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Original Article

OPTIMIZATION OF ROLL COMPACTOR VARIABLES AND FORMULATION OF ANTI-RETROVIRAL TABLET BY ROLL COMPACTION METHOD

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ABSTRACT

Objective: This study emphasis on roll compaction variable and how the processing parameters influence the formation of granules in process of formulations of antiretroviral IR Tablet with help of optimization technique.

Methods: In this present work we aimed to develop a stable pharmaceutical dosage form with anti-retroviral drug tenofovir disoproxil fumarate. % retention of granules over # 60 mesh in roll compaction method by sizing with 50G co-mill screen was assessed by optimization and results were evaluated by Design expert 12.0 software. Various parameters and optimization of the parameter for formulation for better product was done by using 2^3 factorial design and dry granulation technique for manufacturing tablets. Three operating parameters the roller speed, the hydraulic pressure and the gap width on the Chamunda CPMRC-200/150 Roll Compactor were varied. The planned response variable for study was % retention over #60 ASTM mesh. % retention of granules was calculated by weighing granules on digital electronic balance with respect to how much premix material was taken for compaction.

Results: Excipients compatibility study gave positive way showing no change in physical appearance of drug-excipients mix. It reviled that drug was compatible with excipients used.

By formation of granules with required ratio, the value of Compressibility index changed from 29 to 21.89, showed that flow properties were improved i.e. from poor to passable.

Design expert 12.0 gave optimized solution for formation of required quantity of granules. Pareto chart showed envaulted positive and negative impact of factors on response as explained in results.

The results clearly indicate that how granules manufacturing in roll compaction process are influenced by roller pressure, roller gap and speed. 70 % flakes formation and granules retention were observed with 4000 kg/cm^2 pressure, 1 mm roller gap width and 6 rpm speed of roller.

Pareto chart clearly indicate major impact is of roller pressure. Comparative dissolution profile graph showed that drug release pattern is similar with the innovator tablet.

A stable, robust tablets were formed at the end of process.

Conclusion: In this study, by optimizing processing variables stable antiretroviral immediate release oral solid dosage form was formed.

Keywords: Dry granulation, Roll compactor, Optimization, Antiretroviral, Tenofovir disproxil fumarate (TDF), Immediate release tablet

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INTRODUCTION

An awesome fact is that since time immemorial i.e. over the past decades oral ingestion has long been the most convenient and commonly employed route of drug delivery. Oral route is the most preferred route of drug administration due to its non-invasive nature, administration convenience, and highest patient compliance with low production cost and design flexibility. Despite tremendous advancements in drug delivery, the oral route retains the ability of being the preferred route for the administration of therapeutic agents [1-3]. A granulation process step is often mandatory when Active pharmaceutical ingredients or formulation excipients have very poor flow property. The flowability of powders has major impact in successful formulation of tablets. If the powder is 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]. Tenofovir disproxil fumarate (TDF) belongs to class of anti-retroviral drugs knows as nucleotide analogue reverse transcriptase inhibitors (NtRTIs) which blocks reverse transcriptase an enzyme crucial to viral production in HIV-infected people. Chemically, TDF is 9[(R)-2-[[bis [[(isopropoxycarbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate [5, 6]. The unit dose of the drug is 300 mg. The drug is white to off white amorphous powder, is fine, fluffy in nature and exhibits poor flowability. Poor flow of powder results in bridging in hopper, arching, rat holing, no flow [7]. Granulation, excipient combination has effect on flow ability. Hence here granulation method chosen as dry granulation by roller compaction method. Roll Compaction/Dry Granulation (RCDG) is a granulation method in which is densification/compaction of powder(s) is done by passing it between two counter-rotating rollers [8]. The RCDG technique has significant effect on fluidity, compressibility and compactibility influencing drug release profile and tablet properties. The word optimize means perfect, effective or functional as possible. The term optimization is often used in pharmacy relative to formulation and processing. In general terms, the optimum solution is those value of the factors which, when taken together, give the best values for two or more dependent variables. Optimal factor values depends on the process objective i.e. to maximize process yield or reduce product variability [9]. As given in ICH guidelines for quality by design (Qbd), Quality cannot be tested into the product that is quality should be built in by design [10]. Three operating parameters the roller speed, the hydraulic pressure and the Auger speed on the Chamunda CPMRC-200/150 Roll Compactor were varied. The planned response variable for study was % retention over #60 ASTM mesh. Factorial designs are the design of choice for simultaneous determination of the effects of several factors and their interactions. Roll compaction/dry granulation (RCDG) is a technique of choice for dealing out/processing of physically or chemically moisture sensitive drugs, as no liquid binder is essential in the granulation. This

literature review exemplifies the advancement and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations.

The aim of study was to optimize various parameter that affect manufacturing of flakes and ultimately reteained granules so the final effect will be on stable dosage form [11].

MATERIALS AND METHODS

Tenofovir Disproxil Fumarate (Hetero Lab), Lactose monohydrate (Signet Chemicals pvt ltd.), Microcrystalline cellulose Avicel PH 102(FMC Biopolymer), Sodium starch glycolate (Sigma chemicals India), Croscarmellose Sodium (Colorcon pvt ltd.), Magnesium stearate (Nitika pharma). The compaction was done on Chamunda GMP roll compactor Model-CPMRC 200/150. Screening of flakes into granules was done by using Qudro co-mill (M/s Gansons Ltd. India)

In this study, three aspect of the control of roller compactor were adjusted to evaluate the effect on the resultant granulate namely roller speed, compaction force and roller gap as discussed.

Physicochemical characterization of drug

Bulk density and tapped density of the API (100 gm) was determined as per method-1 (USP 30-NF 25, measurement in a graduated cylinder) using powder density tester (Electrolab). The compressibility index and hausner ratio were studied to determine flow property [12]. The drug excipient compatibility was done on 40 °C/75% RH, the accelerated storage condition [13] [ICH Q1A (R2)] for a period of 4 w.

Formulation of dosage form under optimization of process variables of compaction process

Tablets were formulated by using composition as shown in table 1.

Table 1: Composition of tablet

S. No.	Ingredients for tablet	%
	Compaction Part	
1.	Tenofovir Disproxil Fumarate (TDF)	43.47
2.	Lactose Monohydrate	20.86
3.	Microcrystalline Cellulose PH 102	14.28
4.	Magnesium stearate	0.14
	Lubrication Part	
5.	Microcrystalline Cellulose PH 102	14.28
6.	Croscarmellose Sodium	2.86
7.	Sodium Starch Glycolate	2.29
8.	Magnesium stearate	1
	Core Tablet weight Total-690 mg	100
9.	Opdry II Red 85F25215	3% Weight gain
	Coated Tablet weight Total-710 mg	--

TDF, Lactose monohydrate were co-sifted through 30# sieve. Then microcrystalline cellulose was sifted through 40# sieve. All sifted material was mixed in double cone blender for 10 min. Magnesium stearate sifted through 60# sieve, then added in blender and mixed for 5 min. This premix material was used for compaction. After compaction flakes or ribbon produced were sized by using quadro co-mill. Screen used was 050 grated (1.20 mm). After that this sized material was sifted by using 60# sieve. 60# retained granules were collected in polybag and 60# passed fines in another polybag.

If desired weight of granules is achieved then granules and fines were mixed in double cone blender for 5 min. Blended with extra granular sifted excipients for 10 min. Finally lubricated with Magnesium stearate sifted through 60# sieve for 3 min. This blend was compressed by using 16.5 X 8.5 mm punch on Karnavati compression machine to form tablets.

Roll compaction

A roll compactor generally consists of three major units: a feeding system, which conveys the powder to the compaction area between the rolls; a compaction unit, where powder is compacted between two counter rotating rolls to a ribbon by applying a force; and a size reduction unit, for milling the ribbons to the desired particle size. Several operational parameters can be adjusted/controlled to modify the product granulate; the compaction force, the gap width and the milling size, roller rpm, auger rpm being the main variables. For this study, the variation in the compaction force and the gap width, roller rpm was investigated with respect to the quality and quantity of the granulate [14].

Design of experiments/factorial design for granulation process

Factorial design is an efficient method of indicating the relative significance of number of variable and their interaction. In present study, Hydraulic pressure/compaction force, roller speed, roller gap width effects were considered. These three variables were considered at two level i.e. lower and upper level hence it was a 2^3 factorial design. The factors and range for roller compaction parameters were as shown in table 2.

Table 2: Critical process parameter for factorial design

Factor	Name	Unit	Low level	High level
Factor 1	Roller speed	Rpm	3	9
Factor 2	Hydraulic pressure/Compaction force	kg/cm2	2000	4000
Factor 3	Roller gap width	Mm	1	2

According to factorial design and considering these three variables, eight experiments had been performed. The response was % of granules over 60# ASTM sieve. Each experiment involved three cycles for compaction to achieve desired ratio of granules to fines. Finally, after eight batches, optimized process parameters were taken for compaction and final batch compacted and evaluated for flow properties. This optimized batch granules were taken for formulation of tablet. Finally, tablets were coated for 3 % weight gain per tablet. Tablets were compressed at parameters as shown in table 3.

The tablets of optimized batch were evaluated for weight variation, Assay, disintegration test, *In vitro*-dissolution test [15]. *In vitro*-drug release study was carried out using USP (Apparatus 2-paddle method) dissolution apparatus at 37+0.5oC with constant stirring rate of 50 rpm/min. The formulated tablets were tested for drug

release in 0.1 N HCl for 45 min. A sample volume of 10 ml 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 259 nm. Six tablets were taken from each batch for dissolution study and average value at each time point was taken for drug release study. Film coating of tablets was done by using auto coater to maintain the physical and chemical of tablets. The parameter for coating is as shown in table 4.

Table 3: Compression parameter for tablet

S. No.	Parameter	Limit
1.	Appearance	White to off white capsule shape tablet plain on both side
2.	Weight	690 mg+5 %
3.	Thickness	5.80+0.2 mm
4.	Hardness	NLT 50 N
5.	Disintegration Test	NMT 15 min.
6.	Friability Test	NMT 1 %

Table 4: Coating parameter for tablets

S. No.	Parameter	Limit
1.	Pan RPM	12-16 rpm
2.	Inlet air Temperature	50-70 oC
3.	Exhaust air Temperature	40-60 oC
4.	Bed Temperature	40-45 oC
5.	Atomizing air pressure	2-4 kg/cm^2
6.	Spray pump RPM	5-15 rpm
7.	Spray rate	5-10 ml/min
8.	Spray gun Nozzle diameter	1.5 mm

RESULTS AND DISCUSSION

Physicochemical characterization of drug was done. The results of flow property test indicated poor flow of drug. Hence to improve flowability and compressibility dry granulation was done. The results were as shown in table 5.

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 as shown in table 6.

Therefore it was concluded that the drug can be formulated by combining drug with mentioned excipients.

Optimization of roller compactor variables

The optimization with regard to one or more attributes has always been a subject of importance and attention. The word "optimize" means perfect, effective or functional as possible. The term "optimization" is often used in pharmacy relative to formulation and processing. In general terms, the optimum solution is those values of the factors which, when taken together, give the "best" values for two or more dependent variables. Optimal factor values depend on the process objective i.e. to maximize process yield or reduce product variability [16, 17].

Certainly, human input is an essential ingredient of the creative process. In addition to the art of formulation, techniques are available that can support the scientist's choice of formulation components which will optimize one or more product attributes [18, 19].

Design of experiments run details and observation are tabulated in table 7. It was concluded that slow speed for roller provides more compaction as it gives sufficient time to form cohesion/bridge between particles. Hence slow roller speed provides more agglomeration of material. Hydraulic pressure/compaction force has direct relation with compaction.

Table 5: Physicochemical characterization of drug

S. No.	Test	Specification	Results
1.	Description	White to off white powder	White to off white powder
2.	Solubility	Sparingly Soluble in Ethanol and Methanol	Complies
3.	Moisture content	NMT 1%	0.76%
4.	Bulk Density	--	0.460 gm/ml
	Tapped Density	--	0.644 gm/ml
	Hausner's ratio	--	1.4
	Compressibility Index	--	29
5.	Melting Point	114-118 °C	114.5 °C
6.	Assay on dried Basis	NLT 97% and NMT 101% w/w	99.5 % w/w

Table 6: Drug excipients compatibility study

S. No.	Combination	Ratio	Physical appearance	Observation at 40 °C/75 % RH			
				1 W	2 W	3 W	4 W
1.	API	--	Off white	NC	NC	NC	NC
2.	API-Lactose Mono.	1:10	Off white	NC	NC	NC	NC
3.	API-Microcrystalline cellulose PH102	1:10	Off white	NC	NC	NC	NC
4.	API-Croscarmellose Sodium	1:2	Off white	NC	NC	NC	NC
5.	API-Sodium Starch Glycolate	1:2	Off white	NC	NC	NC	NC
6.	API-Magnesium Stearate	1:0.5	Off white	NC	NC	NC	NC

Description: NC–No change

Table 7: Design of experiment run and observation

Batch code	Factor 1 roller speed (RPM)	Factor 2 compaction force (kg/cm²)	Factor 3 roller gap width (mm)	Cycles (No.)	Response % retention over 60# sieve
FB1	3	2000	1	3	57%
FB2	9	2000	1	3	56%
FB3	3	4000	1	3	72%
FB4	9	4000	1	3	67%
FB5	3	2000	2	3	58%
FB6	9	2000	2	3	55%
FB7	3	4000	2	3	62%
FB8	9	4000	2	3	61%
OB1	6	4000	1	3	70%

Description: FB–Factorial Batch, OB-Optimized Batch

A high compaction force gave more compacted flakes and resulted into more granules. Harder granules obtained when high pressure was given while low compaction force provide soft granules in less quantity. Less roller gap results into more densification/compaction of material. A combined effect of slow roller speed, high hydraulic pressure and less roller gap results into high densification/ compaction. Three compaction cycles taken in present study. Eight factorial design batches taken and evaluated toward highest productivity of granules. % retention of granules over 60# sieve varied between 55 to 72 % in these eight different trials. As compared to roller speed and gap width, more impact is of compaction force. By using Design of experiment calculation excel sheet optimum parameters value for roller speed, compaction force, roller gap width decided to get higher desired response value i.e. % retention over 60 # sieve. Compaction force was kept to higher side i.e. 4000 kg/cm², Roller gap kept to lower side i.e. 1 mm. Roller speed was kept at 6 rpm by giving emphasis on both on quality as well as output i.e. production of granules. Finally, by using this optimum solution for factor, compaction was done in optimized batch OB 1. Resultant granules that retained over 60 # sieve was 70 %. Rest of manufacturing process was done as described previously to formulate tablet.

Pareto chart

Pareto chart is a useful tool for showing others the relative size of effects. These are useful to separate the "vital few" from the "trivial many" issues. Pareto charts are useful in gaining a deeper understanding of root cause or discovering possible "high-leverage" points to begin to impact change.

Here Hydraulic pressure/compaction force factor has a major effect on the particle size. It indicates the Hydraulic pressure/compaction force factor have most significant effect in formation of flakes. Factor below t-limit has non–significant effect. Qualitatively it can observe from Pareto chart that the range in which turret speed was used have least effect. Roller gap width has more effect than Roller speed.

Hydraulic pressure/compaction force showing positive effect. It can be considered to have highest effect for formation of flake. While roller speed has least effect.

Pareto chart was as shown in fig. 1.

Characterization/evaluation of tablet

Bulk density of granules was found to be 0.449 gm/ml while tapped density was found to be 0.568 gm/ml. Compressibility index and hausner's ratio were calculated from these values i.e. 21.89 and 1.27 respectively. These micrometrics properties show passable flow property and compressibility. Physical characteristics or post compression parameters of tablets were evaluated. Results were satisfactory and as shown in table 8.

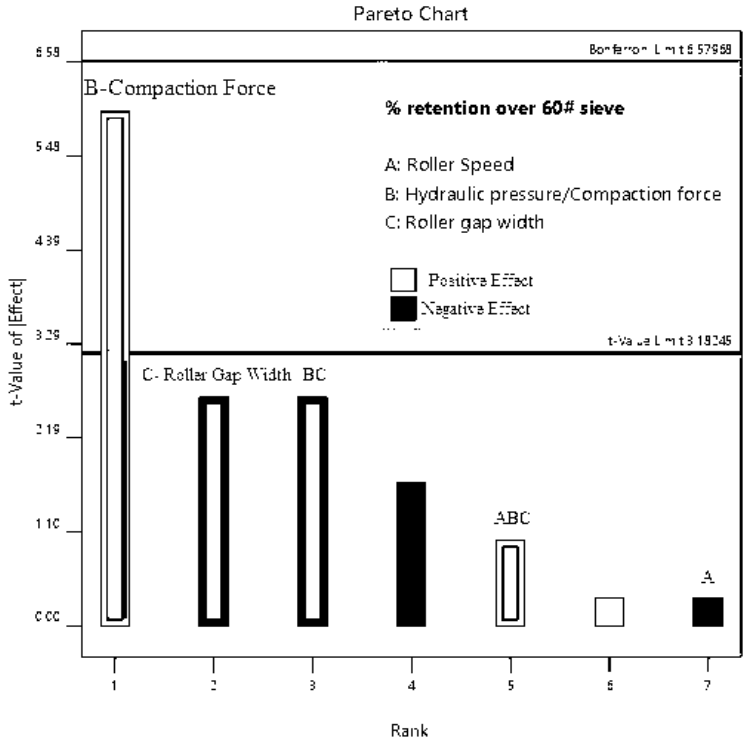

Fig. 1: Pareto chart created by design expert v.12.0 related to the given data

Table 8: Characterization of tablets

S. No.	Property	Core tablets	Coated tablets
1.	Appearance	White colored, biconvex, capsule shaped	Orange colored, biconvex, capsule shaped
2.	Average Weight	688–700 mg	708-715 mg
3.	Thickness	5.75–5.84 mm	5.90–5.96 mm
4.	Hardness	50–90 N	120–140 N
5.	Friability	0.09 %	--
6.	Disintegration Time	1 min 45 sec	2 min to 2 min 10 sec

Assay of tablets was found to be 99.0 to 101.3 %. The drug release from tablets was ranged from 96.5 to 100.1%. Detailed results about dissolution study was as shown in table 9. Dissolution profile of formulated tablet was compared with innovator (Viread) Tablets and shown in fig. 2.

Table 9: Dissolution profile at different point of formulation

Time (min)	% Drug release from formulated tablets	% Drug release from Innovator (Viread)
0	0	0
5	40.2	37.2
10	61.9	56.1
15	79.5	73.5
30	97.8	97.2
45	100.3	99.3

Note-Results of dissolution are average value.

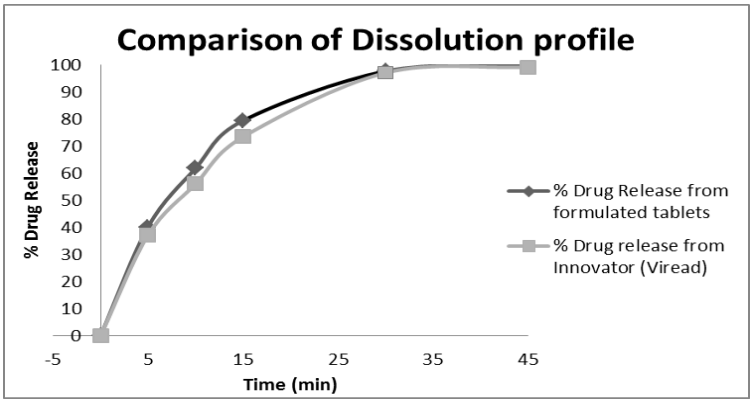

Fig. 2: Comparison of dissolution profile of innovator with test

CONCLUSION

The use of dry granulation, that is, Roller Compaction, has increased recently in the development and manufacturing of pharmaceutical dosage forms. In present study, a successful attempt has been made to formulate an antiretroviral molecule into immediate release tablet by dry granulation/roller compaction method. Critical variable having impact on compaction process has been identified and controlled to produce desired target response. Pareto chart is a useful tool for showing others the relative size of effects. It gives deeper understanding that root cause in formation of flakes and retained granules is majorly compaction force after that distance between rollers is major factor. 2^3 factorial design, Design expert software, Pareto chart are the new technique to find out important factor that impact quality.

With respect to Quality by Design requirements, these results demonstrate that it is possible to control Critical Process Parameters in order to achieve required retained granules % and granules properties.

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AUTHORS CONTRIBUTIONS

Individually worked in this piece of work.

CONFLICT OF INTERESTS

The author declared no conflict of interest.

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