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https://doi.org/10.31925/farmacia.2026.2.14 **ORIGINAL ARTICLE**

PRECOMPRESSION STUDIES OF SOME MATERIALS BASED ON RIVAROXABAN DRY NANOSUSPENSIONS

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Abstract

To ensure suitable powder flowability, compactability, and, implicitly, tablet quality, precompression studies are essential assessments carried out on tablet powder blends before final compression. Various investigations are performed on tablet formulation materials as part of precompression research. These analyses aim to evaluate the flow and compressibility of powder blends to determine whether their physicochemical properties meet processing requirements. This study reveals the influence of dry nanosuspension formulations on the physical characteristics of materials intended for the direct compression process. Six direct compression blends were prepared: three containing dry nanosuspensions of rivaroxaban (RIV), Poloxamer 188 (P188), and hydroxypropyl methylcellulose (HPMC), and three containing their simple physical mixtures. Various formulations based on microcrystalline cellulose and spray-dried lactose were analysed to evaluate their flowability and compressibility properties to determine their suitability for direct compression. It was concluded that a higher amount of HPMC and the use of the lyophilisation technique result in blends unsuitable for direct compression.

Rezumat

Pentru a asigura o curgere și o compactibilitate adecvate ale pulberii și, implicit, calitatea comprimatelor, studiile de precomprimare sunt evaluări esențiale efectuate asupra amestecurilor de pulberi de comprimare înainte de comprimarea finală. Diverse investigații sunt efectuate asupra materialelor de formulare a comprimatelor ca parte a cercetărilor de precomprimare. Scopul acestor analize este de a evalua curgerea și compresibilitatea amestecurilor de pulberi pentru a determina dacă proprietățile lor fizico-chimice îndeplinesc cerințele de procesare. Acest studiu relevă influența formulărilor de nanosuspensii uscate asupra caracteristicilor fizice ale materialelor destinate procesului de comprimare directă. Au fost preparate șase amestecuri de comprimare directă: trei conținând nanosuspensii uscate de rivaroxaban (RIV), Poloxamer 188 (P188) și hidroxipropilmetilceluloză (HPMC), iar trei conținând simplelor lor amestecuri fizice. Diverse formulări pe bază de celuloză microcristalină și lactoză uscată prin pulverizare au fost analizate pentru a evalua proprietățile lor de curgere și compresibilitate și a determina dacă acestea sunt adecvate pentru comprimarea directă. S-a concluzionat că o cantitate mai mare de HPMC și utilizarea tehnicii de liofilizare duc la amestecuri nepotrivite pentru comprimarea directă.

Keywords: precompression studies, rivaroxaban, dry nanosuspensions, direct compression

Introduction

Direct compression (DC) is the most studied method for manufacturing solid dosage forms, involving the direct processing of a mixture of active substance and excipients into tablets without intermediate wet or dry granulation steps. In an era focused on sustainability and cost efficiency, DC has become the preferred method in the pharmaceutical industry. However, its success depends entirely on the intrinsic physicochemical properties of the raw materials, making excipient selection a critical step in tablet development (1).

The transformation of a powder into a tablet depends on the micromeritic properties of the powder mixture. Flow and compressibility studies are not simple routine tests; they are fundamental to predicting production processes and directly influence dose uniformity, mechanical stability, and the disintegration and dissolution behaviour of the finished product (2, 3). For this reason, current pharmacopoeias include clear monographs that establish methods to identify the flow behaviour of mixtures to be compressed.

Nanosuspensions – colloidal dispersions of pure drug particles with submicron sizes, stabilised by surfactants or polymers – have emerged as a robust solution to increase dissolution rate and solubility saturation. However, liquid nanosuspensions exhibit long-term physical instability, including sedimentation, agglomeration, and crystal growth by Ostwald ripening. Therefore, transforming them into dry nanosuspensions (solid forms) has become essential

for the stability of the commercial product. Also, dry nanosuspensions offer additional benefits beyond increasing the solubility of the incorporated active ingredients, such as improved chemical stability (the absence of water reduces hydrolysis) and the potential for incorporation into solid pharmaceutical forms, such as capsules and tablets (4-6).

This study aimed to develop appropriate direct compression blends containing dry nanosuspensions of rivaroxaban (RIV), Poloxamer 188, and hydroxypropyl methylcellulose (HPMC). Various formulations based on microcrystalline cellulose and spray-dried lactose were analysed to evaluate their flowability and compressibility properties for establishing their suitability for the direct compression process. RIV was selected as the active ingredient for the nanosystems because of its low aqueous solubility, which limits its dissolution and absorption performance.

Rivaroxaban is a direct, selective, and reversible inhibitor of Factor Xa (FXa), effectively stopping thrombin production without affecting existing thrombin, thereby reducing the risk of arterial and venous thrombotic events (7). Classified as a Class II compound in the Biopharmaceutical Classification System (BCS), it has high membrane permeability but extremely low aqueous solubility (approximately 5 - 7 mg/L). Suspending the molecule in a hydrophilic polymer matrix, such as HPMC, prevents recrystallisation and maintains the substance in a thermodynamically "activated" state, enabling rapid and complete release (8, 9).

Different dry RIV nanosuspensions were prepared by varying the mass ratio of active ingredient, polymer, and surfactant (RIV, Poloxamer 188, and HPMC) to 1:1:1, 1:2:1, and 1:1:2. The three systems were characterised for their pharmacotechnical properties. The nanosystems were then blended with varying amounts of directly compressible excipients, and the mechanical properties of the powders were assessed in comparison to the active ingredient complexes. The aim was to select formulations of dry nanosuspensions and excipients suitable for direct compression technology to transform them into fast-release tablets.

Materials and Methods

Materials

Labormed-Pharma SA, Romania, kindly provided micronised RIV (Form I) manufactured by Neuland Laboratories Limited. Poloxamer 188 (P188) (poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) copolymer) and hydroxypropyl methylcellulose (HPMC) were purchased from Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany. Avicel® PH 102 was manufactured by International Flavors and Fragrances Inc. (IFF), USA, and Flowlac® 100 by Meggle GmbH & Co. KG, Germany. EXPLOTAB® was supplied by JRS PHARMA GmbH & Co. KG, Rosenberg, Germany, and LIGAMED® MF-2-V by Peter Graven NV, Netherlands.

All chemicals and solvents used were of analytical reagent grade.

A Mettler Toledo AT261 balance with a sensitivity of 0.01 mg was used to weigh the materials.

Methods

Formulations of the materials for direct compression

To produce tablets with a total weight of 200 mg, corresponding to a concentration of 10 mg RIV, the amounts of the constituent ingredients were calculated. Three of the six series of compounded powders contained dry nanosuspensions as active ingredients, while the other three contained simple physical mixtures. Table I shows the selected formulations for each system.

Table I

The composition of the direct compression materials

Ingredients	Formulation / Amount (%)					
	F1	F2	F3	F4	F5	F6
RIV-P188-HPMC (1:1:1 dry nanosuspension)	15	-	-	-	-	-
RIV-P188-HPMC (1:1:1 physical mixture)	-	15	-	-	-	-
RIV-P188-HPMC (1:2:1 dry nanosuspension)	-	-	20	-	-	-
RIV-P188-HPMC (1:2:1 physical mixture)	-	-	-	20	-	-
RIV-P188-HPMC (1:1:2 dry nanosuspension)	-	-	-	-	20	-
RIV-P188-HPMC (1:1:2 physical mixture)	-	-	-	-	-	20
Avicel® PH 102 – microcrystalline cellulose	41.5	41.5	39	39	39	39
Flowlac® 100 – spray-dried lactose	41.5	41.5	39	39	39	39
EXPLOTAB® - Sodium starch glycolate	1.00	1.00	1.00	1.00	1.00	1.00
LIGAMED® MF-2-V-Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00

The effects of excipients and nanosystems utilized as active ingredients on the characteristics of the materials were examined. Avicel® PH 102 (microcrystalline cellulose) and Flowlac® 100 (spray-dried lactose) were chosen for all formulations due to their reliable filling, binding, and disintegrating qualities, but primarily for their efficient flowability and compressibility—essential characteristics for the direct compression process, particularly for amorphous active ingredients with poor flow properties (10). Explotab® (sodium starch glycolate) was chosen as a superdisintegrant, and Ligamed® MF-2-V (magnesium stearate) was utilised for its gliding qualities (11).

Manufacturing of the direct compression materials

The ingredients (except for the magnesium stearate) were sieved (20-mesh sieve), weighed, and then mixed in a CMP 12 Plexiglas cube mixer from Pharmag GmbH, Germany, for 15 minutes at 25 rpm. Magnesium stearate was added at the end, and the blend was stirred following the same conditions for 2 minutes.

Pharmacotechnical analysis of the blends

Every nanosystem, physical mixture, and their direct compression blend was analysed.

Fineness was examined by analytical sieving (12) using a CISA sieving shaker Mod. RP 10, produced in Spain by Cisa Cedaceria Industrial. The sieves were placed in decreasing order of fineness. 10 g of each powder was poured onto the top sieve, then the system was shaken at an amplitude of 600 rpm for five minutes. Each sieve's residual powder was gathered and weighed.

Moisture content was estimated as the loss on drying (12) determined by the thermogravimetric method with a HR 73 Mettler Toledo halogen humidity analyser produced by Mettler-Toledo GmbH, Switzerland.

Flowability was indicated by the flow time, flow rate, and angle of repose (12) recorded after passing 10 g of each sample through an orifice with a standard diameter. The test was conducted using an Automated Powder and Granulate Testing System PTG-S3 from Pharma Test Apparatebau GmbH, Germany. The test starts with the smallest diameter nozzle, 10 mm, and no stirring. If the powder does not flow through this orifice, stirring is applied at increasing speeds: first 5 rpm, then 10 rpm, 15 rpm, and finally 25 rpm. If the powder still does not flow, the nozzle is changed to one with a larger diameter, 15 mm, and agitation is applied at the same speeds. If the powder does not flow, the nozzle with the largest orifice, 25 mm, is used, and agitation is applied at the same speeds.

Compressibility was evaluated by calculating bulk and tapped densities, the Carr Index (CI), and the Hausner ratio (HR) (12). Ten grams of each sample were placed in the cylinder of the Vankel Tap Density Tester (Vankel Industries Inc., USA), and the bulk volume was measured. The cylinder was then subjected to 1,250 mechanical shocks, after which the tapped volume was determined. Finally, HR and CI were calculated using the following formulas:

$$HR = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (1)$$

$$CI(\%) = 100 \times \frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{tapped}} \quad (2)$$

where ρ_{tapped} is the tapped bulk density of the blend (g/cm^3) and ρ_{bulk} is the loose bulk density of the material (g/cm^3).

The powder is free-flowing if the HR value is less than 1.25, and the material has good flowability and compressibility if the CI value is less than 10 (13).

Each analysis was performed in triplicate, and the results are expressed as mean ± standard deviation. Data analysis was performed using XLSTAT Premium v.2025.2.0.1232 (USA) and Microsoft Excel v. 16.0 19328 (USA).

Results and Discussion

Particle size

When employing direct compression technology, the consistency and integrity of tablets, die filling, and powder flowability are all determined by the particle size of the materials. Achieving an optimal particle size distribution is necessary to manufacture tablets with acceptable pharmacotechnical and biopharmaceutical properties (14). The pre-compression experiments are necessary to ascertain the range of the particle size distribution.

The recorded histogram for the powders under investigation is displayed in Figure 1, where granulometric classes are used to present the particle size distribution.

The samples clearly differ in the fineness of the powders. Most particles in all materials are between 125 and 250 µm in size. According to Wünsch I. *et al*., resistance to compression rises as particle size decreases, most likely because deformation mechanisms during compression play a major role (15).

The differences between the primary compounds are not that evident, but in every instance, the physical mixtures contained a greater percentage of particles in the 160 - 250 µm range than the dry nanosuspensions, indicating that the preparation technique impacts particle size. In the physical mixtures, the percentage of particles between 80 and 250 µm ranges from 60.84% (RIV-P188-HPMC 1:2:1 physical mixture) to 76.03% (RIV-P188-HPMC 1:1:2 physical mixture), while in the nanosystems, it ranges from 62.94% (RIV-P188-HPMC 1:2:1 dry nanosuspension) to 76.88% (RIV-P188-HPMC 1:1:2 dry nanosuspension). Additionally, RIV-P188-HPMC 1:1:2 dry nanosuspension has the highest proportion of particles below 80 µm (23.12%). Meanwhile, no primary system contains particles larger than 600 µm, and both RIV-P188-HPMC 1:1:1 and RIV-P188-HPMC 1:1:2 dry nanosuspensions do not have particles larger than 250 µm.

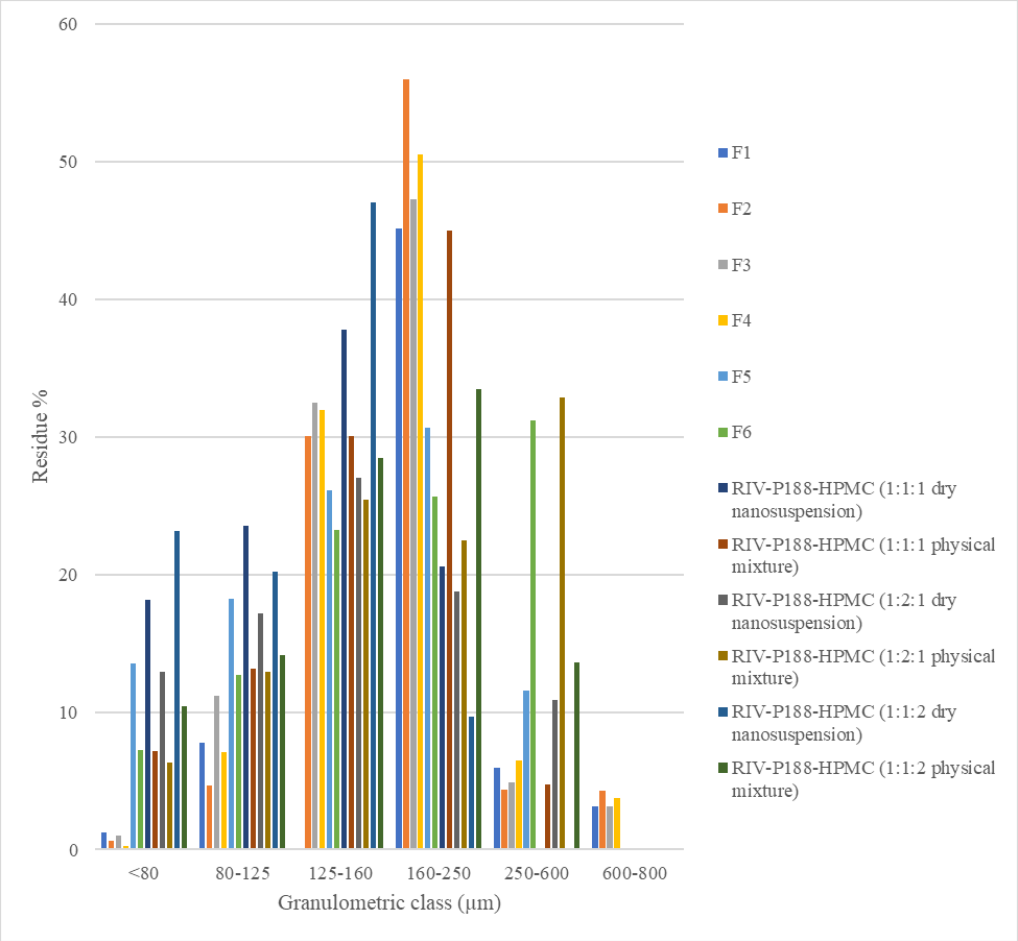

Figure 1.
Granulometric evaluation of the materials

However, the excipients added to the active substances significantly impact powders for direct compression. In comparison to the primary systems, there is a notable shift in particle size distribution for F1 - F6, with a significant increase in particle size. Particles larger than 250 µm were observed in these cases. The distinction between materials based on physical mixtures and those incorporating dry nanosuspensions remains similar to initial data, with the highest quantity of particles in the 250 - 600 µm range. While F2 and F4, which contain RIV-P188-HPMC 1:1:1 and 1:2:1 physical mixtures, respectively, have less than 1% of particles below 80 µm, F6, based on the RIV-P188-HPMC 1:1:2 physical mixture, has a higher percentage of particles in this class (7.24%). In the compression blends containing the dry nanosuspensions, F1 and F3 have low amounts of particles below 80 µm (around 1%), while F5 presents a large amount of small particles (13.51%).

The results show that both the preparation method and the mass ratio between the components strongly influence the particle size distribution of the systems. Moreover, the addition of excipients significantly changes the granulometric classification of the powder particles.

Nevertheless, it can be observed that the formation of the nanosystems and the lyophilisation technique led to lower particle size, while the simple physical mixture results in coarser particles. Also, using the RIV-P188-HPMC 1:1:2 mass ratio produces smaller particles.

It is reasonable to assume that the materials will behave differently in terms of flow and compression due to the observed variations.

Moisture content

The moisture level of the powder is an important factor that affects both the final tablet quality and the homogeneity and behaviour of the mixture during compression (16). The humidity content of the samples is shown in Figure 2.

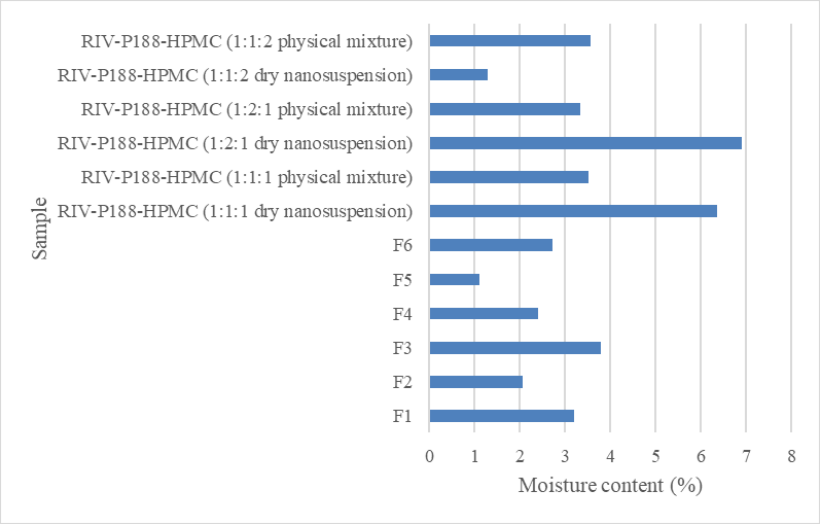

Figure 2.
Moisture content of the materials

Since the nanosuspensions were produced in liquid phase and then freeze-dried, it was expected that the samples would contain a specific amount of moisture. Because water vapour fills the pores in the hygroscopic zone and condenses on the capillary contour, Koumbogle K *et al*. explained that moisture transfer occurs predominantly by vapour diffusion (17).

The cohesion and flow energy of powders increase with higher water content (18). This is because moisture content affects the two fundamental forces between particles: adhesion force and frictional force (19). Higher cohesive forces and capillaries between particles might emerge from liquid bridges that form when moisture is deposited on the particle surface (20). This can cause powder agglomeration, reducing flowability (21). Still, water molecules can act as a lubricant between powder particles, reducing friction and improving flowability (22). For this reason, a certain low amount of moisture is required in the powder blend, but it should not exceed. According to Crouter A. and Briens L. (23), moisture has a plasticising impact on the powders. Also, Abu Fara D *et al*. (24) showed that the compressibility of solids was drastically diminished once the water was removed. Furthermore, the authors demonstrated that high moisture content decreases interparticulate linkages, which lowers tablet hardness. These findings can explain the behaviour of the materials studied in the present work.

While only slight variations were observed among the physical mixtures, there is a significant difference between the dry nanosuspension systems. Notably, the RIV-P188-HPMC 1:1:2 dry nanosuspension has a low moisture content (1.29%) compared to the corresponding physical mixture (3.57%) and the other two nanosuspensions, RIV-P188-HPMC 1:1:1 (6.35%) and RIV-P188-HPMC 1:2:1 (6.91%). This demonstrates the significant influence of the component ratio in the systems, revealing drastic differences in the structure of the obtained compounds. Additionally, a significant difference between the primary compounds and the direct compression materials was identified. These variations result from the addition of the excipients, which significantly diminishes the powders' moisture content. The direct compression blends exhibited the same pattern as the primary systems, with F5 having the lowest moisture content (1.11%), less than half the humidity of F1 or F3.

The results mainly reveal the significant impact of the proportions between the ingredients in the primary systems on the physical properties of the materials.

Flowability

The results registered for the flowing parameters are shown in Table II.

Regarding the flowability of the primary systems, even with the largest nozzle (25 mm) and the fastest stirring speed (25 rpm), the RIV-P188-HPMC (1:1:2 dry nanosuspension) did not flow. This is caused by both the freeze-drying method, which produces amorphous powders (25), and the high amount of HPMC in the system.

For all primary systems, measurement was possible only with a 25 mm nozzle and a 25 rpm stir, indicating poor flowability. Among these, all physical mixtures exhibited a faster flow rate than the corresponding dry nanosuspensions, demonstrating low flow performance for the lyophilised systems. The influence of the mass ratio of the components was again observed, with the best behaviour in the 1:1:1 system. The resistance of the powder to flow is determined by the existence of interparticle interactions. Blanco D. *et al*. (26) explained that the powder flow is determined by a variety of interparticle forces, including van der Waals, electrostatic forces, capillary forces, mechanical interlocking, and other frictional

and gravitational forces. Also, Shah D.S. *et al*. (27) concluded that determining powder flow is crucial to guarantee product performance. The authors state that inter-particulate friction, or resistance to particle movement, is indicated by the angle of repose and consider it a better parameter for evaluating material flowability than the flow rate through an orifice, which is too influenced by the method used and is not an intrinsic attribute of the powder.

Table II

Flowing parameters

Sample	Flow time (sec)	Angle of repose (θ degrees)	Flow rate (g/s)
RIV-P188-HPMC (1:1:1 dry nanosuspension)	4.21 ± 0.36*	45.12 ± 2.16*	2.375*
RIV-P188-HPMC (1:1:1 physical mixture)	3.96 ± 0.17*	42.95 ± 2.07*	2.525*
RIV-P188-HPMC (1:2:1 dry nanosuspension)	6.09 ± 0.08*	48.61 ± 3.02*	1.642*
RIV-P188-HPMC (1:2:1 physical mixture)	4.76 ± 0.24*	46.77 ± 2.86*	2.100*
RIV-P188-HPMC (1:1:2 dry nanosuspension)	-*	-*	-*
RIV-P188-HPMC (1:1:2 physical mixture)	5.88 ± 0.43*	49.23 ± 2.06*	1.700*
F1	2.55 ± 0.37**	28.44 ± 1.94**	3.921**
F2	2.19 ± 0.14**	27.92 ± 2.08**	4.566**
F3	2.72 ± 0.35**	29.35 ± 2.64**	3.676**
F4	2.49 ± 0.23**	27.63 ± 1.28**	4.016**
F5	3.79 ± 0.45*	35.69 ± 2.83*	2.638*
F6	2.66 ± 0.28**	29.24 ± 2.71**	3.759**

*25 rpm stirring, nozzle: 25 mm; **10 rpm stirring, nozzle: 15 mm.

On the other hand, all six blends for direct compression demonstrated significantly better flow behaviour, but only F5 didn't pass through the 15 mm nozzle with 10 rpm stirring. F5 managed to pass only when a larger nozzle and a higher stirring were used. However, none of the samples meets the European Pharmacopoeia requirements (12) for good or excellent flow performance, but F1-F4 and F6 exhibit appropriate flow behaviour for the direct compression process.

The materials with a 1:1:1 mass ratio of RIV-P188-HPMC showed the highest flow rates: 3.921 g/s for the blend containing the dry nanosuspension and 4.566 g/s for the blend with the physical mixture. As anticipated, formulations based on physical mixtures exhibited better flow rates than those containing lyophilised nanosuspensions. Similar to the primary systems, the 1:1:2 mass ratio RIV-P188-HPMC blends displayed the lowest flow rates, demonstrating that the proportion of components affects the materials' flowability.

Compressibility

Table III displays the recorded results for the powders' volumetric characteristics.

$$HR = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (1)$$

$$CI(\%) = 100 \times \frac{(\rho_{tapped} - \rho_{bulk})}{\rho_{tapped}} \quad (2)$$

Table III

Volumetric characteristics

Sample	Bulk density (g/mL)	Tapped density (g/mL)	Carr Index (CI) (%)	Hausner's ratio (HR)
RIV-P188-HPMC (1:1:1 dry nanosuspension)	0.220	0.455	51.64	2.07
RIV-P188-HPMC (1:1:1 physical mixture)	0.316	0.568	44.37	1.79
RIV-P188-HPMC (1:2:1 dry nanosuspension)	0.203	0.481	57.79	2.37
RIV-P188-HPMC (1:2:1 physical mixture)	0.305	0.529	42.34	1.73
RIV-P188-HPMC (1:1:2 dry nanosuspension)	0.197	0.501	60.67	2.54
RIV-P188-HPMC (1:1:2 physical mixture)	0.315	0.574	45.12	1.82
F1	0.413	0.597	30.82	1.44
F2	0.458	0.655	30.07	1.43
F3	0.394	0.611	35.51	1.55
F4	0.426	0.680	37.35	1.59
F5	0.350	0.713	50.91	2.03
F6	0.407	0.638	36.20	1.56

For evaluating flowability and anticipating compaction or segregation issues, volumetric features like the Hausner ratio and the Carr index are crucial. These characteristics are essential for determining the materials' potential for compressibility since they indicate how particle interactions influence flow behaviour. For powders that flow freely, these interactions are insignificant and only slightly alter the bulk and tapped densities. For materials with poor flow qualities, on the other hand, there is a noticeable difference between these densities because the particle interactions are stronger. Because

voluminous blends enhance the powder compression processing, an increase in bulk density is beneficial for die filling in tablet manufacturing. As many factors can affect the compressibility index, it has been proposed as an indirect measure of bulk density, particle size and shape, moisture content, surface area, and material cohesiveness (28).

The dry nanosuspensions have "very, very poor flowability" (29), with CIs above 50% and HRs above 2, according to the volumetric analysis results, which are in line with the flowability findings. Again, RIV-P188-HPMC (1:1:2 dry nanosuspension) had the highest values of 2.54 for HR and 60.67% for CI.

The findings certify that the employed mass ratio and the procedure used to acquire the systems have an impact on the materials' flowability and compressibility.

Surprisingly, F5 shows higher CI and HR values than all other direct compression blends and even the primary physical mixtures, indicating it is not suitable for direct tablet processing.

For the other tablet materials, a significant change in the trend of volumetric parameters is observed. Compared to the primary systems, the powders for direct compression showed better flowability and acceptable compressibility because the excipients, especially the lubricant and fillers, were appropriately chosen. Lower values for CI and HR indicate that the formulations with physical mixtures have superior flowability compared to those with dry nanosuspensions. The best results were observed in the 1:1:1 RIV-P188-HPMC systems.

Except for F5, the other direct compression materials have "passable flowability" in agreement with the European Pharmacopoeia specifications, meaning they can be processed by direct compression.

According to investigations by Prescott J.K. and Garcia T.P. (30) on content uniformity problems in tablets produced by the direct compression method, the most frequent technological issues include inappropriate particle distribution (agglomeration) and segregation of powders during compression operations. This reveals the importance of formulating materials with suitable physical characteristics, this being the first main role of the selected excipients.

As demonstrated by Zakhvatayeva A. *et al*. (31), unlike other physical properties of powders, which depend on various fundamental characteristics as well as material and ambient factors, flowability is a derived powder attribute. Particle size distribution, particle shape, moisture content, and inter-particle interactions – which ultimately indicate particle surface energy – are known to influence the intricate phenomena of powder flow.

Shah D.S. *et al*. (27) explained the importance of particle size on powder behaviour. They stated that the van der Waals force is the most significant force contributing to powder cohesion in fine dry particles. Gravitational forces become less significant as particle size decreases. Powder flowability is dominated by weak polarising van der Waals interactions between particles at sizes under 100 μm. The powder becomes extremely cohesive, and the particles flow as aggregates rather than individually when these attractive forces are at least an order of magnitude greater than the particle weight. The relatively large surface area of small particles causes a high degree of surface adhesion and contact with nearby particles.

However, when shear pressure is applied, the large particles will flow over one another and exhibit less coherent and stable behaviour. This is because cohesive forces from electrostatic, capillary, or van der Waals interaction make external forces like gravity far more important for larger particle sizes than interparticle forces. For any given powder, the smaller particle size increases the surface area per unit mass, giving more space for surface cohesiveness, interactions, and flow obstacles. According to Mullarney M.P. *et al*. (32), if these coherent forces could be reduced, the powder's flow characteristics would be much improved.

In their research, Leung L.Y. *et al*. (33) demonstrated that minimising interparticle cohesive forces rather than interparticle friction is a more effective way to enhance pharmaceutical powder flow.

Janjatović D. *et al*. (34) concluded that the attraction of interparticle forces influences both flowability and compressibility characteristics.

Another significant element that remarkably impacts the powders' flowability is moisture content. The powder flow is hampered by the strong liquid bridges that are created between the particles due to the high liquid concentration.

Emery E. *et al*. (35) concluded that moisture strengthens van der Waals forces, reducing the distance between particles. Because water is conductive, electrostatic forces diminish as moisture content increases. Moisture decreases the surface roughness of the particle solids, minimising friction and interlocking that impede powder movement.

According to Tomasetta I. *et al*. (36), on microcrystalline cellulose, the powder's mechanical characteristics change dramatically when moisture is present. The influence was explained by the water's plasticising effect, which modifies the powder's flowability.

In their investigation, Deng T. *et al*. (37) found that segregation during container discharge through a sealed vertical chute was the cause of a reduced active ingredient content in the tablets manufactured by direct compression. The air inside the pipe was forced upward as the powder was gravitationally transmitted through it, causing the powder bed to permeate and tiny particles to suspend. The blend was subjected to air elutriation tests, which verified

the occurrence of air-induced segregation because it contained active ingredient particles that were bigger in size than the particles of the excipients. The changes in tablet concentration during the tabletting process were explained by the accumulation of fine excipients reaching the press at the end of the compression and the earlier discharge of coarse API particles into the machine. The effects of powder cohesiveness and flowability were investigated. The findings showed that less cohesive, free-flowing mixtures are more vulnerable to air-related segregation during gravitational transfer through a vertical pipe.

Powder flow refers to its ability to move freely and uniformly under the influence of gravity or mechanical forces. In the context of a DC method, flowability determines process efficiency (38). The powder must flow quickly and steadily from the hopper into the dies. Poor flow causes incomplete or inconsistent filling of the dies, resulting in tablets with varying weights and, consequently, non-compliant active ingredient doses (39).

In direct compression, the absence of moisture often results in primary powder particles having high surface energies (40). Powder flow is a complex phenomenon governed by the balance between driving forces, such as gravity, and r interparticle resistance forces, including Van der Waals forces that cause cohesion and can halt flow in the hopper (bridging phenomenon or "salt bridge"), as well as electrostatic forces generated by friction (triboelectric effect) during mixing. These forces can cause the powder to adhere to the walls of the compression machine. Unlike liquids, powders exhibit internal shear resistance even at rest.

As particle size decreases, especially below 50 μm, the surface area-to-volume ratio increases, and cohesive forces become dominant over particle mass. This leads to phenomena such as bridging (the formation of particle bridges above the discharge orifice) or ratholing (preferential discharge through the centre, leaving dead zones along the hopper walls) (41-43). Standardised evaluation methods, such as the angle of repose, Carr index, and Hausner ratio, provide valuable information about powder flowability.

If flowability ensures powder transport, compressibility defines solid tablet formation. Compressibility is a system's ability to reduce its volume under pressure, while compactibility refers to the resulting mechanical strength. The major challenge in powder design is often the antagonism between these two properties. Large, spherical particles flow well but have little contact surface area for bonding. Conversely, fine particles offer superior compactibility, but block the production process (44, 45).

The transition from a liquid nanosuspension to a solid form (dry nanosuspension) involves a competition between the rate of solvent removal and the rate of particle aggregation. According to the DLVO theory (Derjaguin, Landau, Verwey, and Overbeek), the stability of the system depends on the balance between Van der Waals attractive forces and electrostatic repulsive forces (46). During drying by either spray drying or lyophilisation, as the droplet shrinks, the concentration of nanoparticles increases exponentially. If the diffusion time of the stabiliser to the interface is longer than the evaporation time, the particles will collide and fuse (coalescence), negating the benefits of nanoformulation. Therefore, selecting polymers that isolate individual nanoparticles is critical to create a mechanical barrier between the nanocrystals before they reach the critical point of aggregation (47, 48).

Another important challenge for tablet technology is the flowability of powders obtained by lyophilisation. In contrast to spray-drying, which tends to produce spherical particles, lyophilisation often generates a porous, irregular, and highly hygroscopic structure with poor rheological properties. Lyophilised particles are highly porous because the ice has sublimed, leaving voids. This results in very low bulk density, making gravitational forces too weak to overcome cohesion. The large contact surface also increases the likelihood of Van der Waals and hydrogen bond formation between particles (49).

For lyophilised nanosuspensions, flow is even more problematic because the nanoparticles are dispersed in a solid matrix. Redispersibility – the ability to return to a nanosuspension upon contact with water – depends on porosity. However, industrial processing of the powder requires a compromise between porosity and density to ensure adequate flow (50).

Conclusions

It can be observed that the primary factor affecting the behaviour of the powder blends is the mass ratio between the components of the nanosuspensions, followed by the manufacturing technique used. It can be concluded that a higher amount of HPMC and the lyophilisation technique result in blends unsuitable for direct compression. Therefore, it is assumed that F5 cannot be processed into tablets by direct compression, as its flowability and compressibility are insufficient for the required transformations during this procedure.

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Conflict of interest

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