab 21 AN) as diluent and Sodium Starch Glycolate (Primojel) as super disintegrant used from DFE Pharma, Mannitol (Pearlitol 100 SD) as diluent used from ROQUETTE, Silicified Microcrystalline Cellulose (PROSOLV® SMCC HD 90) as diluent used from JRS PHARMA GmbH & Co. KG, Germany and Magnesium stearate as lubricant used from Mallinckrodt. The manufacturing of Pre-RC blend mixture and RC blend mixture (lubricated blend) were carried out by following formula composition (table 1). The diluents were used in equal quantity with and without dry binders. There were two water soluble dry binders such as hydroxy propyl cellulose and hydroxy propyl methyl cellulose evaluated maximum at 2%w/w concentration along with diluent mixture. The compaction process was repeated for more than one cycle at an optimum roller pressure with an objective to achieve better granule property.

Methods

Table 1

Formula composition for Roller compaction			SET-1(With HPC as binder)				SET-2(Without binder)				SET-3(With HPMC as binder)			
Sl. No.	Raw material	Rationale(Ratio)	% w/w	RC-MET -T1 (Mg/tab)	RC-MET -T2 (Mg/tab)	RC-MET -T3 (Mg/tab)	% w/w	RC-MET -T4 (Mg/tab)	RC-MET -T5 (Mg/tab)	RC-MET -T6 (Mg/tab)	% w/w	RC-MET –T7 (Mg/tab)	RC-MET –T8 (Mg/tab)	RC-MET –T9 (Mg/tab)
1	Metformin Hydrochloride	Active	66.67	500	500	500	66.67	500	500	500	66.67	500	500	500
2	Microcrystalline cellulose (Avicel pH 102) + Lactose Super Tab 21 AN	Diluents (1:1)	26.33	197.50	0	0	28.33	212.5	0	0	26.33	197.50	0	0
3	Microcrystalline cellulose (Avicel pH 102) + Mannitol (Pearlitol 100 SD)			0	197.50	0		0	212.5	0		0	197.50	0
4	Lactose Super Tab 21 AN + Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90			0	0	197.50		0	0	212.5		0	0	197.50
5	Hydroxy propyl cellulose (Klucel -EXF)	Dry binder	2	15	15	15	0	0	0	0	2	0	0	0
6	Hydroxy propyl methyl cellulose (Methocel E3 LV)			0	0	0		0	0	0		15	15	15
7	Sodium Starch Glycolate Type-A	Super-disintegrant	3	22.5	22.5	22.5	3	22.5	22.5	22.5	3	22.5	22.5	22.5
8	Magnesium stearate (Intra+ Extra granular)	Lubricant (1:1)	2	15	15	15	2	15	15	15	2	15	15	15
Total			**100**	**750**	**750**	**750**	**100**	**750**	**750**	**750**	**100**	**750**	**750**	**750**

Preparation of Pre-RC blend mixture and lubricated blend (RC-blend) of Cycle 1 and Cycle 2

Pre-RC (pre-roller compaction) blend mixture prepared by Step (1) Metformin hydrochloride passed through mesh # 20 ASTM. Step (2) other ingredients such as diluent mixture, dry binder, super-disintegrant were passed through mesh # 20 ASTM. Step (3) Step 1 and step 2 materials were mixed for 200 revolutions using 1 liter octagonal blender Step (4) #60 passed 1 % magnesium stearate (intra-granular) was mixed with Step 3 materials for 50 revolutions using same 1 liter octagonal blender (Pre-RC blend). Step (5) Pre-RC blend compacted at different roller pressure such as 30, 50, 75 and 100 bar and using roller compactor Alexanderwerk BT 120 at a screw feeder speed of 40 RPM, roller speed of 5 RPM, at roller gap of 2 mm Step (6) The flakes were passed through mesh # 20 ASTM. Step (7) #60 passed 1 % magnesium stearate (extra-granular) was mixed with Step 6 materials for 50 revolutions using same 1 liter octagonal blender (RC -blend). Step (8) Lubricated granules (RC -blend) were subjected for physical characterization such as bulk density and solid fraction. Step (9) Lubricated granules of 75 bar roller pressure is considered as optimum roller pressure and hence total blend separated into two parts and one part was subjected for second cycle without any additional lubricants to study the impact of recycling or recompaction on granule property for different formula composition. The roller compaction parameters are kept same as step -5. The compacted flakes passed through # 20 ASTM Step (10) Lubricated blend of both the cycle were subjected for the compression profiling. Step (11) Lubricated granules (RC -blend) of both cycle 1 and cycle 2 were subjected for

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physical characterization such as bulk density, particle size distributions, flowability, solid fraction and tabletability [8].

Characterization of API, Pre-RC blend and RC blend

A. Evaluation of bulk density, tapped density and compressibility index

Bulk density is the mass of the materials divided by the volume occupied that include interstitial space. Tapped density is the apparent powder density obtained under stated condition of tapping. Physical characterization of API, Pre-RC blend and RC blend of optimum roller pressure (75 bar) were carried out using conventional USP method. Bulk density and tapped density were measured according to USP method <661> . To a dry graduated 100 ml cylinder, weighed quantity (w) of API was transferred. The powder was levelled without compacting and volume (V) was noted and bulk density calculated by weight / Volume.

Tapped density tester (Model- Electro lab ETD-1020) was used to evaluate the tapped density of all powder. Tapped density was calculated at a rate of 300 taps per minutes for 10,500 and 1250 taps. Volume (V_{1250}) is considered as final tapped volume. Tapped density (g/ml) = weight/V_{1250}. Same procedure was followed to evaluate the bulk density and tapped density of pre-RC and RC blend [9].

B. Evaluation of True density of API and Pre-RC blend

True density or absolute density is the ratio of mass and its volume, excluding open and closed or blind pores. Helium gas Pycnometer (AccuPyc, Micromeritics – 1340) was used to evaluate the true density of API and pre –RC blend. It is a laboratory device used for measuring the density or more accurately the volume of solids of different shape such as regularly shaped, porous, non-porous, monolithic, and granular or powder by employing some method of gas displacement and the volume: pressure relationship known as Boyle's Law. It is a technique of gas displacement method used to measure volume accurately, in these inert gases such as helium used as displacement medium [10].

C. Impact of roller pressure on density of different formula compositions

Uniform mixture of Pre-RC blend was compacted at different roller pressure and impact of roller pressure on densification was determined by using conventional USP method<661>. RC blend of both cycle1 and cycle 2 were compared at optimum roller pressure for different formula composition [11].

D. Impact of roller pressure over solid fraction(%) of cycle 1 flakes of Metformin hydrochloride of different formula compositions

Envelope density apparatus (GeoPyc, Micromeritics – 1360) was used to evaluate the envelope density of flakes. The envelope density can be define as the ratio of mass of solid substance to the envelope volume, where envelope volume is the imaginary boundary surrounding the particles. The results are reported in the percentage porosity and specific pore volume. The solid fraction can be derived by hundred minus percentage porosity. The true density information used for the calculation of percentage porosity and GeoPyc determines the envelope volume and density of the solid object by the displacement of solid medium (dry-flo) [12].

E. Impact of roller pressure on granule size of different formula compositions

Vibratory Sieve shaker (Electro lab EMS-8) was used to evaluate the particle size distributions. Mesh no #60 ASTM (250 µm) used to differentiate the granule size. The granules retained above the #60 ASTM called as coarse granules and granules which passed through the #60 and deposited above pan considered as fines. Particle size of fines are lesser than 250 µm [13].

F. Impact of roller pressure on flowability of different formula compositions

Flowability tester (Erweka GT) was used to evaluate the flow property using nozzle of diameter 11.3mm. Approximately 20g of blend passed through the nozzle by opening the valve and time was extrapolated to blend quantity of 100g and noted [14].

G. Impact recycling of compaction on solid fraction(%) of cycle 2 flakes of Metformin hydrochloride of different formula compositions

Envelope density apparatus (GeoPyc, Micromeritics – 1360) was used to evaluate the envelope density of flakes produced at optimum roller pressure of 75of bar. The percentage solid fraction of different composition were compared with solid fraction of cycle 1 compacted flakes [15].

H. Impact of cycle 2 compaction on density of Metformin hydrochloride blend of different formula compositions

Physical characterization of cycle 2 lubricated blends produced at optimum roller pressure of 75 bar were carried out using conventional USP method <661> and compared with cycle 1 lubricated blend of same roller pressure to find impact of recycling of the compacted mass [16].

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I. Impact of cycle 2 compaction on flowability (Seconds/100g) of Metformin hydrochloride blend of different formula compositions

Flowability tester (Erweka GT) was used to evaluate the flow property of both cycle 2 and cycle 1 lubricated blend. Flowability of lubricated blend of both the cycle was compared to find impact of recompaction over flow behaviour of the final blend [17].

J. Impact of cycle 2 compaction on particle size distribution or granule size of Metformin hydrochloride blend of different formula compositions

Vibratory Sieve shaker (Electro lab EMS-8) was used to evaluate the particle size distribution (PSD) using sieve #60 ASTM. Particle above the #60 mesh considered as the coarse granules and particle below #60 mesh (< 250µm) considered as fines. The PSD of both the cycle 1 and Cycle 2 compared to see the impact of recompaction on particle size distribution [18].

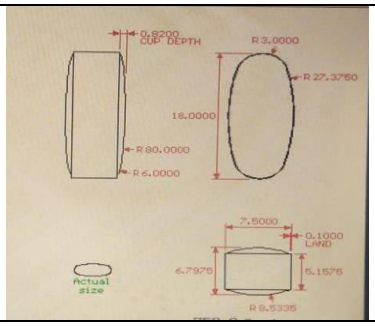
K. Impact of Cycle 2 of compaction on tablet physical property - % friability , Disintegration time and Tensile strength of tablets of different formula compositions

Lubricated blend of cycle 1 and cycle 2 produced at optimum roller pressure of 75 bar were compressed at an unit weight of 750 mg using D-tooling , Standard concave oval shaped punch of dimension 18 mm x 7.50 mm. The Compression machine used is Karnavati (Mini press-SF) and tablet were subjected for physical characterization such as thickness using Vernier calliper (Mitutoyo CD-6"CSX) , disintegration test was performed using tablet disintegration Tester (Electro lab ED-2AL), % friability was evaluated using tablet friability tester (Electro lab EF-2) , hardness test was evaluated using hardness tester (Erweka –TBH 320D) and weight of tablet was measured using analytical balance Sartorius (BT 423S). The observed maximum main compression force, thickness and hardness of tablet noted and used to calculate the tensile strength of tablets.The tablet tensile strength (δ in Mpa)) calculated using formula [19].

$$\sigma_t = \frac{2}{3}\left(\frac{10P}{\pi D^2\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)}\right)$$

Where, P= Break force (N), D= Length of short axis (m), t= tablet thickness (m), W= Tablet wall height (m).

Table 2
Tooling used- D-tooling , Standard concave
Dimension -18 mm x 7.50 mm
Shape of tablets - Oval shape



RESULT AND DISCUSSION
Characterization of API, Pre-RC blend and RC blend

(A) Evaluation of bulk density, tapped density and compressibility index

Description	BD-Bulk density(g/ml), USP Method Test-616 (N=1)		TD-Tapped density(g/ml)	% CI -Car's Index Flowability (method USP 1174)	HR - Hausner's ratio	Flow character
Metformin hydrochloride (#20 passed API)	-	0.41	0.757	45.84	1.846	Very Very poor
Formulation trials	Pre-RC blend	**RC blend (Cycle 1 - Lubricated blend), 75 bar roller pressure**				

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RC-MET-1	0.330	0.58	0.72	19.44	1.24	Fair
RC-MET-2	0.320	0.55	0.75	26.67	1.36	poor
RC-MET-3	0.340	0.62	0.73	15.07	1.18	Good
RC-MET-4	0.350	0.52	0.73	28.77	1.40	Poor
RC-MET-5	0.340	0.52	0.70	25.71	1.35	Poor
RC-MET-6	0.320	0.53	0.73	27.34	1.38	Poor
RC-MET-7	0.350	0.55	0.76	27.63	1.38	Poor
RC-MET-8	0.330	0.56	0.79	29.11	1.41	Poor
RC-MET-9	0.320	0.58	0.75	22.67	1.29	Passable

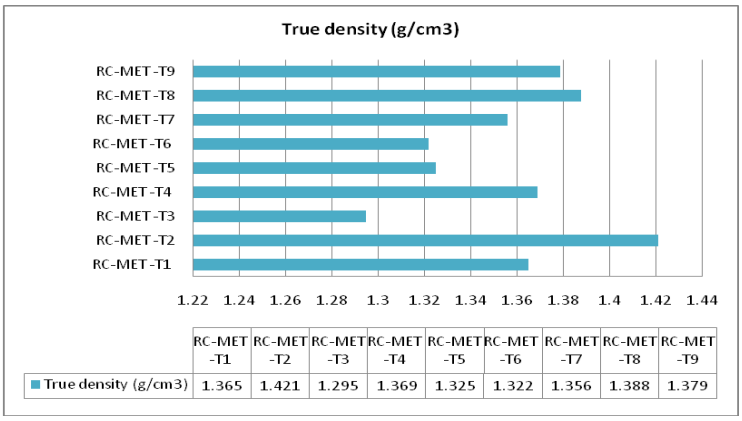
The bulk density of pure API is 0.41g/ml with % car's index 45.84 and Hausner's ratio 1.846; this shows that the API has very poor flow. This is physical property of API which at higher drug load has direct impact on processability. Among all lubricated blend produced in cycle 1 at optimum roller pressure of 75 bar the formula composition of RC-MET-3, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows good flow behaviour . The presence of dry binder helps in flowability even at single compaction cycle due to its efficient densification in comparison to formula composition RC-MET-6, which is having same diluent mixture but without dry binder.

(B) Evaluation of True density of API and Pre-RC blend

True density of Pre-C blend of different formulations

Instrument used – AccuPyc , Helium gas Pycnometer

True density of Metformin Hydrochloride Pre-RC blend		Metformin Hydrochloride (API)
Formulations	True density (g/cm3)	True density of Metformin Hydrochloride -1.371 g/cm³
RC-MET -T1	1.365	
RC-MET -T2	1.421	
RC-MET -T3	1.295	
RC-MET -T4	1.369	
RC-MET -T5	1.325	
RC-MET -T6	1.322	
RC-MET -T7	1.356	
RC-MET -T8	1.388	
RC-MET -T9	1.379	



The true density of pure API when passed through mesh no # 20ASTM is 1.371 g/cm³. Among all pre-RC blend RC-MET -T2 with formula composition microcrystalline cellulose (Avicel pH 102) and Mannitol (Pearlitol 100 SD) with 2% w/w of dry binder hydroxy propyl cellulose shows highest true density of 1.421 g/cm³. The second highest true density is 1.388 g/cm³, where diluents microcrystalline cellulose (Avicel pH 102) , Mannitol (Pearlitol 100 SD) with 2% w/w of dry binder Methocel E3 LV. This shows pre-RC blend with Mannitol has slightly higher true density in comparison to other formula composition [20].

(C) Impact of roller pressure on density of different formula compositions

There is significant increase in the density of lubricated blend with increase in the roller pressure. This shows that density of the RC –blend is directly proportional to the roller pressure. The Formula composition with binder has better densification with increase in roller pressure. This can be said that dry binder has direct impact in the dry granulation process. The composition of RC-MET-3, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows highest bulk density 0.620 g/ml even at roller pressure of 75 bar and further increases to 0.667 g/ml with increase in roller pressure to 100 bar. Same trend is also followed by RC-MET -T1, where diluents are microcrystalline cellulose (Avicel pH 102) and Lactose Super Tab 21 AN with dry binder 2% w/w of dry binder hydroxy propyl cellulose [21].

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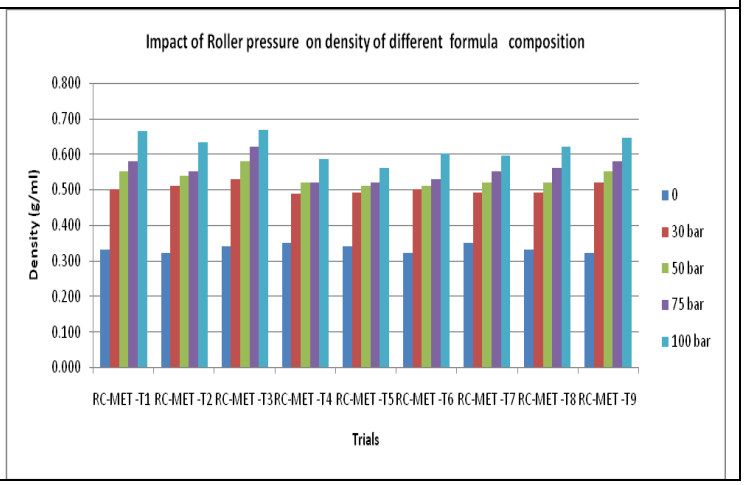
Impact of roller pressure on density of different formula compositions

Formulations trials	Bulk density (g/ml) Vs Roller pressure (Bar)				
	Pre-RC blend	Metformin hydrochloride Lubricated blend (g/ml) -Cycle 1			
	0	30	50	75	100
RC-MET -T1	0.330	0.500	0.550	0.580	0.663
RC-MET -T2	0.320	0.510	0.540	0.550	0.632
RC-MET -T3	0.340	0.530	0.580	0.620	0.667
RC-MET -T4	0.350	0.488	0.520	0.520	0.585
RC-MET -T5	0.340	0.490	0.510	0.520	0.560
RC-MET -T6	0.320	0.500	0.510	0.530	0.600
RC-MET -T7	0.350	0.490	0.520	0.550	0.595
RC-MET -T8	0.330	0.490	0.520	0.560	0.620
RC-MET -T9	0.320	0.520	0.550	0.580	0.645

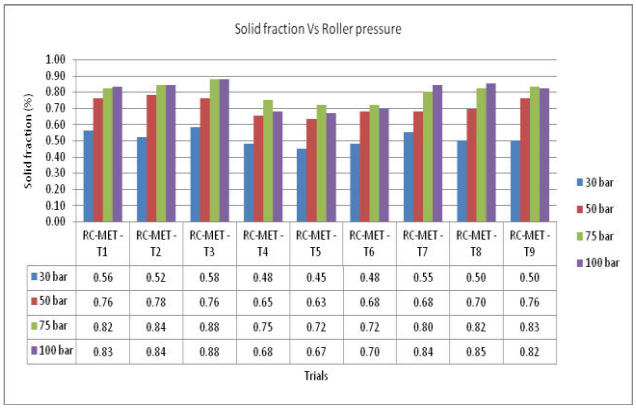


(D) Impact of roller pressure over solid fraction of different formula compositions

Impact of roller pressure over solid fraction of different formula compositions

Instrument used- GeoPyc, Solid fraction of Metformin Hydrochloride Flakes (Cycle-1)

Formulations Trials	Roller pressure (Bar)			
	30 bar	50 bar	75 bar	100 bar
RC-MET -T1	0.56	0.76	0.82	0.83
RC-MET -T2	0.52	0.78	0.84	0.84
RC-MET -T3	0.58	0.76	0.88	0.88
RC-MET -T4	0.48	0.65	0.75	0.68
RC-MET -T5	0.45	0.63	0.72	0.67
RC-MET -T6	0.48	0.68	0.72	0.70
RC-MET -T7	0.55	0.68	0.80	0.84
RC-MET -T8	0.50	0.70	0.82	0.85
RC-MET -T9	0.50	0.76	0.83	0.82



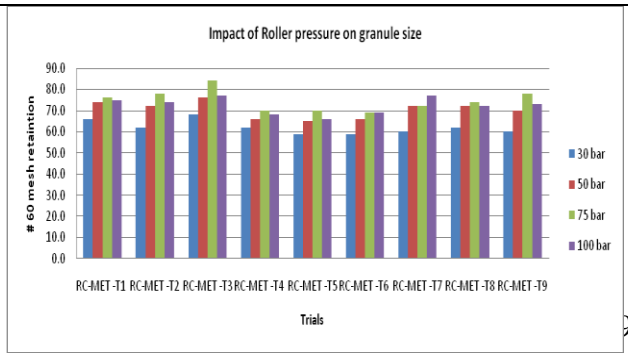
There is significant increase in the solid fraction with increase in the roller pressure irrespective of nature of diluents and presence or absence of binder. Presence of dry binder even at 2% w/w level helps in the achieving solid fraction of 50% at lower roller pressure of 30 bar. 75 bar roller pressure may be considered as optimum roller pressure, where all formula composition attains highest solid fraction. Further increase in the roller pressure above 75 bar has no major impact on the percentage of solid fraction. The formula composition of RC-MET-3, which has API, Lactose Super Tab 21 AN, Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows highest solid fraction of 88% w/w. Increase in solid fraction with increase in the roller pressure reflects in the increase in the density of the granules and thereby increase in flowability of the lubricated granules [22].

(E) Impact of roller pressure on particle size distribution or granule size of different formula compositions

% Metformin Hydrochloride lubricated Granules (Cycle 1) retained above 60 ASTM mesh(> 250 µm)

Formulation Trials	Roller pressure (Bar)			
	30 bar	50 bar	75 bar	100 bar
RC-MET -T1	66.0	74.0	76.0	75.0
RC-MET -T2	62.0	72.0	78.0	74.0
RC-MET -T3	68.0	76.0	84.0	77.0
RC-MET -T4	62.0	66.0	70.0	68.0
RC-MET -T5	59.0	65.0	70.0	66.0
RC-MET -T6	59.0	66.0	69.0	69.0

Impact of roller pressure on granule size of different formula compositions



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RC-MET -T7	60.0	72.0	72.0	77.0
RC-MET -T8	62.0	72.0	74.0	72.0
RC-MET -T9	60.0	70.0	78.0	73.0

There is increase in the particle size with increase in the roller pressure. The formula composition of RC-MET-3, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows highest retention of granules up to 84% w/w above mesh no # 60 ASTM . Highest particle size can be observed in the formula composition with binders and the percentage of retention particle is more at 75 bar roller pressure [23].

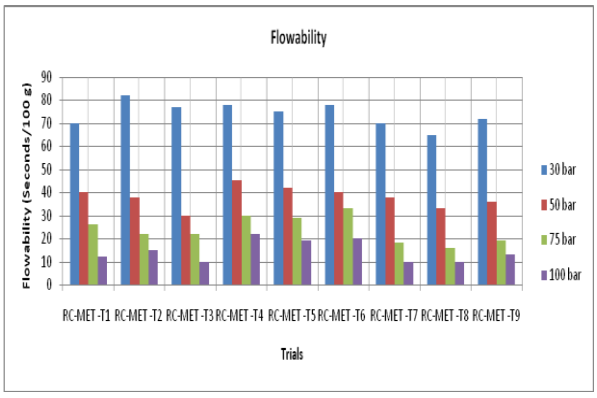
(F) Impact of roller pressure on flowability of different formula compositions

Impact of roller pressure on flowability of different formula composition

Instrument used - Erweka GT , Nozzle: 11.3mm

Flowability of Metformin hydrochloride lubricated blend (Seconds/100g) – Cycle 1

Formulation trials	Roller pressure (Bar)			
	30 bar	50 bar	75 bar	100 bar
RC-MET -T1	70	40	26	12
RC-MET -T2	82	38	22	15
RC-MET -T3	77	30	22	10
RC-MET -T4	78	45	30	22
RC-MET -T5	75	42	29	19
RC-MET -T6	78	40	33	20
RC-MET -T7	70	38	18	10
RC-MET -T8	65	33	16	10
RC-MET -T9	72	36	19	13

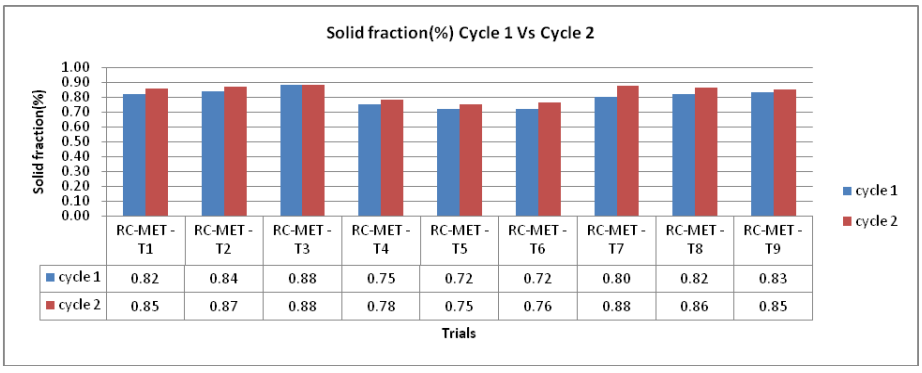


There is significant increase in the solid fraction with increase in the roller pressure irrespective of nature of diluents and presence or absence of binder. This helps in increase densification and hence help in enhancing flowability.

(G) Impact of cycle 2 compaction on solid fraction (%) of Metformin hydrochloride Flakes different formula compositions

Impact of cycle 2 compaction on solid fraction(%) of Metformin hydrochloride Flakes

Formulation trials	At roller pressure of 75 bar	
	cycle 1	cycle 2
RC-MET -T1	0.82	0.85
RC-MET -T2	0.84	0.87
RC-MET -T3	0.88	0.88
RC-MET -T4	0.75	0.78
RC-MET -T5	0.72	0.75
RC-MET -T6	0.72	0.76
RC-MET -T7	0.80	0.88
RC-MET -T8	0.82	0.86
RC-MET -T9	0.83	0.85



There is increase in the solid fraction of the flakes with increase in the number of compaction cycle from single cycle to second cycle. This increase in the solid fraction was observed to be higher in the presence of the dry binder. This increase in solid fraction gives an option to increase in the density of granules, thereby increases the flowability of the granules and reduces the risk improper die filling during compression even at higher speed. This compaction and recompaction process can also be utilized to increase in dissolution rate of the poorly wettable molecule, where dissolution is challenging due to poor wetability of active in dissolution bowl [24].

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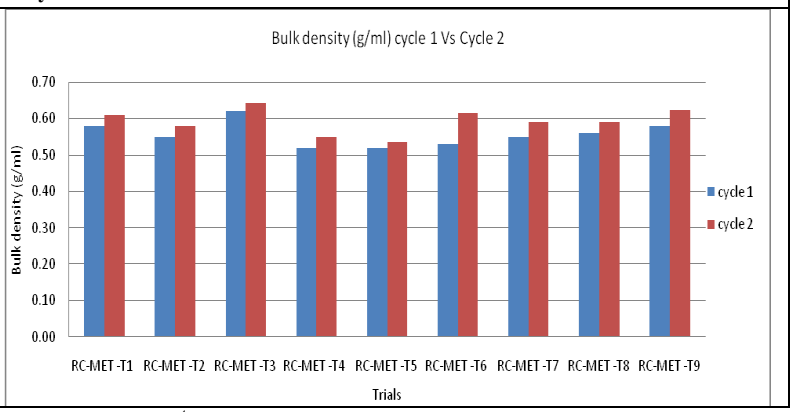
(H) Impact of cycle 2 compaction on density of Metformin hydrochloride blend of different formula compositions

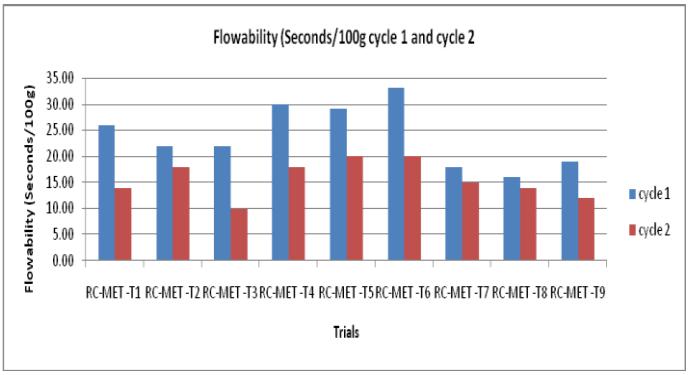
Impact of cycle 2 compaction on density of Metformin hydrochloride blend		
Formulation trials	**At roller pressure of 75 bar**	
	cycle 1	**cycle 2**
RC-MET -T1	0.580	0.610
RC-MET -T2	0.550	0.580
RC-MET -T3	0.620	0.642
RC-MET -T4	0.520	0.550
RC-MET -T5	0.520	0.535
RC-MET -T6	0.530	0.615
RC-MET -T7	0.550	0.590
RC-MET -T8	0.560	0.590
RC-MET -T9	0.580	0.622



There is an increase in the density can be seen from 1st cycle to second cycle at all formula composition at a roller pressure of 75 bar and the increase in the density is significant in the presence of the dry binder. The formula composition of RC-MET-3, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows highest density of 0.642 g/ml in cycle 2 at this roller pressure. The formula composition of RC-MET-9, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl methyl cellulose shows second highest density of 0.622 g/ml in cycle 2 . This increase in the density of the granules helps in overcoming flow and compressibility challenge associated with the Metformin hydrochloride [25].

(I) Impact of cycle 2 compaction on flowability (Seconds/100g) of Metformin hydrochloride blend of different formula compositions

Impact of cycle 2 compaction on flowability (Seconds/100g) of Metformin hydrochloride blend		
Formulation trials	**At roller pressure of 75 bar**	
	cycle 1	**cycle 2**
RC-MET -T1	26	14
RC-MET -T2	22	18
RC-MET -T3	22	10
RC-MET -T4	30	18
RC-MET -T5	29	20
RC-MET -T6	33	20
RC-MET -T7	18	15
RC-MET -T8	16	14
RC-MET -T9	19	12



There is significant increase in the flowability of granules with recompaction. This can be concluded that when granules of 1st cycle subjected for the recompaction there is further densification of the granules. The formulation with dry binder shows better flowability of the blend in comparison to the formula composition without binders. Presence of binder even at 2% w/w helps in flowability of the granules. Cycle 2 granules of the composition RC-MET-3, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl cellulose shows better flowability of 10 seconds/ 100 g at optimum roller pressure of 75 bar followed by the cycle 2 granules of the formula composition of RC-MET-9, which has API , Lactose Super Tab 21 AN , Silicified Microcrystalline Cellulose PROSOLV® SMCC HD 90 and 2% w/w of dry binder hydroxy propyl methyl cellulose [26].

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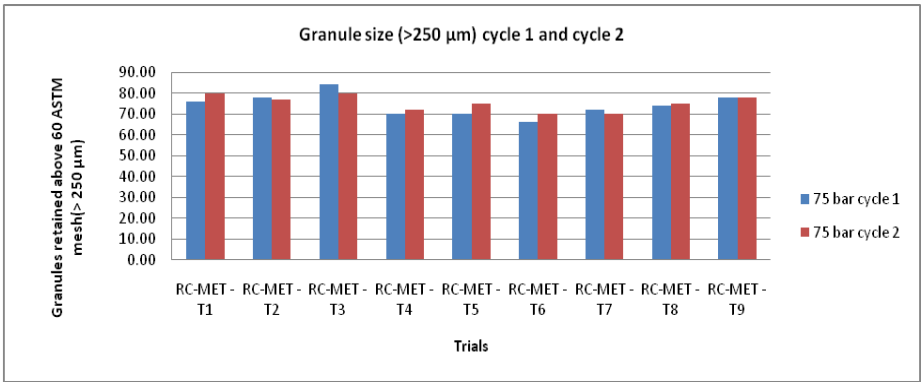
(J) Impact of cycle 2 compaction on granule size of Metformin hydrochloride blend of different formula compositions

Recompaction process also helps to increase the granule ratio in the blend. Presence of binder in the mixture gives additional advantage of increase in the granule size in comparison to the composition which is without binders. Impact of hydroxy propyl cellulose as binder in the increase in granule size is more than the hydroxy propyl methyl cellulose as binder. There is common trend of increase in particle size was observed from 1st cycle compaction to second cycle compaction [27].

Impact of cycle 2 compaction on granule size of Metformin hydrochloride blend, % Metformin Hydrochloride lubricated granules retained above 60 ASTM mesh(> 250 µm)

Formulation trials	At roller pressure of 75 bar	
	Cycle 1	Cycle 2
RC-MET -T1	76.0	80.0
RC-MET -T2	78.0	77.0
RC-MET -T3	84.0	80.0
RC-MET -T4	70.0	72.0
RC-MET -T5	70.0	75.0
RC-MET -T6	66.0	70.0
RC-MET -T7	72.0	70.0
RC-MET -T8	74.0	75.0
RC-MET -T9	78.0	78.0



(K) Impact of Cycle 2 of compaction on tablet physical property - % friability , Disintegration time and Tensile strength of tablets of different formula compositions

Physical characterization flakes and tablet
Impact of Cycle 2 of compaction on tablet physical property , % friability and Tensile strength of tablets

Formulation Trials →	Cycle 1, RC-MET-1	Cycle 2, RC-MET-1	Cycle 1, RC-MET-2	Cycle 2, RC-MET-2	Cycle 1, RC-MET-3	Cycle 2, RC-MET-3	Cycle 1, RC-MET-4	Cycle 2, RC-MET-4	Cycle 1, RC-MET-5	Cycle 2, RC-MET-5	Cycle 1, RC-MET-6	Cycle 2, RC-MET-6	Cycle 1, RC-MET-7	Cycle 2, RC-MET-7	Cycle 1, RC-MET-8	Cycle 2, RC-MET-8	Cycle 1, RC-MET-9	Cycle 2, RC-MET-9
Average .Weight (mg), n=10	645	752	748	748	748	748	748	748	750	748	748	748	748	748	748	748	748	748
%w/w friability	0.3	0.33	0.52	0.4	0.22	0.22	0.36	0.3	0.22	0.35	0.11	0.23	0.36	0.42	0.26	0.32	0.33	0.4
Disintegration time (minutes)	5	7	4	5.5	4.5	7	4	5	5	6	5	5	6	7.5	6	7	5.5	7.5
Tablet compression force (N)	3800	4800	2800	3600	3000	3600	2800	3200	3500	4600	2900	3650	3000	3899	3000	4600	3200	4788
Average Thickness (mm), n=5	6.79	6.8	6.8	6.81	6.8	6.81	6.82	6.78	6.85	6.8	6.82	6.83	6.82	6.8	6.82	6.82	6.83	6.8
Average .Hardness(N), n=3	144	180	100	98	160	197	133	162	128	150	156	177	135	154	167	156	178	210
Tensile strength (Mpa)	1.187	1.481	0.823	0.805	1.317	1.619	1.091	1.338	1.044	1.235	1.279	1.449	1.107	1.267	1.37	1.279	1.457	1.728
Solid fraction (%) of flakes	0.82	0.85	0.84	0.87	0.88	0.88	0.75	0.78	0.72	0.75	0.72	0.76	0.8	0.88	0.82	0.86	0.83	0.85
Compression pressure(F/A)	8.35	10.54	6.15	7.91	6.59	7.91	6.15	7.03	7.69	10.11	6.37	8.02	6.59	8.57	6.59	10.11	7.03	10.52

For robust manufacturing process and to have an option of recompaction, the most important step is to study the impact of compaction and recompaction of the granules and their change in compressibility behaviour during compaction process. As the granule behaviour has direct impact on tabletability. Physical evaluation of tablet shows that the % friability is well within limit (NMT 1%) and the disintegration time of all formula composition are below 15 minutes. From the tablet tensile strength data it can be concluded that with increase in compaction cycle the tensile strength of tablet increases. The increase in tensile strength is due to increase in solid fraction of flakes during recompaction. Tensile strength of tablet produced from cycle 2granules of formula composition RC-MET-9 is highest (1.728 Mpa) followed by the RC-MET-3, which has tensile strength of 1.619 Mpa. This is mainly due to better recompactibility of lactose Super Tab 21 AN and plastic deformation of silicified microcrystalline cellulose. This shows presence of dry binder also helps in achieving better solid fraction and hence better tensile strength of tablet could be achieved in the recompaction process. [28].

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CONCLUSION

From this experimentation with Metformin hydrochloride as a model molecule with high drug load, it can be concluded that compaction and recompaction can be considered as an option to target better tablet physical property. The quality target product profile of finished product can be designed with proper initial risk assessment for high drug load formulations. The most important thing is to perform the initial risk assessment for critical material attributes (CMA) such as nature of raw material like their solid state characteristics, their physical properties such as their surface morphology , particle size distribution, their compressibility and impact on roller compaction process. There is an expected challenge in the recompaction is the chance of losing compressibility of functional diluents, but this expected risk also can be mitigated by using qualitatively proper functional ingredients at a pre-defined quantitative mixture. From the above studied diluents or combination of diluents at 1:1, mixture of microcrystalline cellulose and lactose Super Tab 21 AN, mixture of microcrystalline cellulose and Mannitol, mixture of lactose Super Tab 21 AN and silicified microcrystalline cellulose, it can be concluded that combination of diluent with minimum percentage of dry binder up to 2% w/w can be used as functional ingredients to attain high quality target product profile with wider design space and with lower risk of process failure during scale up. Initial process development to be done to find impact of 1st cycle of roller compaction, if this is not helping for the cause or helping to get desired granules with targeted flowability, density, compatibility, tabletability and compressibility then, there is always an option available to go for recompaction. Recompaction in the presence of dry binder also gives add on impact to overcome manufacturing process related challenges associated with Metformin hydrochloride like molecule. It is critical to do careful selection of raw materials with suitable qualitative and quantitative ratio for their major diluent, consider their surface behaviour, their compressibility as individual excipients and also in combination. In the current study mixture of lactose Super Tab 21 AN and silicified microcrystalline cellulose is the most suitable diluent combination at a ratio of 1:1 to accommodate high drug load Metformin hydrochloride, this is due to the brittle fracture and plastic deformation of silicified microcrystalline cellulose and minimal loss of compactibility of lactose Super Tab 21 AN during roller compaction.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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