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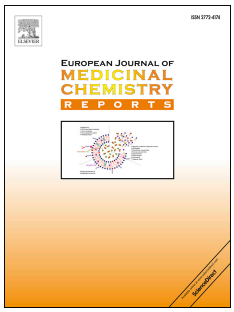

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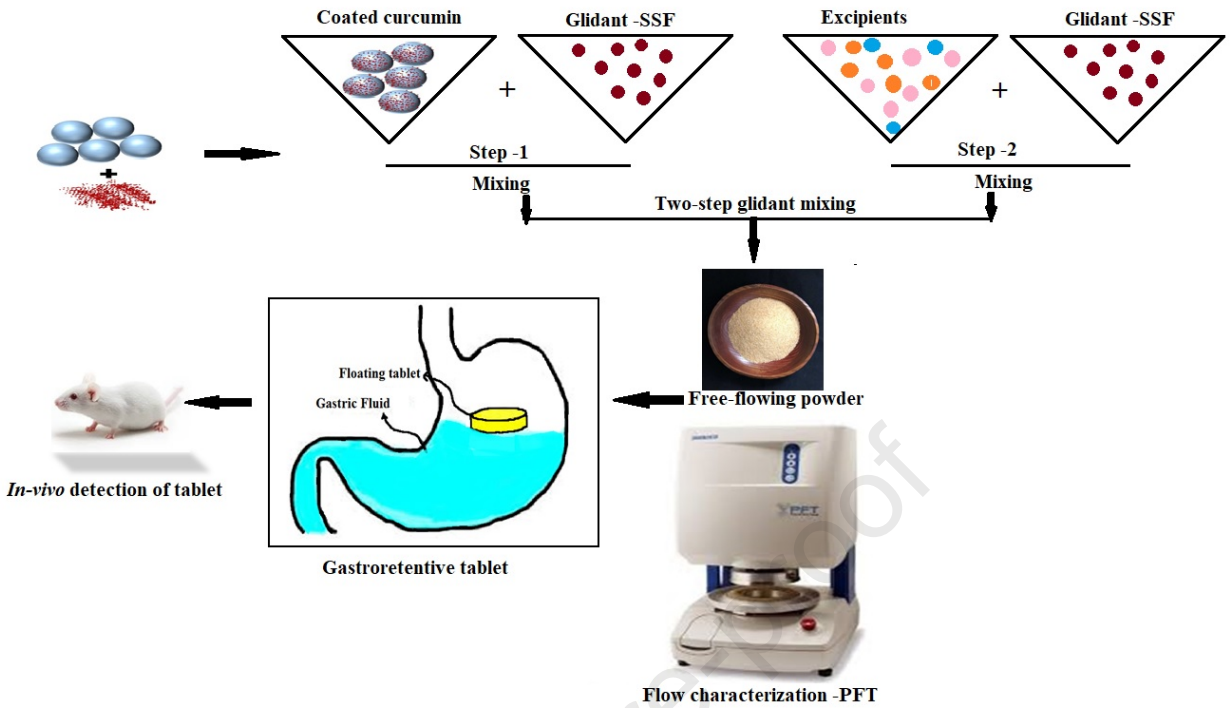

Title Page

Impact of two-step glidant mixing process on flow performance of coated curcumin - in vitro, *in vivo* investigation

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Impact of two-step glidant mixing process on flow performance of coated curcumin - in vitro, *in vivo* investigation

Abstract:

Curcumin is a well-known phenolic compound obtained from *Curcuma Longa L.* It is used popularly as an antioxidant, anti-inflammatory, antispasmodic, antithrombotic, anticancer as well as immune-modulator. In the last couple of years, few studies showed the usefulness of curcumin against *Helicobacter pylori* along with the potential to restore gastric damage. However, limited solubility, poor alkaline pH stability and flow property have rendered the industrial application of curcumin. The current research focuses to address this limitation by modifying the flow property using coating and two-step glidant mixing process and then converted into dosage form. Furthermore; to have reproducible and reliable results, flow property was investigated by the advance methodology- powder flow tester (PFT). Initially, curcumin powder was coated with HPMC and further mixed with glidant Sodium Stearyl Fumarate by two methods viz. one-step and two-steps mixing operation. Both blends were investigated for various parameters viz. flow function test, wall friction test and bulk density. We found that a two-step glidant mixing operation to coated curcumin enhanced powder to flow significantly more than one-step. In the lateral stage, both blends were converted into gastroretentive tablets by using the direct compression method. Tablets prepared by using a two-step blend process showed more satisfactory results than one-steps with floating time of 24 h and 21 h respectively. Coating, two-step glidant mixing and PFT were found unique combined

approach to prepare the direct compression tablet of curcumin, as it enables the industry to overcome production problems and ensure high-quality products.

Keywords: Curcumin; direct compression; two-step mixing and coating; powder flow tester; Gastroretentive tablet.

1.0 Introduction

Curcumin, a bioactive phenolic compound isolated from Curcuma Longa L. has already proven ability as antioxidant, anti-inflammatory, antispasmodic, antithrombotic, anticancer as well as immune-modulator(Gowthamarajan, Jawahar, Wake, Jain, & Sood, 2012). Recently, *in vitro* and *in vivo* studies showed promising results of curcumin against *Helicobacter pylori*. Curcumin not only prevents the growth of *H. Pylori* but also helps to restore the gastric damage(Foryst-Ludwig, Neumann, Schneider-Brachert, & Naumann, 2004). Curcumin gave evidence of control on inflammation in H. pylori-infected human gastric epithelial cells. Moreover, it has also illustrated the healing capacity of severe peptic ulcer(Treesinchai, Puttipipatkhachorn, Pitaksuteepong, & Sungthongjeen, 2019). Nevertheless, the low solubility of curcumin, instability at alkaline pH and photodegradation has limited its clinical applications(Ansari, Ahmad, Kohli, Ali, & Khar, 2005; Ashif Khan, Akhtar, Sharma, & Pathak, 2015). Despite these key limitations, many medicinal, as well as nutritional companies utilize curcumin in different dosage forms due to the promising patient-oriented results(Pourmadadi, et al., 2022; Rajabzadeh-Khosroshahi, et al., 2022; Samadi, Yazdian, Navaei-Nigjeh, & Rashedi, 2021).

Curcumin present in powder form, its micrometrical properties plays a crucial role in the overall performance of dosage form and its profitability. The poor flow property is one of the major constraints on the industrial application of curcumin; and as we know that flow property of material can affect the overall performance of the dosage form which leads to a lack of content uniformity, significant variation in the drug release

151 profile, and ultimately safety as well as efficacy(Ruzaidi, Mandal, & Chatterjee,
152 2017). Hence to make effective use of curcumin in the treatment of peptic ulcers, there
153 is a need to address these limitations by modifying/improving in flow property
154 approach first and then converting into a dosage form which increases the gastric
155 residence time to avoid alkaline degradation at the intestine and susceptibility to
156 photodegradation.

157 Conventionally, flow property can be estimated by using official methods such as
158 angle of repose, Housner ratio, Carr's index and dispersibility. Even though these
159 methods are easy, economical and rapid, they are more dependent on the skill of the
160 person and results are not reproducible(Tan, AV Morton, & Larson, 2015). Hence,
161 discrepancies observe between engendered data and the actual performance of the
162 solids. Conventional evaluation methods are insufficient to focus on some key
163 parameters of flow behaviour that affect the overall *in vitro* as well as *in*
164 *vivo* performance of the prepared tablet(Zhu, Zhou, Yang, & Yu, 2008). These
165 precincts motivated researchers to develop advanced techniques for the
166 characterization of powders in terms of flow, our previous review stated detailed
167 methods to improve powder flow(Shah, et al., 2023). Now a day's, the behaviour of
168 solid materials is investigated by various new attributes such as flow function, internal
169 friction angle, hopper design, hopper half angle, internal frictional angle, rat hole and
170 arching dimensions by using newly developed automated technology. These methods
171 provide comprehensive data of material which is reproducible and trustworthy(Leturia,
172 Benali, Lagarde, Ronga, & Saleh, 2014). The fully automated Powder Flow Tester
173 (PFT); one of the advanced technology which overcomes the conventional method

issues. By using PFT any amateurish person can obtain desired data (powder analysis) short duration(Berry, Bradley, & McGregor, 2015).

By considering the therapeutic benefits of curcumin and its associated limitations, the proposed research work addressed those issues. It includes, a) coating of curcumin by HPMC, b) modification and compare of flow property by one-step (conventional) and two-step glidant mixing process and evaluation of flow property from a fully automated powder flow tester (PFT) which provided more reproducible and reliable results like flow function, internal friction angle, hopper design, hopper half angle, internal frictional angle, rat hole, and arching dimensions than the conventional testing method, and c) This improved curcumin was further converted into a gastro retentive tablet dosage form which can overcome the utmost limitations associated with the curcumin to target the peptic ulcer. However; this study provides more emphasis on a detailed investigation of the flow property of tablet blend by using advanced technology as powder flow tester. Nevertheless; there is no direct relation between the flow property and the gastro retention ability of tablets, but because of modified/improved flow of blend, it might leads to improve the overall performance of tablets(Jakubowska & Ciepluch, 2021). Using coating with HPMC, a two-step glidant mixing, and PFT is not a novel approach, but its combined application in context with curcumin is a unique approach and these comprehensive effects on the development of gastro retentive curcumin tablets is yet not addressed in the literature to the best of our knowledge.

2.0 Material and methods:

2.1. Material:

Sigma Aldrich, Mumbai, India, gifted curcumin and piperine as a free sample for purely research purposes. Hydroxypropyl methylcelluloseK15M (HPMC K15M) and sodium bicarbonate were provided by Colorcon Asia Pvt. Ltd, ltd. Goa, India, and JRS Pharma, Rosenberg, Germany respectively. As a gratis sample from Signet chemical corporation Pvt, Ltd, Mumbai, India, sodium stearyl fumarate (SSF) was given. Microcrystalline cellulose as well as Maltodextrin DE12 was received from Hi-Media Laboratories Pvt. Ltd. Bombay, India as gift samples.

2.2 Coating to curcumin by using HPMC polymer

The curcumin powder was subjected to coating by using a well known pan coating machine (ACG, Mini Quest, India)(Lingam, Ashok, Venkateswarlu, & Madhusudan Rao, 2008). For coating purposes, HPMC aqueous solution (1%) was used. To achieve uniform coating, the spraying rate (8-10ml/min), viscosity and air flow rate were regulated. Excess moisture from coated curcumin was removed by drying process at 45 ± 5 ℃ after 30 min of coating. Coated curcumin was used for further investigation.

2.3 Two-steps mixing processes of glidant - SSF

A dualistic mixing approach was tried in two-steps glidant blending process. Sodium Stearyl Fumarate (SSF) was used as a glidant material. An equal quantity of SSF (10mg each) was added separately in coated APIs as well as excipients. In this two-step, glidant blending process, the covering of SSF for about 20 minutes in double

cone blender (General Machinery Co., Mumbai) had been done with treated curcumin (coated curcumin) and all other excipients (table 2) respectively(Dun, Osei-Yeboah, Boulas, Lin, & Sun, 2018). This blend was further used for comparative flow property investigation.

2.4 One-step mixing process of glidant - SSF

In the one-step glidantmixing process, coated API, excipients as well as SSF are mixed together at a time.This is the most conventional approach to mixing of glidant with a tablet blend.The blend obtained after this unit operation was used for checking of influenceof the blending process in comparison to the previous blend(Pingali, et al., 2011).

2.5 Investigation of Curcumin and excipients for flowability by using Brookfield Powder flow tester (PFT):

The Brookfield PFT (Brookfield Engineering Laboratories, USA) which is a type of ring shear tester was used for flow property investigation. The PFT drives a compression vertically through the lid into a powder sample filled in the annular trough. A defined volume of sample powder was placed into the stationary lid at room temperature and weighed before the start of the test. Two types of lids were used for testing powder flow. The Vane lid was used to carry out the 'Standard flow function test 'while, the flat lid for the 'Standard wall friction tests. For the standard flow function tests and standard wall friction test, the applied uniaxial normal stress was in the range of 0.2 - 4.8kPa and 0.4 - 4.8 kPa respectively. A torque sensor was used to measure the resistance of the powder against the annular shear cell moving at a define

rotational speed (1 rev/h). A sequential normal and consolidated stress was applied to the powder by calibrated beam load annular cell which is controlled by the 'powder flow pro software. After analysis of data, the software gave flow function curves, hopper half-angle, bulk density graph, wall friction angle graph, yield locus, angle of internal friction and time consolidation information.

2.5.1 Flow Function Test:

The primary measure of powder flow property is the powder flow function test, which gives a measure of the amount of strength the material retains at a stress-free surface following consolidation to a given stress level. The curcumin and all excipients were subjected to a flow function test using PFT. The material under investigation was placed in a cylindrical cell and compacted under normal stress. The mould was then carefully removed to reveal a compacted column of powder and then the normal stress acting on the column of powder was gradually increased until failure occurs. The peak normal stress was recorded. This uniaxial unconfined failure test was conducted over a range of consolidation stresses and the flow function was constructed by plotting the unconfined failure strength versus the consolidation stress(Salehi, Barletta, & Poletto, 2017). Depending on value of flow function (ff) given by software material can be classified as given below;

Table 1. Value of flow function (ff)

Value of ‘ ff ’	**Nature of flow**
ff<1	Non flowing

1<ff<2	Very cohesive
2<ff<4	Cohesive
4<ff<10	Easy flowing
10<ff	Free flowing

258

259 **2.5.2 Wall Friction Test**

260 Drugs as well as excipients were subjected to a wall friction test by using Brookfield
261 PFT. It mainly involves the determination of the friction between the powder and
262 the wall of the hopper. It is one of the useful tools for assessing mass-flow hopper, half
263 angles and gravity flow chute angles. The larger the coefficient of wall friction, the
264 greater is the wall friction and vice versa. The friction acting at the wall/powder
265 interface has a significant influence on the stress distribution within processing
266 vessels, silos and hoppers. The higher the wall friction, the more of the powder weight
267 is transferred down through the silo/vessel/container walls, rather than compacting the
268 bulk solid below. The lower the friction, the more the self-weight is transmitted
269 through the bulk solid. This is popularly known as the Jassen effect. The wall friction
270 test provides an idea of the wall friction angle (chute angle) which represents the angle
271 to which a wall surface must be inclined to cause the powder to slip. The wall friction
272 angle is typically in the range of 10 to 45 degrees(Leaper, 2021).

273 **2.5.3 Bulk density**

274 Estimation of the bulk density of the material by using PFT gives a bulk density curve.
275 It represents the ability to control the stress acting on powder when it is flowing or

static. By using Brookfield PFT, one can check bulk density during the flow function test or can also be determined separately. In this study, we subjected curcumin and all excipients for investigation of the bulk density curve as a separate test. If material is a free-flowing, then it is incompressible or less compressible and shows a small increase in density with stress and vice-versa(Koynov, Glasser, & Muzzio, 2015).

2.5.4 Comparison of flow properties between curcumin and coated curcumin

To investigate the impact of coating on the flow characteristics of curcumin, HPMC-coated curcumin was subjected to evaluation of flow function test, wall friction test, bulk density and wall friction angle by using Brookfield PFT.

2.5.5 Comparison of flowability between Two-Step and One-Step Glidants Operations by using PFT

The impact of the method of addition of glidant i.e. one-step and two-step mixing was determined by subjecting obtained tablet blend for evaluation of flow characteristics with the help of Brookfield PFT. The blend was evaluated for various parameters such as flow function test, wall friction test, bulk density and wall friction angle to confirm the flow characteristics and ultimately impact of the same on the dissolution profile of the tablet.

2.6 Development of floating tablets:

The sample size for the experimental batch in this experiment was 2 kg. Composition is shown in table 2. Initially all ingredients were passes separately from sieve number 40. Curcumin was then subjected for coating by using HPMC and pan coater as

297 described in early step. The coated curcumin is blended with SSF as per procedure for
298 one-step and two-step glidant mixing. Finally, both blends i.e. obtained by one-step
299 and two-step glidant were subjected for tablet preparation by using direct compression
300 techniques. Tablets were prepared by using Cadmach ® rotary tablet press machine.
301 Tablets were compressed at fixed compression forces and rpm. In preparation of tablet
302 piperine was added to improve the absorption and bioavailability of drug. The
303 prepared tablets then evaluated for various parameters to confirm desired standards in
304 tables.

305 **Table 2.** Optimized composition of floating tablet

Ingredient	**Quantity (mg)**		**Role**
	Two-step	**One-step**	
Curcumin	500	500	Active
Piperine	5	5	Improve the curcumin absorption
Sodium bicarbonate	200	200	Effervescent
HPMC K15M	210	210	Polymeric binder
MCC	40	40	Density modifier
Maltodextrin	30	30	Diluent
Sodium stearyl fumarate	20	20	Hydrophilic lubricant

306

307 **2.7 Post compression evaluation**

Prepared tablets were evaluated for various parameters as described below;

2.7.1 Thickness and Hardness

The hardness and thickness of a tablet were measured by using a hardness tester (Pfizer, Mumbai) and a digital Vernier calliper scale (Vernier, Mumbai) respectively(K. K. Moravkar, Ali, Pawar, & Amin, 2017).

2.7.2 Weight variation

Weight uniformity in prepared tablets was determined as per the procedure given in Indian Pharmacopoeia-2018.

2.7.3 Friability

The tablet should possess enough strength to withstand various vibrations. It measures by using friability. It involves, the determination of percent weight loss of 10 tablets tumbled in a friabilator at 25 rpm for 4 min. As per USP, friability should be less than 1%(K. K. Moravkar, et al., 2017).

2.7.4 Swelling index

The swelling index of prepared tablets was determined by using USP dissolution apparatus type II. Six tablets of known weight were placed in dissolution apparatus containing 0.1N HCl as dissolution medium. The temperature was maintained at 37 ± 0.5 ^{o}C . Tablets were removed after 1 h and excess water was blotted by using tissue paper. Wet tablets were subjected to weighing again and the swelling index was calculated by using the following formula(Gattani, Londhe, Chalikwar, & Amrutkar, 2010).

$$Swelling\ Index = \frac{Wet\ weight\ of\ tablet - Dry\ weight\ of\ tablet}{Dry\ weight\ of\ tablet} X100$$

2.7.5 Determination of Floating Lag Time (FLT) and Total Floating Time (TFT)

For gastro-retentive tablets, the determination of the floating lag time (FLT) and total floating time is the most important *in vitro* parameters that can be correlated with *in vivo* gastric retention. Floating lag time is the time needed for the tablet to come to the surface and float. Total floating time is the total time for which the tablet floats in the dissolution medium

Prepared tablets (one-step and two-step glidant mixed) were subjected to FLT and TFT determination by using USP dissolution apparatus II (Electrolab TDT- 08L plus, Dissolution Tester USP Mumbai, India) by utilizing 900 ml HCL buffer pH 1.2, maintained at 37±0.5 °C and at 50 rpm (Sapate, PV, & Godbole, 2014).

2.7.6. *In vitro* drug release study

In vitro drug release study of prepared tablets was performed using a type II (paddle) apparatus. The tests were carried out in 900 ml of dissolution media containing 0.8% SLS in 1.2 pH buffers for 24 h at 50 rpm at 37±0.5 °C. The aliquot (5ml) was withdrawn at different time intervals viz. 0, 2, 4, 6, 8, 12, 20 and 24 h and analyzed for drug content by using a UV spectrophotometer at 423 nm. Data obtained from the drug release study was further subjected to describe drug release kinetics(Patel, Modasiya, Shah, & Patel, 2009).

2.7.7. Statistical test- in-vitro drug release study:

Applications of fit factors or similarity indices were calculated as follows to compare the dissolution profile of conventional-one-step glidant mixing and two-step glidant mixing process. The factor f1 is the average % difference of cumulative drug dissolved in overall time points (t) and the factor f2 is the value between 0 to 100 to access the dissolution similarity; where Rt is a percent of drug dissolved from product reference batch, Tt is a percent of drug dissolved from product of test batch, and n is the number of time points(Kassaye & Genete, 2013; Peh & Wong, 2000)

$$f2 = 50.log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0.5}\times 100\right\}$$

and

$$f1 = \left\{\left[\sum_{t=1}^{n}|Rt-Tt|\right]/\left[\sum_{t=1}^{n}Rt\right]\right\}\times 100$$

2.7.8. Accelerated Stability Studies and Storage Conditions (as per ICH guide lines)

The optimized floating tablet batch was sealed in aluminium packaging coated inside with polyethylene and placed in the humidity chamber maintained at 40 °C and 75% RH for 3 months (CHM-10S Remi Lab, Mumbai) as per ICH guidelines. At regular time intervals (after every month), samples were analyzed for the drug content, *in vitro* dissolution study, floating behaviour and other physicochemical parameters.

2.7.9. Shelf- life estimation of prepared tablet

The calculated amount of drug at each specified time interval was used to estimate the shelf life (t_{90}) of the optimized formulation. The curcumin content of the formulations was plotted against the time period (months) and the obtained graph was extrapolated to 90% of the activity in the tablet by using the Sigma Plot® software (V12.5, Cranes Software International limited, Bangalore, India) (Dangre, Tattu, Borikar, Surana, & Chalikwar, 2021).

2.8. In vivo gastric retention:

Assessment of stomach retention time of prepared curcumin loaded Gastroretentive tablet was investigated on Wistar rats with the slight modification described in Xitong Zhang et al. 2017(Zhang, et al., 2017). Rats (30) were divided into 5 groups (n=6). All rats were fasted for 12 h after receiving water and were anaesthetized with ether. The 3 mm curcumin tablet (prepared by using the optimized formula of a two-step glidant mixing process) was administered intragastrically and rats from specified groups were sacrificed after 0.5, 2, 4, 6 and 8h of treatments. Through the dissection process, stomach tissue along the great curvature was collected and checked for the presence of a tablet.

3.0 Result and discussion:

3.1 Investigation of Curcumin and excipients for flowability by using Brookfield Powder flow tester (PFT)

At the initial stage curcumin as well as all excipients i.e. Piperine, Sodium stearyl fumarate, HPMC K-15 M, Maltodextrin, Microcrystalline cellulose and sodium bicarbonate were subjected to determination of flow properties by using Brookfield

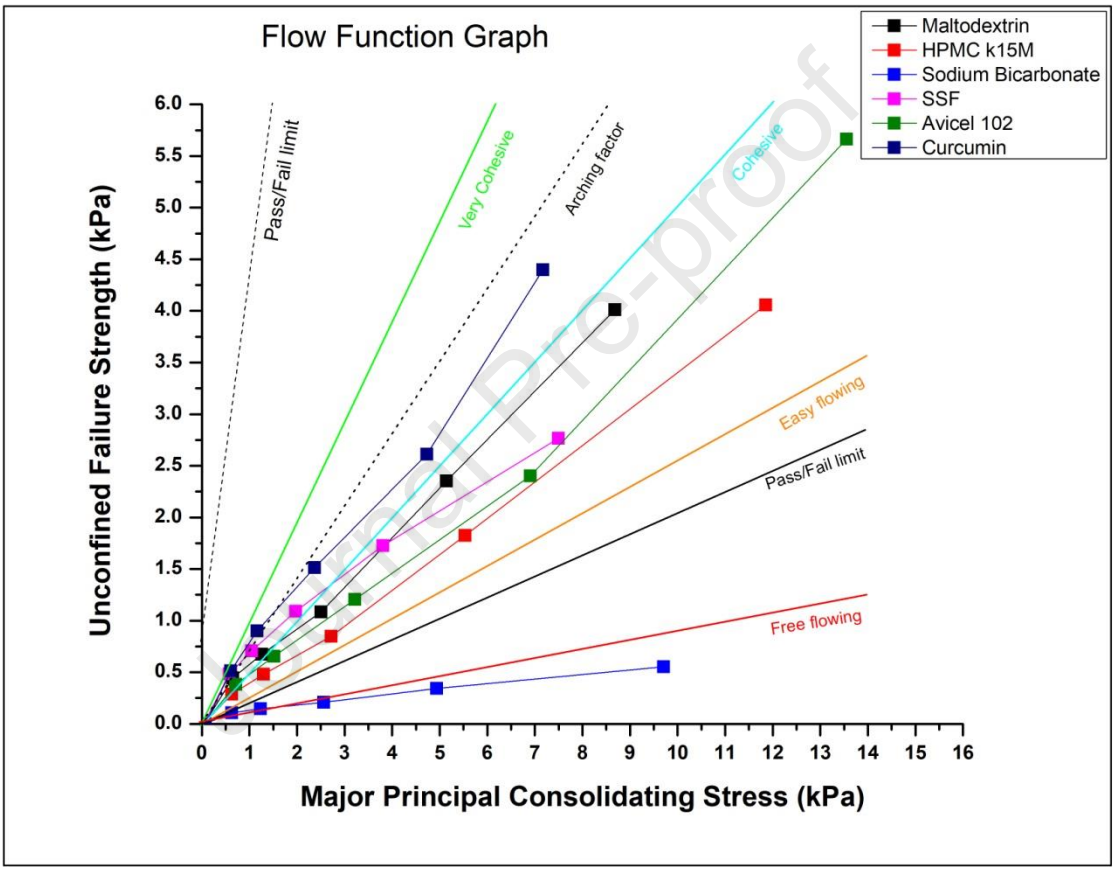
PFT (optimized formulae taken from our previous research lab work, Moravkar et. al., 2022). All materials were analyzed for various parameters such as flow function, bulk density, effective angle of internal friction and wall friction angle to understand the possible interaction of these substances in context with flow property and ultimately overall performance of tablet dosage form.

3.1.1 Flow Function Test:

Drug and all excipients were subjected to the determination of flow function and flow function curves were generated by *'powder flow pro software* which is the plot of major principal consolidating stress vs. unconfined failure strength (figure 1). As per Jenike's flowability principles, the flow function curve is divided into four parts according to the flow index value.

Initially, curcumin was found to be in the very cohesive region at initial small values of major consolidation stresses which then shifts towards a cohesive region or less cohesive region after the major consolidation stress. Amongst all excipients, sodium bicarbonate showed free-flowing properties with increasing major principle consolidation stresses (0.289 to 4.858 kpa). The MCC and HPMC exhibited cohesive to easy-flowing properties during the entire stress point. However; the impact of consolidation stress was less intense on MCC as well as HPMC in comparison to the rest of the material. SSF and maltodextrin both were present in the very cohesive regions at a low value of consolidation stress. After increasing stress, both excipients disclosed improved flow properties and entered from a very cohesive region to a cohesive region which indicates significant dependability of material on applied stress

414 points. From the result, it can be concluded that out of all raw materials, curcumin
415 possesses high cohesivity and hence poor flow properties. It also suggests the need for
416 proper glidant to improve the flow property of the drug as well as selected excipients
417 in order to ensure content and weight uniformity along with a reproducible dissolution
418 profile.



419

420 **Figure 1.** Standard flow function graph with regions of the flow behaviour of
421 curcumin and excipients results obtained by five-point point data set with powder flow
422 software.

423 Stress is only one factor that has been correlated here with flow property. As a
424 manufacturing expert one also needs to focus on two other factors which may hamper

the flow property. It includes particle size and moisture content. It has been observed that as particle size decreases, friction between particles increases due to increased surface area which decreases the flow property. Moisture content also increases the cohesiveness of material by forming solvent bonds between particles(K. K. Moravkar, et al., 2022). As curcumin possesses a smaller particle size with high moisture content, it leads to poor flow properties in comparison to all selected ingredients.

3.1.2. Wall Friction Test

The wall function test is the measurer of the development of friction between the powder and constraining surface which can affect the flow property as well as flow pattern when a vessel ejected material. It also provides highlights on the tendency for the powder to flow or hang on the surface of a chute. The wall friction test involves the determination of the chute angle (wall friction angle) which ranges from 10-45^{o}.

All raw materials were subjected to the exploration of the wall function test and the comparative result is shown in figure 2. It is the plot of wall friction angle vs. increased consolidation stresses.

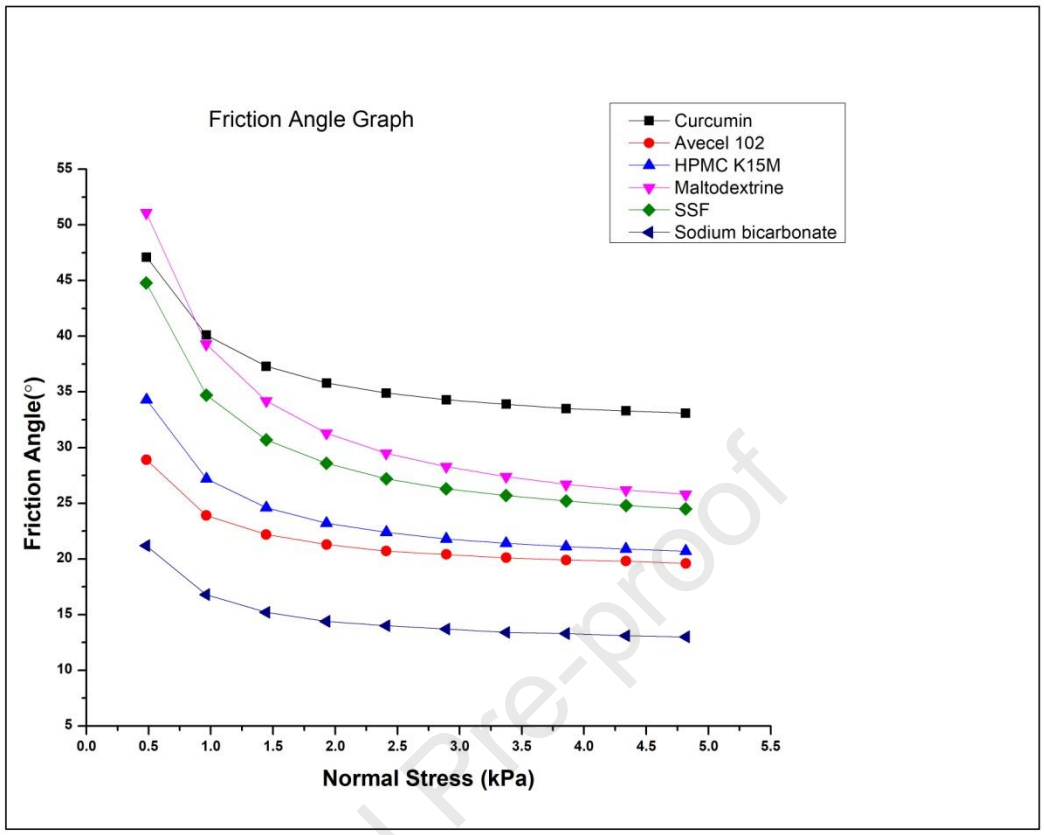


Figure 2. Wall friction angle of curcumin and excipients results obtained by five-point point data set with powder flow software.

The curve indicates that at higher stresses (4.819 kPa) powder material possesses a chute angle in the range of 13-33.1°. On another hand at the lowest stresses (0.483kPa) material showed a chute angle at the higher side i.e. 51.1-21.2°. Generally, the smaller is the chute angle, the lesser is the wall friction and the better the flow property. From obtained results, it is clear that all material possesses poor flow property at low applied stress which increases greatly with increasing stress. Comparatively, curcumin showed significantly poor flow properties even at high stress. Results support the finding of

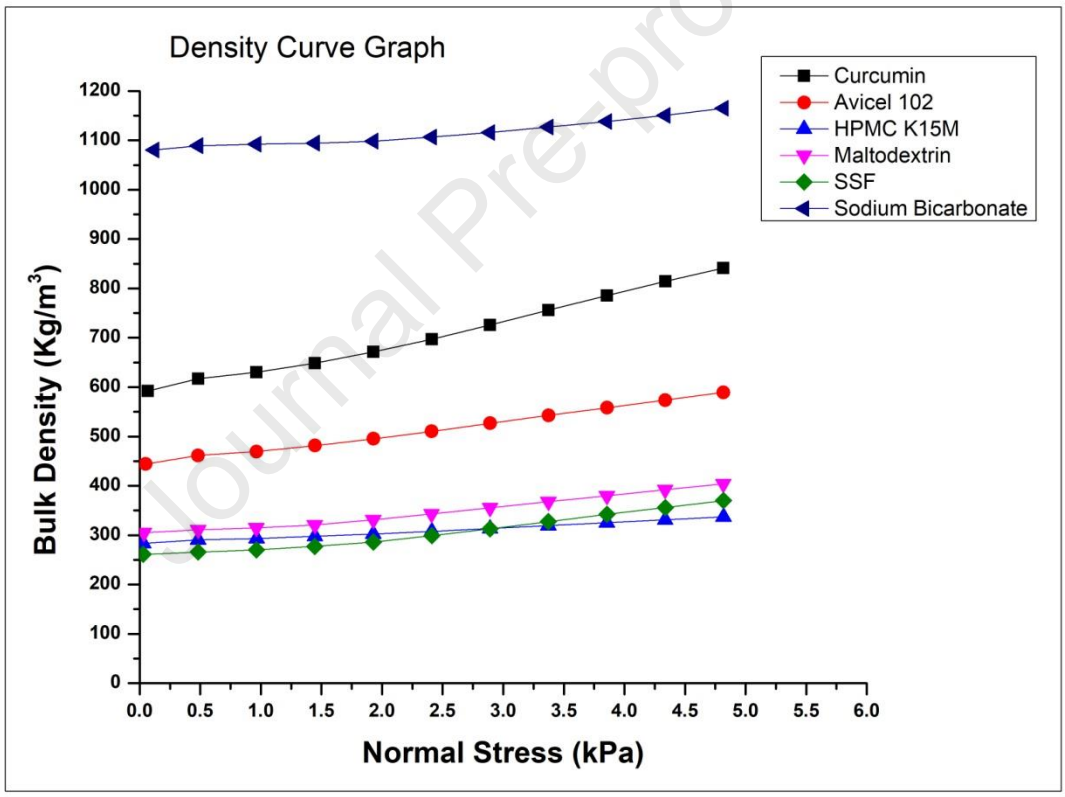
451 the flow function test. Sodium bicarbonate and MCC exhibited less wall friction than
452 the rest of the materials.
453 The value of the wall fiction angle depends on two kinds of factors intrinsic and
454 extrinsic. Intrinsic factors include particle size and moisture content. Large particle
455 size and less moisture content results in a lower value of chute angle and henceforth,
456 good flow property. Extrinsic factors include temperature, storage time of material and
457 internal structure of the hopper. Less temperature, minimum storage time and a hopper
458 with a smooth inner surface favor the flow of material and ultimately the value of the
459 chute angle decreases(K. Moravkar, et al., 2020; K. K. Moravkar, et al., 2022).
460 From the results of wall friction test it can be concluded that all selected material
461 possesses the poor flow property at low stress which may get modified with increased
462 stress. However, reducing the input of energy requires improving the flow of material
463 by applied stress there is a need for the use of proper glidant.
464

465 **3.1.3. Bulk density**

466 Determination of bulk density is one of the crucial parameter that can be correlated
467 with arrangements of particles with each other, presence of voids and ultimately flow
468 pattern of the powder of granules. Bulk density not only indicates flow of material but
469 also represents comportment of material over various compaction load. The value of
470 bulk density is highly dependent on consolidation stress. The bulk density curve
471 obtained from Brookfield PFT is shown in figure 3.

472 Usually, the higher the bulk density of the material, the grander will be the flow of
473 powder. In bulk density estimation by using PFT, it involves the determination of

474 change in densities starting from initial fill density to final consolidation. If there is
475 only a slight change in density from initial fill density to final consolidation (%
476 compressibility index), then it indicates free-flowing property. The bulk density curve
477 of such material possesses flat nature. On the other hand, a change in density by 25-
478 50% from initial fill density to final consolidation, indicates poor flow property(K.
479 Moravkar, et al., 2020; K. K. Moravkar, et al., 2022). The percent compressibility
480 index of all materials is depicted in table 3.



481

482 **Figure 3.** Bulk density of drug and excipients results obtained by five-point point data
483 set with powder flow software.

484 **Table 3.** Compressibility index of selected material

Material	% compressibility index
Sodium bicarbonate	7.20
HPMC	16.06
MCC	24.60
curcumin	29.51
maltodextrin	24.57
SSF	29.34

From the data, it is clear that all material possesses cohesiveness of varied intensity except sodium bicarbonate. Curcumin and SSF showed a maximum change in density indicating significant poor flow properties in comparison to other raw materials.

From the investigation of the flow properties of all materials by using Brookfield PFT, it can be concluded that all the selected excipients (except sodium bicarbonate) as well as curcumin suffer from poor flow properties. Nevertheless; curcumin possesses significant cohesiveness and deprived flow property which needs to be overcome in order to achieve content uniformity in the final dosage form.

3.2. Comparison of flow properties between curcumin and coated curcumin

Curcumin which is a Phyto-constituents possesses significantly high cohesiveness and poor flow properties. Additionally, it also undergoes photolytic degradation. There is a need to improve the flow property as well as the photo stability of curcumin.

The coating led to significant improvement in physical stability, wetting by aqueous media, dissolution rate, powder flow, and tabletability. Thus, it can be seen that coating cohesive powders with polymeric solution has an important application in

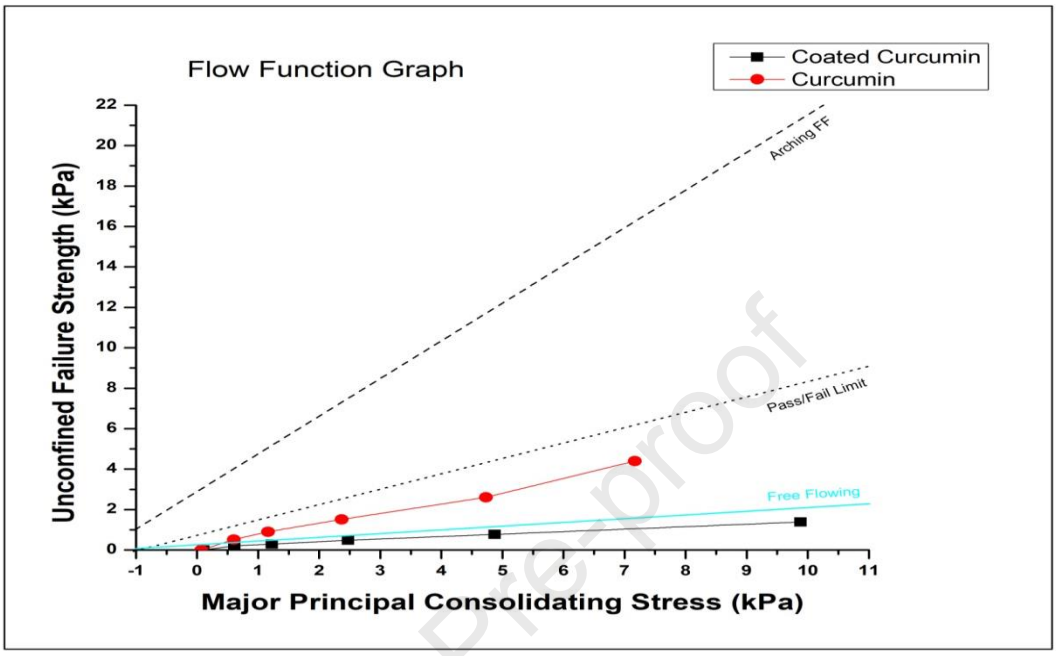
improving the flow of powders(Li, et al., 2019). Curcumin was coated with a thin layer of HPMC to improve flow property and stability. Coated curcumin and plain curcumin were then subjected to the determination of flow property by using Brookfield PFT. The result of the flow function test, wall friction test and bulk density are shown in figure 4. Comparative results of coated and uncoated curcumin are depicted in table 4.

Table 4. Comparative results of coated and un-coated curcumin

Evaluation Parameter	**Curcumin**	
	Uncoated	**Coated**
Flow function test	Curve in cohesive region	Curve in the free flowing to easy flowing
Bulk density (%CI)	29.60%	6.31
Wall friction angle	~47-35^{o}	~28-18^{o}

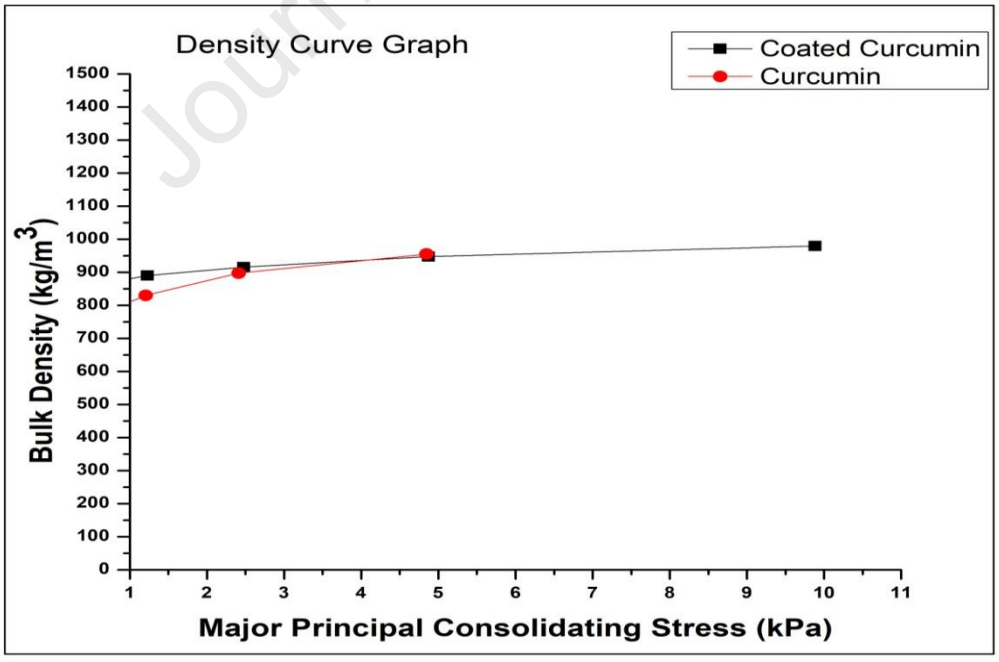
The coated powder showed improved physical properties since polymer treatment affected the particle size. Morphology evaluation by PFT revealed a decrease in the cohesiveness of the API due to the formation of symmetrical particles, a decrease in moisture content and an improved homogeneity of the particle surface. The enhancement in flow properties increased as the uniformity of the HPMC layer increased. An increased flow of the powder was noted due to the trace amounts of hydroxypropyl methylcellulose deposited onto the particle surfaces. Furthermore,

515 HPMC will also help to protect curcumin from photolytic degradation(Genina, et al.,
516 2010).



517

518 **a)**



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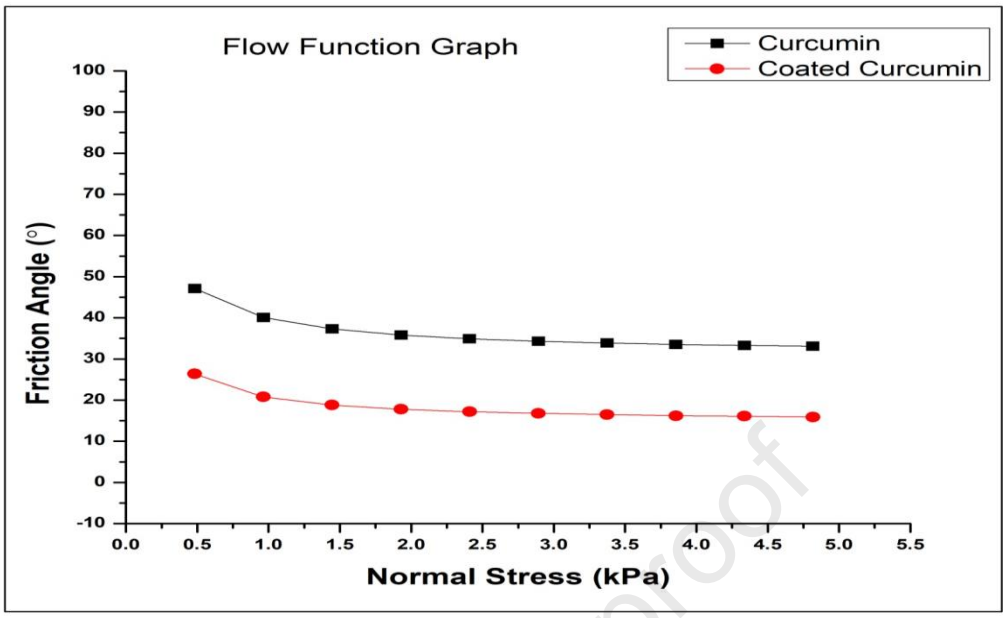
520 **b)**



c)

Figure 4. Comparison of flow properties between curcumin and coated curcumin a) flow function, b) bulk density, c) wall friction angle, results obtained by five point data set with powder flow software.

3.3 Comparison of flowability between Two-Step and One-Step Glidants Operations by using PFT

Flow property which is also known as the manufacturing property plays a decisive role in the development of stable and effective solid dosage forms like tablets. Content uniformity, weight uniformity, dissolution profile of tablet and ultimately safety and efficacy of tablet depends on the flow property of the blend from hoper to compression station. Curcumin and all selected excipients when studied individually for flow parameters by using Brookfield PFT showed poor flow properties (except sodium

bicarbonate). The study indicates that there is a need to add a glidant to achieve desired flow property. Therefore, based on the literature SSF was selected as the glidant. The addition of glidant in tablet blend is possible in two ways as one-step mixing (conventional) and two-step mixing (novel approach).

An important factor of concern in this approach is the glidant which eventually affects the inter-particle forces and the flow properties. Jallo et al. found high interaction potential due to a significant difference in surface energies between host material in a dry powder system and glidant and its mixing process is also required for optimal coating of glidant (Jallo, Ghoroi, Gurumurthy, Patel, & Davé, 2012). Mixing affects glidant's effectiveness: energy type and intensity are crucial for uniform dispersion on host particles (Fitzpatrick, Barringer, & Iqbal, 2004; Ghoroi, Gurumurthy, McDaniel, Jallo, & Davé, 2013)

It is crucial to mix glidants in the correct order to optimize their effectiveness in improving the flow of powders (Pingali, et al., 2011). A specific order of mixing of glidants plays an important role as described by Kalyana et.al in their study on two glidants i.e., Cab-O-Sil (CS) and Magnesium Stearate (MgSt)(Pingali, et al., 2011). The mixing of glidants in the tabletting blends leads to the formation of microlayers which in turn affect the product properties. Particles form microlayers on their surface, making mixing order cruacial.

Generally, adding separate glidants into two different phase's i.e. API-glidant mixture and pharmaceutical excipient-glidant mixture is used to optimize powder flow and its distribution in tablets, including both micronized and expanded particles. The glidant

557 is mixed with coated curcumin in this introduced two-step process, another glidant is
558 combined with the direct compression vehicles, and these two mixed powders are
559 utilized for compression. This approach enables the various glidant forms to adjust
560 their right concentrations for each particle characteristic at each glidant mixing
561 point(Abe, Yasui, Kuwata, & Takeuchi, 2009).

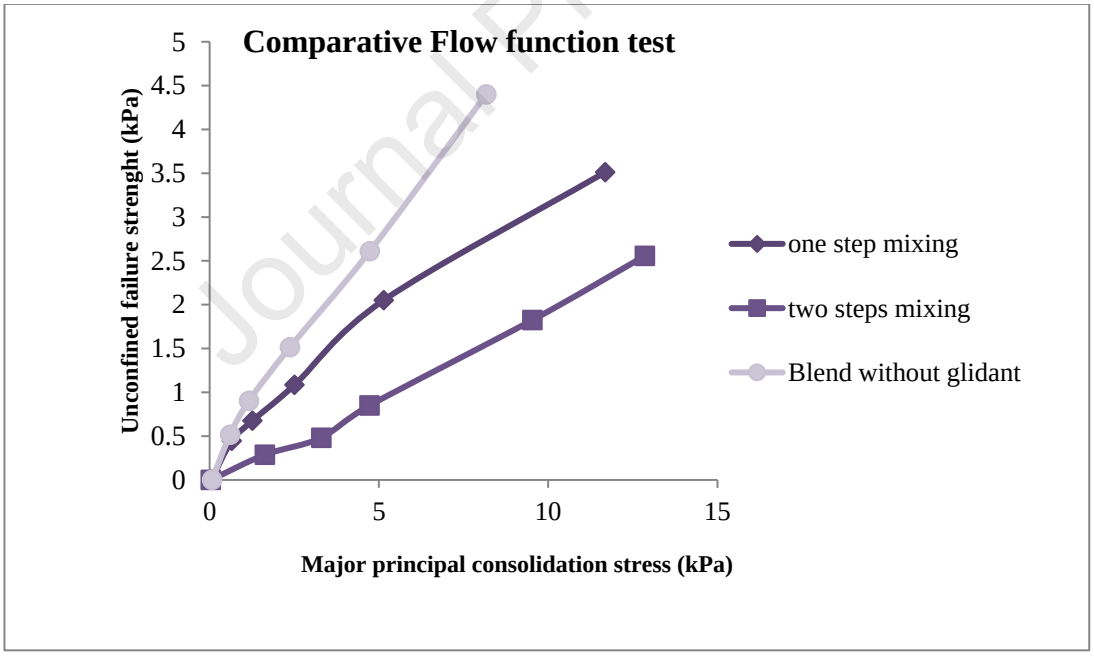
562 The flow function, wall friction, bulk density, critical orifice diameter and
563 compressibility index are better in the two-step process as compared to the one-step
564 mixing process, hence the increased flow over the one-step operation. Through a
565 meticulous two-step process, we have successfully eliminated the powder flow
566 bottleneck. As a result, we are now able to confidently proceed with improvement
567 trials through direct compression.

568 The Tablet blend was subjected to glidant operation by both methods and evaluated
569 for change in flow property. Comparative results are depicted in table 5.

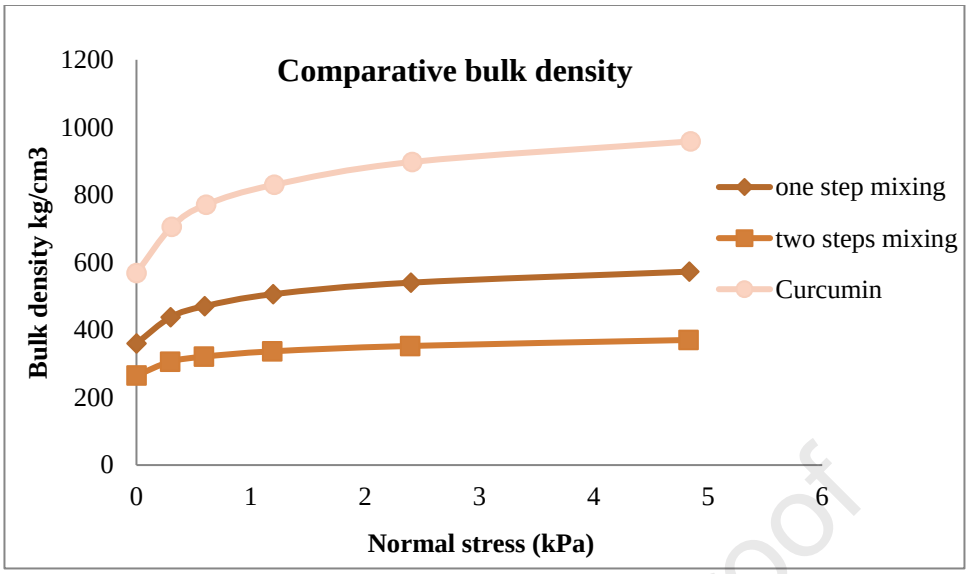
570 **Table 5.** Comparative results of two-steps and one-step glidant mixing operation

Evaluation Parameters	**Blend without glidant**	**One-steps operations**	**Two-steps operations**
Flow function test	Curve in very cohesive region	Curve in cohesive region	Curve in the free flowing to easy flowing
Nature of flow	Lower	Lower	Higher
Percent	34.19	16.29	9.32

compressibility (%CI)			
Wall friction angle	~55-45º	~41-33º	~38-25º
Effective angle of internal friction	41.5º	38.6º	34.4º
Density (Kg/cm^3)	958.4	878.7	813.2



(a)



(b)

Figure 5. Comparative study a) flow function test b) bulk density (results obtained by five-point point data set with powder flow software)

Based on obtained results it can be concluded that the addition of the glidant by the two-step method results in dramatic changes in the flow property of the blend in comparison to a one-step. Results also support our initial findings of the need for glidant to maintain the proper flow of powder.

Glidant results in flow modification by altering the ratio of van der Waals and the gravitational forces or a ball-bearing type of action. Glidant forms the layer surrounding the granules or powder and separates out from each other. It reduces van der Waals force and improves the gravitational force which increases the flow property of material under compression. In a one-step glidant process, it is difficult to form an appropriate layer of glidant in the surroundings to blend different-sized particles or granules which results in poor flow nature to material. On the other hand, a two-step glidant process allows the glidant to form the appropriate layer on the drug

and vehicle separately. This allows a significant reduction in frictional force and leads to better flow. Additionally, the two-step process removes the key principal bottleneck of powder flow and allows direct compression to be additional value applied for the formulation and process development trials(Abe, et al., 2009).

3.4. Post compression evaluation

After an in-depth evaluation of pre-compressional parameters, the blend of tablets prepared by using one-step as well as two-step glidant mixing was subjected to compression to obtain gastro-retentive tablets.

Tablets of both batches were then evaluated for various parameters viz. appearance, hardness, thickness, weight variations test, floating lag time, total floating time and in vitro dissolution test etc. to confirm the desired standard. The obtained results are shown in following table 6.

Table 6. Evaluation of tablet prepared by using two-step and one-step glidant mixed blend (n=3; mean ± SD).

Evaluation Parameters	**Formulation codes**	
	Two-steps (F1)	**One-steps(F2)**
Appearance	Smooth	Smooth
Color	Yellow to orange	Yellow to orange
Cracks	Absent	Absent
Hardness (kg/cm^2)	5.5 ± 0.4	6.2 ± 0.2
Friability (%)	0.3 ± 0.05	0.9 ± 0.02

Thickness (mm)	5 ± 0.5	5.2 ± 1.23
Weight variation (mg)	1015 ± 1.46	1021 ± 5.43
% Swelling	117 ± 5	114 ± 3
Floating lag time (Sec)	50 ± 3	70 ± 4
Total floating time (h)	>24	>21
% CDR ± SEM	96.01 ± 1.146	88 ±1.436

A significant difference between the results of tablets prepared by using a two-step and one-step glidant mixing process was observed. Tablets prepared by a two-step glidant mixing process showed more uniform and simillar drug release in comparison to one-step process and reference tablet respectively (figure 6). The percent dissolved also evaluated by statistically fit factor (f1 & f2) in order to compare the percent drug release profile of single and two-step. In general the value should be between 0-15 for f1 and 50-100 for f2, whereas the f1 value is towards 0 and the f2 value is toward 100 indicates the identical pattern of drug release profile and bioequivalent with the reference(Kassaye & Genete, 2013; Peh & Wong, 2000). The difference factor (f1) & similarity factor (f2) was found to be 11 and 57 respectively compared with tablet prepared with one-step as a reference and two-step as a test sample; considered to be more dissimilarity in drug release profile table 7. The statistical fit factor was also checked with the reference (InnoVixLabs, High Absorption Curcumin, Extended Release Tablets) and it was found as f1-13 and f2 -54 for tablet with one-step glidant mixing process; f1-6 and f-75 for tablet with two-step glidant mixing process. The similarity index (fit factors) of tablet prepared with two-step glidant mixing process was shown more closely similar dissolution

621 profile with the reference than tablet with one-step glidant mixing. The result
622 emphasizes the significance of improvement of flow property by coating of HPMC
623 and two-steps of glidant mixing process. All the above results are average of three
624 (n=3).

625 **Table 7 Statistical fit factors (similarity index) of dissolution profile**

Rt (reference batch)	Tt (test batch)	Result	
		f1	f2
Tablets from one-step glidant process	Tablets from two-step glidant process	11	57
InnoVixLabs, High Absorption Curcumin, Extended Release Tablets	Tablets from one-step glidant process	13	54
InnoVixLabs, High Absorption Curcumin, Extended Release Tablets	Tablets from two-step glidant process	6	75

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627

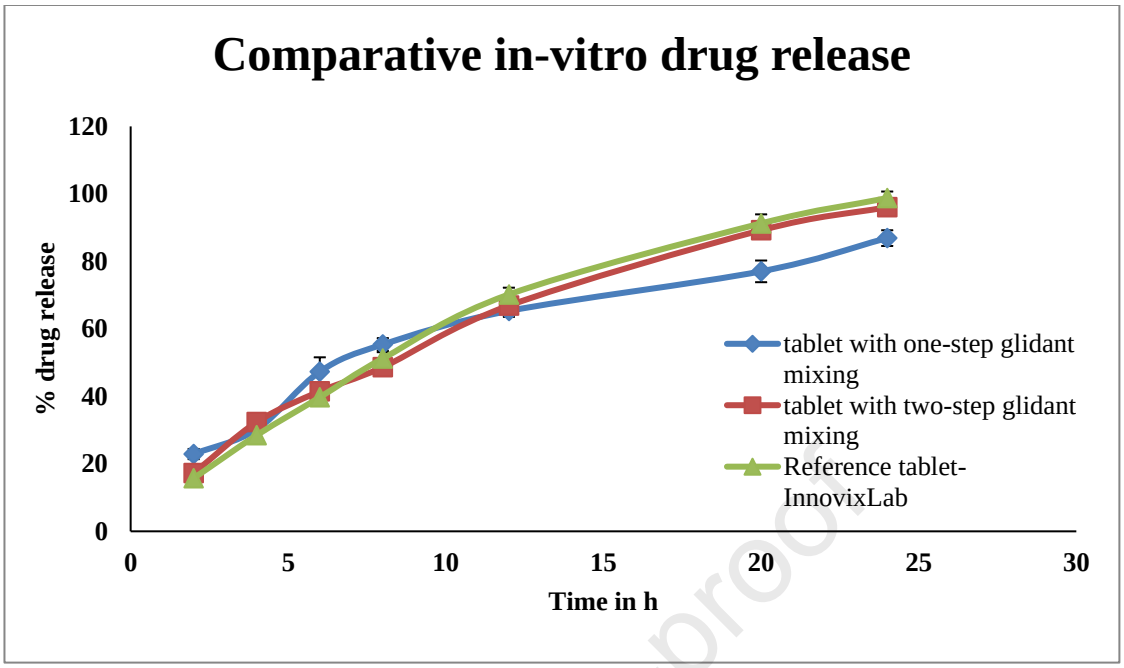
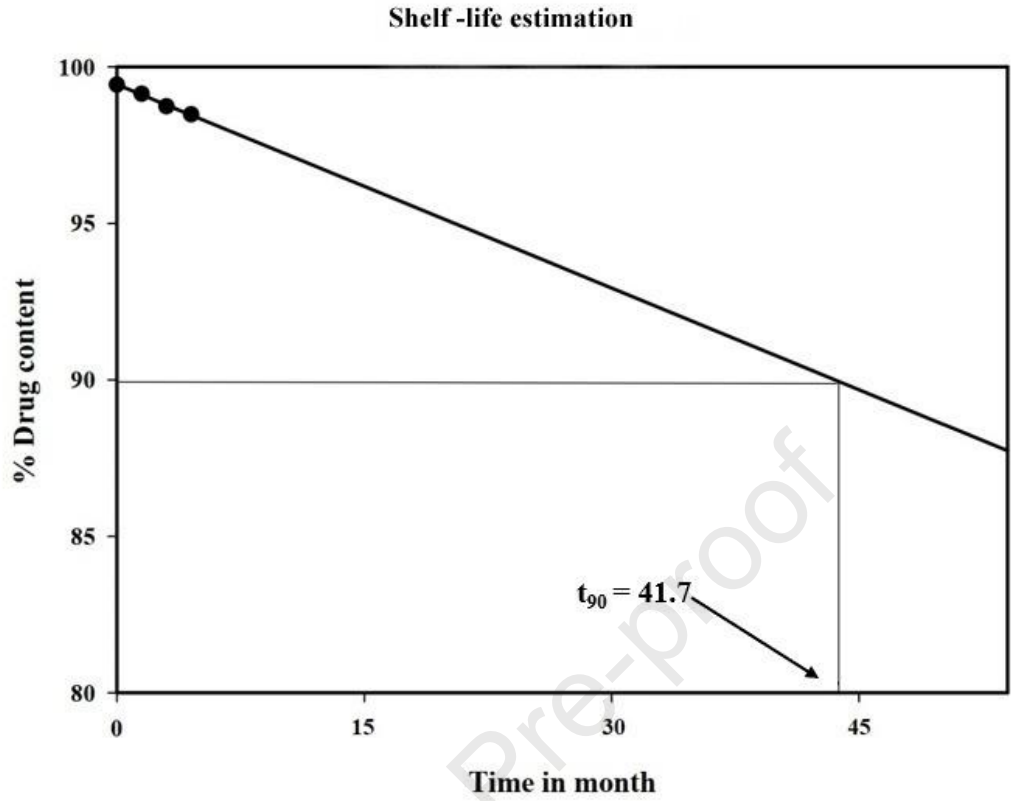


Figure 6. Comparative dissolution profile (n=3; mean ± SD).

4.0 Shelf life estimation:

The accelerated stability studies were carried out for the optimized formulation. The study showed no notable change in the physical appearance of tablets. The shelf life of the optimized formulation was assessed on the basis of drug content obtained during stability studies (Dangre, et al., 2021; K. K. Moravkar, et al., 2022). The drug content of all the formulations was extrapolated by software to t_{90} as shown in figure 7. The estimated shelf life of the optimized formulation was found to be 41.7 months. The shelf-life data revealed that minimum impurities due to SSF(K. K. Moravkar, et al., 2022), coating of curcumin and two-step glidant mixing significantly elicited the stability of the curcumin and the shelf life of the optimized formulation.



640

641 **Figure 7.** Shelf life of gastroretentive curcumin tablet (n=3; mean ± SD).

642 **5.0 *In vivo* gastric retention:**

643 The gastric retention ability of prepared curcumin tablets was investigated in Wistar
644 rats. Animals have been sacrificed at specific time intervals and checked for the
645 presence of tablets. We found that tablet was present in each group even though the
646 size of tablet was of decreasing order as we moved from group 1 to the last group
647 which might be due to the dissolution of a tablet with time. The study reveals the
648 gastro-retention ability of prepared curcumin tablets. HPMC coating and a two-step
649 glidant mixing process leads to significant improvement in the flow properties of the
650 blend; the blends were converted into gastroretentive tablets to retain it for a long
651 duration time at the stomach site, prevent alkaline degradation and target the ulcer.

Furthermore, the viscous nature and thickness of gel structure/swelling formed by the HPMC control the drug release. Additionally, the hydrophilicity and large surface area provided by SSF lubricant characteristically produce many pores and large pore volume to generate an effective buoyant system in two-step glidant mixing(K. K. Moravkar, et al., 2022). As curcumin has already proved its ability in the management of peptic ulcer, based on our shreds of evidence, there is hope to consider that prepared curcumin tablet is the better natural alternative to available treatment(Zhang, et al., 2017).

6.0 Conclusion:

The proposed two-step glidant mixing process to coated curcumin showed a significant improvement in the flow properties of curcumin than the one-step mixing process when investigated by using an advanced powder flow tester. The use of a two-step glidant mixing operation is more worthwhile to improve the flow property of powder to prepare direct compression tablets on large scale. Moreover, a more radically difference was observed in tablets prepared by using a blend obtained by two-step glidant mixing operation than one-step mixing. Tablet prepared by using a two-step glidant mixing process showed a floating time of 24 h with a floating lag time of 50 ± 3 seconds. On the other hand, tablets of one-step glidant mixed blend showed a floating time of 21 h with a floating lag time of 70 ± 4 seconds. There is also hope to consider that the curcumin floating tablets will show similar results during *in vivo* investigation. Prepared curcumin floating tablets will be a breakthrough avenue in the management of peptic ulcers and other gastric complications provided that further investigation requires in future. From all the above results we conclude that two-steps

glidant mixing process and floating tablets of coated curcumin are beneficial for society and industry.

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Authors Agreement-

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Nikhil Girase, Bhushan A. Bhairav, Vijay Lonkar- Writing, reviewing and editing

Shailesh S. Chalikwar- Supervision, Funding acquisition, Project administration.

Animal Rights

Wistar rats were provided by the Central Animal House Facility, R. C. Patel Institute of Pharmaceutical Education & Research, India. Animals were approved by the Institutional Animals Ethics Committee under resolution number IAEC/CPCSEA/RCPIPER/2017-2022. All the mice were maintained and treated following the animal ethics guideline.

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Table caption

Table 1. Value of flow function (ff)

Table 2. Optimized composition of floating tablet

Table 3. Compressibility index of selected material

Table 4. Comparative results of coated and un-coated curcumin

Table 5. Comparative results of two-step and one-step glidant mixing operation

Table 6. Evaluation of tablet prepared by using two-step and one-step glidant mixed blend (n=3; mean±SD)

Figure caption-

Figure 1. Standard flow function graph with regions of the flow behaviour of curcumin and excipients results obtained by five-point point data set with powder flow software.

Figure 2. Wall friction angle of curcumin and excipients results obtained by five-point point data set with powder flow software.

Figure 3. Bulk density of drug and excipients results obtained by five-point point data set with powder flow software.

Figure 4. Comparison of flow properties between curcumin and coated curcumin a) flow function, b) bulk density, c) wall friction angle, results obtained by five point data set with powder flow software.

Figure 5. Comparative study a) flow function test b) bulk density (results obtained by five-point point data set with powder flow software)

Figure 6. Comparative dissolution profile (n=3; mean±SD)

Figure 7. Shelf life of gastroretentive curcumin tablet (n=3; mean±SD)

Highlights:

- Targeted limited solubility, poor alkaline pH stability and poor flow property of curcumin which rendered the industrial application of curcumin
- Modified the flow property of curcumin using coating and a two-step glidant mixing process and then converted it into dosage form
- Investigated the flow property by reproducible and reliable advanced method – Powder flow tester (PFT).
- Follow-up study of previously published work on glidant optimization and development of gastro retentive tablet in JDDST (DOI: 10.1016/j.jddst.2022.103265).
- Detailed post-compression evaluation –in-vitro, in-vivo and shelf life study.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: