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Optimization of Roll Compaction/Dry Granulation (Rcdg) Process for Poorly Flowable Antiviral Formulation

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ABSTRACT

In this investigation, roll compaction/dry granulation (RCDG) process was optimized for formulation of model amorphous drug candidate with fine-fluffy nature and poor flowability. Three operating parameters the roller speed, the hydraulic pressure and the granulator speed on the Alexanderwerk WP 120 Pharma Roll Compactor were varied. The planned response variable for study was % retention over #60 BSS mesh. The number of compaction cycles required to get not less than 90% retention over #60 BSS mesh were evaluated. These optimized operating parameters were used during drug granulation for formulation variable optimization. The granules obtained from process optimization study were compressed at kilogram scale using ingredients in concentration selected from formulation optimization study to evaluate for the loss in tabletability, a phenomenon commonly observed with RCDG technology. The roll compaction operating parameters that simultaneously met all constraints were roller speed 4 rpm, hydraulic pressure 70 bars and granulator speed 30 rpm with course mesh screen of 2.0 mm, fine screen of 1.0 mm and three compaction cycles. The results of the drug release profile and physico-chemical evaluation of tablets confirmed that judicious optimization of process parameters and selection of appropriate excipients could lead to successful drug formulation by RCDG technology.

Keywords: roller compaction, dry granulation, powder flow property, segregation, loss in tablet ability, design of experiments (DOEs)

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INTRODUCTION

With the advancement in pharmaceutical technology and innovations, a number of novel drug delivery systems are in centre of focus and gaining popularity day by day. Oral route is however, the most preferred route of drug administration due to its non-invasive nature, administration convenience, highest patient compliance with low production cost and design flexibility. However, formulating drugs having inconsistent low densities, with poor flow properties and compressibility into solid dosage forms poses a major challenge for the formulation scientist.

Roll Compaction/Dry Granulation (RCDG) is an agglomeration method in which is densification/compaction of powder(s) is done by passing it between two counter-rotating rollers[1]. The RCDG technique has significant effect on fluidity, compressibility and compactibility of the active pharmaceutical ingredient (APIs) and excipients consequently, influencing drug release profile and tablet properties. Since, RCDG excludes any liquid solvent or binder solution it is environmentally safe and cost-effective. Therefore, RCDG is generating increasing interest in research and commercial manufacturing. However, losses of tabletability/reworkability, high fines fraction, non-homogeneity of compacts are few challenges in formulation development using RCDG technology that need to be overcome by judicious optimization of process parameters and selection of appropriate excipients[2,3].

The flowability of the powder(s) is an important aspect for successful formulation of tablets. If the powder is cohesive or with poor flowability, it will lead to segregation of the blend and resultantly non-uniform distribution of blend from hopper to feeder (force/gravity) and leading to non-uniform die-fill volume and content non-uniformity of the prepared tablets[4].

The model drug (code: DDSG-7854) used in the study was an L-valyl ester antiviral (prodrug of ganciclovir) which after oral administration is well absorbed and is rapidly converted to active drug in the intestinal wall and liver by intracellular esterases in the mucosal cells of the gut and by hepatic esterases, respectively. The unit dose of the drug is 450 mg. The drug is white to off white amorphous powder, is fine, fluffy in nature and exhibits poor flowability. The drug is freely soluble in water. The particle size, as determined by malvern mastersizer showed that maximum drug particle had average particles sizes, d (0.9) less than 95 µm in size. The poor flowability of the drug may lead to segregation/demixing during flow from hopper to force feeder during compression and thus content non-uniformity problem.

Therefore, in order to improve flowability and compressibility of the drug as well as to get content uniformity of the drug blend with excipients and subsequently to formulate quality

product complying with all official pharmacopoeal standards, granulation of the drug powder was required. The granulation of the drug can be done in three ways viz. wet granulation, dry granulation or direct compression. Wet granulation method could not be used because addition of solvent along with subsequent removal by drying the granules at elevated temperature might convert amorphous form of the drug into crystalline form[5,6]. Further, direct compression method was ruled out because drug is amorphous, very fine and fluffy in nature with poor flowability. This can influence blend characteristics and content uniformity, being present in high load i.e. more than 50%. Therefore dry granulation is the only alternative available. Dry granulation can be performed in two ways, namely, slugging and roll compaction (RCDG). Slugging tends to be more limiting in terms of uniformity and capacity than roller compaction system. Various disadvantages of slugging includes single batch processing, frequent maintenance changeover, poor process control, poor economies of scale, low manufacturing throughput per hour, excessive air and sound pollution, increased use of storage containers, more energy and time required to produce slugs than roller compact[7]. Based upon the above mentioned facts RCDG technique was explored with the objective to attain a flowable and compressible drug material; to explore an environment friendly, continuous method of production with decreased cost and increased productivity; confirmation of compliance of the product to designed specifications / pharmacopoeal limits**.**

MATERIALS AND METHODS

Materials

Drug Code: DDSG-7854 (prodrug of ganciclovir), supplied from Ranbaxy laboratory limited as is; Crospovidone US-NF (Polyplasdone XL, ISP Technologies, USA); MicroceLac 100 (Meggle, Germany); Magnesium stearate US-NF (Mallinckrodt, USA); all other reagents were of analytical grade and used as such.

Physicochemical Characterization of Drug

Bulk density and tapped density of the drug (100gm) was determined as per method-1 (USP 32-NF 27, measurement in a graduated cylinder) using powder density tester (M/s Campbell Electronics, India). The compressibility index and hausner ratio were calculated from these values[8,9]. The drug and excipient admixtures used were exposed to 40°C/75% RH, the accelerated storage condition[10] [ICH Q1A (R2)] for a period of 4 weeks to determine physical compatibility between drug and excipients.

Analytical Method Development and Validation

Drug solution (10 µg /ml solution in 0.1N HCl) was scanned between wavelength range 200-400nm using UV spectrometer and λmax was determined. The specificity of the method was determined by scanning excipients individually and along with drug solution between 200-400nm wavelength and any influence on λmax of the drug was investigated. The calibration curve of the drug was constructed between drug concentration ranges of 100-700 µg/ml using 0.2mm cuvette at determined λmax of the drug and linearity was established by least square linear regression analysis method.

Accuracy of the method was determined by individually weighing the drug and preparing drug solution of known concentration (325µg/ml, 450µg/ml and 550µg/ml), taking absorbance of these solutions and determining corresponding concentrations from calibration curve. The within day precision assays were carried out through replicate analysis (n=3) of drug solution corresponding to 100-700 µg/ml. The inter-day precision was evaluated through replicate analysis of the pure drug samples for three consecutive days at the same concentration levels as used in within day precision. Similarly LOD and LOQ were determined based on the standard deviation of the response and the slope as per ICH guideline Q2 (R1).

Process Design of Experiments (DOEs)

The various process parameters of the roll compaction/dry granulation (RCDG) that were optimized included roll speed, hydraulic pressure and granulator speed. The following range of these factors was studied in the process DOE:

(a) Roller Speed (4-6 rpm)

(b) Hydraulic Pressure (60-100 bars)

(c) Granulator Speed (25-35 rpm)

(d) Number of compaction cycles to get NLT 90% retention over #60 mesh (one to three).

The upper and lower granulator screen of constant size viz. 2.0 mm and 1.0 mm, respectively were used throughout the process and screw feeder speed was monitored.

Process Description of RCDG for the DOE Batches

The drug was sifted through 45R screen (1143 µm) fitted to a quadro comil (M/s Gansons Ltd,/Quadro Engineering, India) at 50 Hz (1500 rpm) and used for compaction. The RCDG was conducted on a pre-qualified (qualified for installation, operational and performance qualification) Alexanderwerk, model WP 120 Pharma (Alexanderwerk AG, Germany) roll compactor. The knurled rolls of 120 mm in diameter and 40 mm in width were used for roll compaction. The process parameters used for optimization studies are summarized in **Table 1**. A

hopper with a 1 litre of volume was used for charging powder. The ribbons produced were broken using a rotating flake crusher, following which the flakes passed through a two-stage mill having a course mesh screen (2.0 mm) and a fine screen (1.0 mm) to obtain the final drug granules. The resultant granules were passed through a mesh # 60 screen fitted with a vibro sifter.

Table 1. Matrix for compaction trials and results of % granule analysis

Batch Code	Parameters			No. of evaluated compaction cycles	Compaction Cycle			Cumulative retention over sieve no. 60 (%)
	Roller speed (rpm)	Hydraulic pressure (bar)	Granulator speed (rpm)		I	II	III	
					% retention over sieve no. 60			
PC-1	4.0	60	25	1	66.13	---	---	66.13
PC-2	4.0	70	25	1	60.33	---	---	60.33
PC-3	4.0	80	25	1	59.81	---	---	59.81
PC-4	4.0	60	25	1	66.57	---	---	66.57
PC-5	6.0	60	25	1	58.10	---	---	58.10
PC-6	4.0	70	25	1	60.00	---	---	60.00
PC-7	4.0	70	30	1	66.79	---	---	66.79
PC-8	4.0	70	35	1	65.67	---	---	65.67
P-1	4.0	70	30	2	63.00	57.00	---	84.20
P-2	4.0	60	30	3	54.57	59.19	73.26	96.06
P-3	4.0	80	30	2	59.00	65.37	---	85.94
P-4	4.0	70	35	3	55.00	56.63	65.76	90.11
P-5	4.0	70	30	100% granules of above sieve No.60 were taken to evaluate the product characteristics after compression				
P-6	4.0	100	30	1	64.00	---	---	---

Granulator screen: Upper = 2.0 mm, Lower = 1.0 mm and Roller gap: 1.9±0.2 mm

Formulation of Tablets and Evaluation

Microcelac 100 and crospovidone were sifted through 45R (1143µm) screen fitted to a quadro comil at 50 Hz (1500 rpm). Magnesium stearate was sifted through 24R (610µm) screen to break agglomerates if any, formed during storage. The compacted granules in course to fine ratio of 95:05 were taken and mixed with extra-granular excipients with varying concentrations of disintegrant crospovidone (5-30%) as described in **Table 2** and compressed by die-fill method on 21 station compression machine (M/s Cadmach machinery co., Ahmadabad, India) equipped at one of the 21 stations with D type of tooling (18.5×8.25 mm oval shaped punches embossed with 'RX 137' on one side and plain on other side). Blind dies were used at all other positions. The process parameters of optimized batch from batch code P1-P6 **(Table 1)** were used for the compaction of drug. The compacted granules were characterized for physical parameters viz. bulk density, tapped density and particle size distribution (PSD) as per USP 32-NF 27.

Table 2. Composition of various formulated tablets and results of physical evaluation

Name of ingredient	Formulation Code				
	F1	F2	F3	F4	F5
	Qty. / Tablet				
Drug hydrochloride salt equivalent to 450 mg drug base	496.3 mg	496.3 mg	496.3 mg	496.3 mg	496.3 mg
Crospovidone USNF	40mg (5%)	120mg (15%)	160mg (20%)	200mg (25%)	240mg (30%)
Microcelac 100	255.5 mg	175.5mg	135.5mg	95.5mg	55.5mg
Mag. Stearate USNF	8.0 mg	8.0mg	8.0mg	8.0mg	8.0mg

The formulated tablets were characterized and evaluated for physical parameters [weight variation IP, hardness (tablet breaking force, TBF), thickness, diameter, friability USP, disintegration time USP] and chemical parameters (dissolution, assay).

In vitro drug release studies were carried out using USP (Apparatus 2-paddle method) dissolution apparatus at 37 ± 0.5°C with constant stirring rate of 50 rpm/min. The formulated tablets were tested for drug release in 0.1 N HCl (900ml) for 30 minutes. A sample volume of 10ml was withdrawn from each dissolution vessel at regular intervals and replaced with equal volume of fresh dissolution medium. The withdrawn samples were filtered through 0.45 µm nylon filter. The amount of drug released was determined by spectrometer at 256nm. Six tablets were taken from each batch for dissolution study and average value at each time point was taken for drug release studies.

Effect of Different Compaction Parameters on Compression

The optimized prototype formulation selected from batches F1-F5 were compressed at different compression machine speeds (25-35 rpm) at different target tablet breaking force/ hardness (TBF) values viz. low (10-15kP), medium (15-25kP) and high (25-30kP). The resultant tablets were evaluated for drug release profile to investigate the effect of compaction on compression.

RESULTS AND DISCUSSION

Physicochemical Characterization of Drug

The bulk density and tapped density of the drug were found to be 0.476 g/ml and 0.719 g/ml, respectively. The results of compressibility index (CI) (33.80%) and hausner ratio (HR) (1.51) indicated poor flowability of the drug. Thus there is a probability of segregation/demixing during flow from hopper to force feeder during compression and thus content non-uniformity problem. Therefore, to improve flowability and compressibility of the drug, the drug was processed using RCDG technique.

The results of drug-excipient physical compatibility studies revealed that drug was compatible with the excipients studied, as no physical change in the appearance of the drug-excipients mix was observed **(Table 3).** Therefore the drug can be formulated by combining drug with above mentioned excipients.

Table 3: Results of physical compatibility studies

S. No.	Combination	Category	Drug : Excipient ratio	Physical description	Characteristics after storage at 40°C/75% RH			
					1wk	2wk	3 wk	4wk
1.	API	Active	----	Off-White	NC	NC	NC	NC
2.	Lactose	Filler	1:10	Off-White	NC	NC	NC	NC
3.	MCC PH101	Filler	1:10	Off-White	NC	NC	NC	NC
4.	Microcelac 100	Filler	1:10	Off-White	NC	NC	NC	NC
5.	Crospovidone	Disintegrant	1:2	Off-White	NC	NC	NC	NC
6.	Primogel	Disintegrant	1:2	Off-White	NC	NC	NC	NC
7.	PVP-K30	Binder	1:1	Off-White	NC	NC	NC	NC
8.	Mg-St	Lubricant	1:0.5	Off-White	NC	NC	NC	NC

NC: No change Mg-St: Magnesium Stearate

Microcelac 100 was used as filler-binder[11] to minimize the effect of loss in tabletability/loss in reworkability, a phenomenon commonly observed with roll compaction process. To get immediate drug release, crospovidone was selected as super-disintegrant which also have dry binder potential and further contributes to mechanical strength of tablets[12].

Analytical Method Development and Validation

The analytical method development and validation study was conducted as per ICH guideline Q2 (R1). The results of wavelength scanning of drug exhibited absorption maximum at 256nm. Therefore this wavelength was fixed for the further analysis of drug. No peak of different excipients (crospovidone, microcelac 100, magnesium stearate) were observed between 200-400nm when scanned individually or in blend form. Hence it was assumed that excipients didn't affect absorption maxima of the drug. The UV spectra of drug in presence of excipients blend exhibited no change in absorbance and λmax of the drug. However absorbance of the drug decreased in proportion of the drug concentration. Thus the method was found to be specific for drug**.** Figure 1 depicts the standard plot of the drug.

The LOD and LOQ values were found to be 28.29 µg/ml and 85.71 µg/ml, respectively as determined by regression of y- intercept of the regression line. The concentration-absorbance plot was found to be rectilinear over the range of 100-700 µg/ml. The accuracy (% recovery) and RSD values for inter-day and intraday precision were 97.61 ± 0.37 and % RSD < 2% and % RSD <5%, respectively. Hence, the recovery and precision results were found satisfactory.

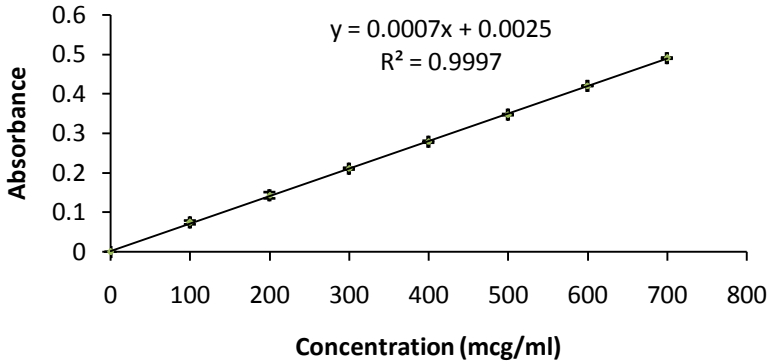

Figure 1: Calibration curve of drug

Process Design of Experiments (DOEs)

The optimization of process variables is very important to get quality product during process development. The major roll compactor parameters which can influence granule properties and final drug formulation include roller speed, hydraulic pressure, screw feeder speed, granulator speed, and roller gap. Since, no binder was added during the compaction of the drug, the roller speed was maintained at low rpm to increase dwell time[13] to give sufficient time for formation of bonds/solid bridges between the particles. High pressure reversibly affects the compressibility of the granules which may have an impact during compression. Further, since the compaction process involves number of compaction cycles to reduce fines content, the compressibility of the drug could be reduced drastically leading to a reduced tensile strength of the tablets[14-16]. The range of roller gap was selected based on the desired particle size of input material to get desired size of compacted granules. At high granulator speed amount of generated fines would be more. Hence granulator speed optimization is required**.**

The result of % retention of drug granules over # 60 and under # 60 (Table 1) revealed that % of granules retained over # 60 were 58.10-66.79%. Since the retention over # 60 was less than the desired requirement of NLT 90% after one compaction cycle. Therefore, multiple compaction approach was explored to get desired retention over #60. Compaction of material more than three times, has been reported to result in a negative impact on the compressibility of material[17,18]. Therefore a maximum of three compaction cycles were investigated. The results of multiple compaction study (Table 1) revealed that at-least three compaction cycles were essential to get over size fraction above #60 NLT 90%.

Process parameters of batch code P-1 (roller speed: 4, HP: 70 and granulator speed: 30) were used for drug compaction for formulation DOEs (F1-F5). Hydraulic pressure of 60 and 80 bars (of batch P2 and P3) were not selected because of less retention over # 60 (54.57% and 59%,

respectively) after first compaction cycle when compared to batch P1 (63%). Similarly, granulator speed of 35rpm (P-4) was not selected due to less retention over # 60 (55%) after first compaction cycle. While parameters of batch code P-5 having 100% drug granules of over # 60 BSS were similar to process parameters of batch P-1 and were evaluated for drug release profile study and is discussed in detail in proceeding section. Process parameters of batch code P-6 further supported establishment of safety window/PAR (proven acceptable range) for hydraulic pressure (60-100bar) process variable.

The BD and TD of the drug compacts to be used for formulation DOEs (F1-F5) were observed to be 0.6298 g/ml and 0.7409 g/ml, respectively. The results of CI (14.995%) showed marked improvement in flowability of the drug after roll compaction.

Characterization/Evaluation of Tablets

The prepared tablets from different batches were characterized and evaluated for physical (weight variation, tablet breaking force/hardness, thickness, diameter, friability, disintegration time) and chemical parameters (dissolution and assay). The average weight of the tablets was found to lie between 800 ± 2.15 mg and the hardness between 15.5 ± 1.3kP. The average diameter of the tablets was found to be 18.55 ± 0.06 mg and thickness 7.15 ± 0.01 mg.

The disintegration time of different tablet formulation (batch code F1-F5) was observed in the range of 6.00 to 6.47 min. There was a gradual decrease in disintegration time of different formulations with an increase in the disintegration concentration (5-30%). There was no significant difference ($p<0.05$) in the time required for disintegration for various formulated batches (Batch F1-F5) thus indicating no role of disintegrating agent in controlling the disintegration time of tablets containing soluble drugs. Similar results indicating negligible influence on of disintegrating agent on the disintegration time of highly soluble drug tramadol HCl have been reported[13]. This might be due to the fact that soluble drugs may erode rather than disintegrate and leading to slow disintegration[19,20]. However, according to USP 32-NF 27, the disintegration time for uncoated tablets should not be more than 15 min. Hence, all tablet formulations passed the disintegration test.

Assay

The assay values of different formulation were in the range over 97.747 ± 0.003% to 104.460 ± 0.001%. The results were within the in-house acceptance criteria limit of 95.0-105.0%. Hence, all tablet formulations passed the assay test.

In Vitro Drug Release Studies

Immediate release drugs are designed to disintegrate in the stomach followed by dissolution in the fluids of the gastrointestinal tract. Dissolution of the drug substance, under physiological conditions, is essential for its systemic absorption. For this reason, dissolution testing is typically performed on solid dosage forms to measure the drug release from the drug product as a test for product quality assurance/product performance and to determine the compliance with the dissolution requirements when stated in the individual monograph[21].

The results of *in vitro* drug release studies from different tablet formulations i.e. F1-F5 are depicted in Table 4. All the formulations started releasing drug within 5 minutes which increased up to 20 min. after which dissolution rate remained more or less constant. An increase in crospovidone concentration (from 5-30%) generally increased dissolution rate up to 15 minute after which no significant effect of disintegrant concentration to enhance dissolution rate was observed. The results were well coordinated with the previously established facts that dissolution is rate determining/limiting step (RDS) for the hydrophobic, poorly aqueous soluble drugs like griesofulvin, spironolactone. If the drug is hydrophilic with high aqueous solubility-like cromolyn sodium or neomycin, then dissolution is rapid[22]. Since the drug used in this study was highly soluble, therefore dissolution was rapid and was not a RDS for the immediate release formulation.

Table 4. Dissolution profile of different formulations (n=6)

Time (Minutes)	Drug Release (%) [Mean ± SD]				
	F1	F2	F3	F4	F5
5	62.51 ± 4.72	70.49 ± 6.17	71.63 ± 5.6	73.74 ± 2.95	68.63 ± 3.32
10	90.43 ± 5.38	98.24 ± 3.92	98.09 ± 4.48	101.87 ± 3.73	99.4 ± 4.07
15	97.24 ± 2.78	98.55 ± 2.88	98.67 ± 3.95	102.91 ± 3.84	101.94 ± 3.39
20	97.87 ± 3.66	98.85 ± 4.37	98.78 ± 5.75	103.96 ± 3.95	103.26 ± 3.26
25	98.82 ± 3.83	99.79 ± 4.41	100.58 ± 4.52	103.27 ± 3.71	103.73 ± 3.18
30	99.5 ± 4.15	101.49 ± 3.22	101.28 ± 4.39	103.55 ± 3.62	103.47 ± 3.49

Results of drug release studies (**Table** 4) revealed that formulation F4 had highest initial release (73.74%) after 5 min. which remained highest till 20 minutes (103.96%). Overall there was no significant difference ($p<0.05$) between the drug release profile of formulation F4 and F5 after 15 min. Hence addition of extra quantity of disintegrant (i.e. 30% in place of 25%) was non-beneficial and non-commercial. Also addition of extra quantity of disintegrant decreases unit content of microcelac 100 and its associated advantage of improved flowability. Hence, based on these observations formulation code F4 having crospovidone in 25% concentration was selected as best formulation and further used to evaluate the effect of compaction parameters (batch P1-P6)on compression with immediate release formulation having desired tensile strength of tablets.

Effect of Different Compaction Parameters on Compression

Loss in tabletability is a very common problem observed for tablets prepared via RCDG technology. Therefore effect of different compaction parameters on compression was studied. Tablets prepared from the drug granules obtained from the process variables optimization study of batch P1-P6 using composition of optimized prototype formulation (formulation code F4) i.e. crospovidone (200mg, 25% w/w), microcelac 100 (95.5 mg), magnesium stearate (8 mg, 1% w/w) were evaluated for physical (weight variation, hardness and friability, diameter and thickness, disintegration test) and chemical parameters (drug release profile). The results of weight variation, hardness, friability, diameter, thickness and disintegration are summarized in **Table** 5. The disintegration time of different batches (P1 to P6) was observed in the range of 6.0 to 8.0 min. According to USP 32-NF 27, the disintegration time for uncoated tablets should not be more than 15 min. Hence, all tablet formulations passed the disintegration test.

Table 5. Effect of different compaction parameters on physical attributes of compressed tablets (Batch code, P1-P6)

Batch Code	Parameters		TBF (kP)	Thickness (mm)	DT (min)	Weight (mg)
	Compression m/c speed	Target TBF	Avg. ± SD (n=10)	Avg. ± SD (n=10)	Avg. ±SD (n=6)	Avg. ± SD (n=20)
P-1	25-35 rpm	10-15kP	13.31 ± 1.16	7.25 ± 0.051	6.0 ± 0.07	803.0 ± 5.41
	25-35 rpm	25-30kP	27.28 ± 1.23	6.60 ± 0.028	8.0 ± 0.10	804.4 ± 6.12
	30 rpm	15-25kP	20.05 ± 1.35	6.96 ± 0.053	7.0 ± 0.04	805.3 ± 4.35
	25 rpm	15-25kP	20.05 ± 1.35	6.96 ± 0.053	7.0 ± 0.06	805.3 ± 5.45
	35 rpm	15-25kP	20.07 ± 1.47	6.92 ± 0.043	7.0 ± 0.08	802.8 ± 5.65
P-2	30 rpm	15-25kP	17.27 ± 0.72	6.98 ± 0.032	7.0 ± 0.04	800.1 ± 4.34
P-3	30 rpm	15-25kP	18.39 ± 1.09	6.98 ± 0.020	7.0 ± 0.04	800.2 ± 4. 39
P-4	30 rpm	15-25kP	16.31 ± 0.99	6.98 ± 0.028	7.0 ± 0.07	804.7 ± 5.21
P-5	30 rpm	15-25kP	15.85 ± 1.29	7.01 ± 0.049	7.0 ± 0.06	810.6 ± 5.36
P-6	30 rpm	15-25kP	19.85 ± 1.03	6.91 ± 0.027	8.0 ± 0.04	805.4 ± 5.16

Friability of all the formulations was less than 0.1%.

Effect of hardness on drug release profile

The effect of hardness on drug release profile of batch code P-1 (Figure 2) showed that an increase in hardness value of the compressed tablets initially led to incomplete drug release after 10 and 20 minute (87.14 and 96.03%, respectively) with 100% release after 30 minutes from all tablets. Compression of tablets at middle hardness value (15-25 kP) was found to be suitable to get required immediate drug release profile without compromising the tablet tensile strength. So, further batches (batch code P-2 to P-6) were compressed with medium hardness values.

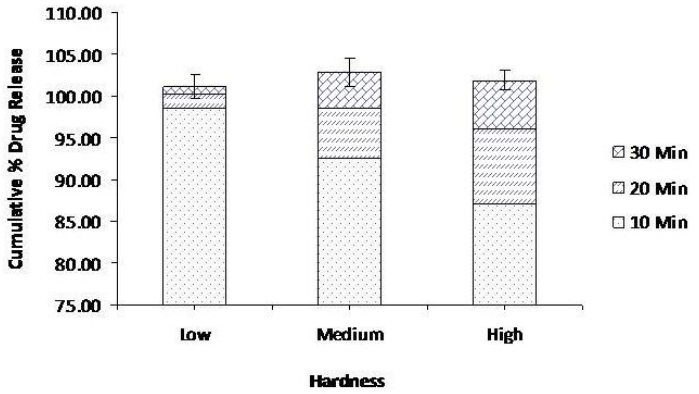

Figure 2: Effect of hardness on dissolution release profile (n=6)

Effect of different compaction parameters on dissolution release profile

Results of drug release studies of batch code P-2 to P-6 trial batches are depicted in **Figure 3.** Drug release from batch P-4 was minimum (94%) after 30 min. This was supposed to be due to use of 100% drug granules of above 60 BSS size. This reveals the importance of small quantity fines during tablet compression. However, all the formulations were releasing more than 90% drug in 30 min. This indicated that all compaction parameters used for preparation of batch P1 to P6 can be used for commercial manufacturing. Therefore, all the trials batches further supported in establishment of the safety window of process parameters for scale-up and commercial manufacturing of the product.

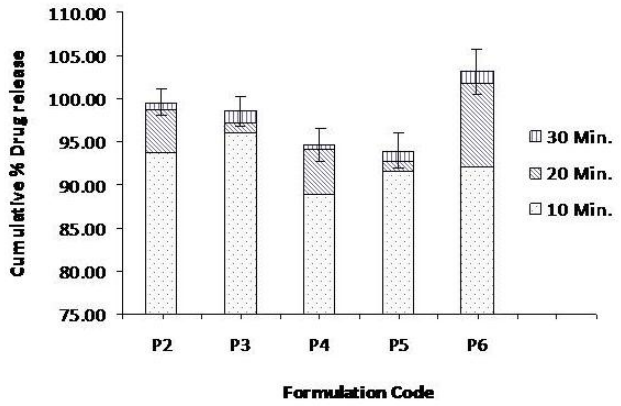

Figure 3: Effect of different compaction parameters on drug release profile (n=6)

Since, all the results of physical parameters and drug release studies were complying with specification therefore it can be concluded that no loss in tabletability phenomenon was observed with the formulated tablets.

CONCLUSION

Roll compaction of model drug was feasible with optimization of processing and formulation parameters. Multiple compaction of drug was effective in minimizing percentage of fines,

leading to improved flowability of the fine and fluffy drug. Use of crospovidone as disintegrant in 5-30% concentration showed no significant difference ($p<0.05$) in the time required for disintegration for various formulated batches. This suggested negligible role of disintegrant in controlling disintegration time of tablets having water soluble drug. Similarly, dissolution was not a rate determining step (RDS) for the immediate release formulation of water soluble drug. Selection of microcelac 100 as a filler-binder was effective in avoiding loss of tabletability phenomenon, as confirmed from the desired tablet breaking force of the tablets. Hence, granulation of drug using RCDG process is valuable as the exclusion of a granulating liquid/binder reduces the possibility of moisture induced degradation and polymorphism with improved flowability.

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