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PROCESS DEVELOPMENT AND OPTIMIZATION OF MOISTURE ACTIVATED DRY GRANULATION OF VALACYCLOVIR TABLETS

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ABSTRACT

Aim is to develop the Moisture Activated Dry granulation technique on Valacyclovir tablets 500 mg. Dry mixing and Granulation were carried out in Rapid Mixer Granulator as per the process specifications. Particle size distribution, bulk density and compressibility index are comparable. This shows that the intermediate processing steps viz sifting and milling operations were satisfactory. Final blend of the batch was subjected for analysis as per in process specification and the results are found to be within the specification limit. Compression of the Valacyclovir Tablets 500mg was carried out at Low hardness, Optimum hardness & High hardness at Optimum speed. Samples are collected from each trail & analyzed as per validated method. The results show that all physical and chemical characteristics of the tablets were within the acceptance limit.

Key Words: Valacyclovir, Moisture activated dry granulation

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INTRODUCTION

Agglomeration-In this stage, all or part of the drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture. During mixing, a small amount of water (1–4%) is sprayed onto the powder blend, water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass.The binder functions as the drug and excipients move in the circular motion caused by the mixer impellers or blades. Dry powder particles adhere to the wet nuclei or wet tacky mass to create moist agglomerates.The resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation. The agglomerates

therefore cannot grow into large, wet lumps. The particle size of the agglomerates generally is in the range of 150–500 μm.It is possible, based on the drug loading technique, to add only part of the drug to the formulation during the agglomeration stage. The remaining drug can be added after the moist agglomerates have been formed. The added drug particles adhere to the wet agglomerates and become incorporated into them.The process does not create large granules, which would need milling, and because very little water is used in the process, the endpoint is not sensitive to blending.

Moisture Distribution and Absorption Stage-In this stage, moisture absorbents such as microcrystalline cellulose or silicon dioxide are added as mixing continues. When these agents come into contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture. The entire mixture thus becomes relatively dry. Although some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact, and some, usually the larger particles, may break up. This process results in a granulation with uniform particle-size distribution. The process continues with the addition of a disintegrant to the mixture, followed by blending for a few minutes.Then, during mixing, lubricant is added and blended for sufficient time to achieve adequate lubricity. This step completes the MADG granulation process. Excluding material loading, the actual processing time for the MADG process is only 10–20 min. Even for a commercial-scale batch, the processing time is essentially the same as it would be for a laboratory- or pilot-scale batch. Beginning with the premixing of the drug and excipients, the final granulation could be ready for tablet compression, encapsulation, or powder filling in about an hour.

Extensive literature review was made for understanding the study and there has been number of reports concerning the applications of MADG in the formulation of different types of dosage forms like immediate release /sustain release / controlled release matrix tablets (1-6). The aim of the present work is the Process Development and Optimization of Moisture Activated Dry Granulation of Valacyclovir Tablets 500 mg. To optimize the process parameter identified during the developmental stage of the formulation.

MATERIALS AND METHODS

Materials

Valacyclovir Hcl (SIPRA LABS Ltd), Microcrystalline Cellulose JP (FMC bio polymers), Crospovidone (ISP Tech), Povidone JP (BASF), Light anhydrousSilicilic acid JP (Evonik industries) and Magnesium Stearate JP (Peter greven).

Methods

Unit formula &quantitative details for Valacyclovir Tablets 500mg

Unit formula is given in table-1

Table-1 Unit formula for Formulation

Sl. No.	Ingredients	Unit formula	% weights
1	Valacyclovir Hydrochloride *	556	79.42857
2	Microcrystalline cellulose (AvicelPH101) **	104	14.85714
3	light anhydrous silicilic acid	7	1
4	Crospovidone (polyplassdone XL)	3.5	0.5
5	Povidone (kollidon 90F)	22	3.142857
6	Purified Water ***		
7	Crospovidone (polyplassdone XL)	3.5	0.5
8	Magnesium Stearate	4	0.571429
Tablet Weight		700	100

Granulation (7, 8)

Granulation involves two major stages- Agglomeration and Moisture Absorption And Distribution Stage

Agglomeration

Granulating fluid Sprayed to the Rapid mixer granulator containing dry mix over a period of 2 min by using Airless Spray System at impeller slow speed.Granulated the mass for 30 sec at impeller & chopper slow speed. Loss on Drying (LOD): 10.72%

Moisture absorption & distribution

Loaded the sifted material of API from step1.1 added into the agglomerated blend at impeller slow speed for 2 min, it's absorb the moisture upto some extent.

Loaded the sifted material of Microcrystalline cellulose & Aerosil from step1.2 into the RMG with impeller slow speed over a period of 2 min. Moisture absorbing agents like MCC come into contact with the moist agglomerates; they pick up moisture from the agglomerates and redistribute moisture within the mixture. Loss on Drying (LOD):8.59 %

Content Uniformity

In this test, 30 tablets were randomly selected contained for sample, and 10 the tablets Valacyclovir should contain not less than 85.0 % and not more than 115.0 % of the label claim. If one unit outside the range of 85 to 115% of the label claim and no units is outside 75 to 125% or if RSD> 6% or if both conditions prevail, test 20 additional units.

Disintegration Test/Time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. Place one tablet into each tube and suspend the assembly in to the 1000ml beaker containing water maintained at 37 ± 2^{o}C and operate the apparatus & observe. Remove the assembly form the liquid. Observe the tablets, if one or two tablets fail to disintegrate completely; repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

In vitro **dissolution study**

The dissolution was carried out to determine the rate of drug release at different time intervals (9).

RESULTS AND DISCUSSION

IR Studies

Compatibility studies were performed using ir interpretation for pure drug and for pure drug and excipients physical mixture and it were found that there were no interactions between the pure drug and the excipients so the further formulation was carried out.Physical Parameters Of Lubricated Blend

Analytical results of pooled sample for description and assay met the specification (Table-2).

Table-2 Physical parameters of Final Blend

S.NO	Test	Specification	Test results
1	Description	White to off white granules	white granules
2	Bulk density	For information only	0.716 gm/ml
3	Tapped density	For information only	0.880 gm/ml
4	Compressibility index	For information only	18.571 %
5	Particle size analysis	For information only	Cumulative %
	#20		1
	#30		3
	#40		8
	#60		15
	#80		18
	#100		22
	#120		25
	#140		31
	Plate		100
6	Flowability	For information only	29
7	LOD at 105 ˚c (on moisture balance)	For information only	7.54 %
8	Assay	NLT 95.0% and NMT 105.0% of the label claim	100.9%

Dissolution rate profile

Core tablets at lower hardness

Dissolution Results for Lower Hardness Tablets is given in Table-3

Table -3 Dissolution Results for Lower Hardness Tablets

Unit No	% Dissolved					
	05min	10min	15min	30min	45min	60min
1	70	86	90	99	99	99
2	81	88	93	97	99	99
3	82	92	96	98	101	101
4	87	87	90	100	101	101
5	74	90	93	98	100	100
6	81	90	92	97	101	101
Mean	79	89	92	98	100	100
Min	70	86	90	97	99	99
Max	87	92	96	100	101	101
RSD	8	2.4	2.2	1	0.6	1

Dissolution Medium:0.1N Hcl pH=1.2, USP Apparatus II, paddle, 50 rpm, 900 ml

The above dissolution profile results for Lower hardness tablets met the specified acceptance criteria.

Core tablets at Optimum hardness

Dissolution Results for Optimum Hardness Tablets is given in table-4

Table-4 Dissolution Results for Optimum Hardness Tablets

Unit No	% Dissolved					
	05min	10min	15min	30min	45min	60min
1	67	80	89	97	99	100
2	79	90	97	98	99	100
3	74	83	85	93	95	98
4	72	77	85	93	95	97
5	71	83	89	93	95	97
6	73	88	89	95	98	97
Mean	73	84	89	95	97	98
Min	67	77	85	93	95	97
Max	79	90	97	98	99	100
RSD	5.8	5.7	5	2.2	1.9	1.5

Dissolution Medium:0.1N Hcl pH=1.2, USP Apparatus II, paddle, 50 rpm, 900ml

The above dissolution profile results for Optimum hardness tablets met the specified acceptance criteria.

Core tablets at Higher hardness

Dissolution Results for Higher Hardness Tablets is given in table-5

Table -5 Dissolution Results for Higher Hardness Tablets

Unit No	% Dissolved					
	05min	10min	15min	30min	45min	60min
1	55	78	87	95	99	100
2	62	84	92	97	99	100
3	64	76	86	90	93	95
4	58	75	83	94	92	95
5	65	81	86	92	96	95
6	61	76	85	93	97	98
Mean	61	79	87	94	96	97
Min	55	75	83	90	93	95
Max	65	84	92	97	99	100
RSD	5.7	4	3.5	2.6	2.8	2.6

Dissolution Medium:0.1N Hcl pH=1.2, USP Apparatus II, paddle, 50 rpm, 900ml

The above dissolution profile results for Higher hardness tablets met the specified acceptance criteria.

All the input raw materials were reviewed and found they all are approved. Raw materials initial sifting was done. Dry mixing and Granulation were carried out in Rapid Mixer Granulator as per the process specifications. Dry mixing Samples were collected from 10 different locations and analyzed for Blend Uniformity as per sampling plan. The results of 10 unit dose samples from the batch are shown that the blend is homogenous.The blend uniformity data of Pre Lubricated blend were found to be in the range of 98.8 % to 103.2 % with a RSD value of 1.3 % The pre-lubricated blend results are within the acceptance criteria of 90.0 % to 110.0 % with RSD Not More Than 5.0 %.

Similarly for Lubricated blend, the blend uniformity data ranges from 98.7 % to 101.9 % with RSD value of 1.1 %. The final blend results are within the acceptance criteria. Particle size distribution, bulk density and compressibility index are comparable. This shows that the intermediate processing steps viz sifting and milling operations were satisfactory.

Final blend of the batch was subjected for analysis as per in process specification and the results are found to be within the specification limit.

Compression of the Valacyclovir Tablets 500mg was carried out at Low hardness, Optimum hardness & High hardness at Optimum speed. Samples are collected from each trail & analyzed as per validated method. The results show that all physical and chemical characteristics of the tablets were within the acceptance limit.

CONCLUSION

The generated data and analytical reports during the Process Development and Optimization of Moisture Activated Dry Granulation of Valacyclovir Tablets 500mg USP studied and results complied with the critical parameters identified at the developmental stage of formulation by wet granulation were reproducing at process optimization batches. % Fluid uptake studies done between the range of 5.0-10.0 %W/W (of dry mix weight) & 3.0-3.5 %W/W for unit weight of Tablet.

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