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Studies in Process Development of Nimusulide 100 mg Tablet Dosage Formulation

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Abstract: Tablet formulation of nimusulide present significant challenges due to its poor inherent compressibility & highly moisture sensitivity. Process development batches (PDB) were taken and evaluated for satisfactory result during sifting, dry mixing, preparation of granulating agent, wet mixing, drying, sizing, lubrication and compression. Process development stage parameter with respect to ruggedness and robustness of manufacturing process were evaluated by trial and error methods. Process development batch PDB1 was taken as per R & D guidelines and evaluated for satisfactory result. Tablet lamination was reported during compression of PDB1, due to excessive moisture content. Hence drying time and inlet air drying time was increased . This changes was done in PDB2 and batch was taken as per same manufacturing process. In order to develop rugged and robust PDB3 was taken as per same manufacturing process. Result obtained from PDB2 and PDB3 was shows that our manufacturing process as well as formulation was found satisfactory for production run.

Keyword: Process development, Uniformity of mixing, Rugged and Robust process.

Introduction

Process development is actual transfer of the manufacturing process from R & D to production along with necessary knowledge & skill to be able to make the product, is refered to as technology transfer. The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product meeting with registered specification & cGMP requirements [1-2].

Today the production of pharmaceutical granules is still based on the batch concept. In early stage of development of solid dosage form, batch size is small. In later stage of the batch produced in pharmaceutical production department may be up to 100 times larger[3-4]. Thus scale-up process is extremely important one. Unfortunately in many case the varity of equipment involved does not facilitate the task of scale-up. During scale-up quality of granules may changes[5,6,7]A change in granule size, distribution, final moisture content, compressibility & compatibility of granule may strongly influence the properties of final tablet such as tablet hardness, friability, distentigration time, dissolution rate of active substance , aging of the tablet etc [8,9,10]. The present work also aim to develop rugged and robust manufacturing process which fulfill all requirement of cGMP.

Materials and Methods:

Nimusulide (Biochem pharma), Maize Starch (Universal starch), gelatin (Gujarat mineral industry), Purified Talc (Gujarat mineral industry), Magnesium sterate (Nikita chemical), sodium starch glycolate (Aditya chemical), colloidal silicon dioxide (Aditya chemicals) & purified Water (INH) was used for this Formulation. All raw material used of I.P. grade and chemicals used in the analysis in the study where of analytical grade.

Machineries:

Machineries and equipments used was as sifter, multimill (Ganson Ltd), rapid mixing granulator

[RMG] (50L,Kevin), steam kettle (Anchor mark), fluid bed drier [FBD] (50L,saffhire), planetary mixer [PLM] (50L,GM Ltd), compression machine 16 station single rotatory BB type (Cadmach), UV-visible spectrophotometer (Shimadzu 1800), Monsanto hardness tester (Rollex), disintegration and friability test apparatus (Electo lab), Mitutoyo thickness tester.

Wet granulation:

Tablet was manufactured by wet granulation method using ingredients shown in table no 1 . After dispensing of required material they were sifted through sifter as shown in table no.1. Nimusulide, sodium starch glycolate, maize starch was dry mixed in RMG at slow speed for time interval of 5min. Granulating agent was prepared in steam kettle, maize starch for paste was dispersed in 1/3 quantity of P/W. Gelatin solution was prepared by dissolving it in P/W. Remaining quantity of P/W was taken in steam kettle, boiled and to this above prepared starch slurry and gelatin slurry was mixed by stirring continuously till homogenous mass was formed. Then cool it upto 45 -50 ^{0}c and unloaded in suitable S.S. container. To dry mixed material granulating agent was added and mixed slow and high speed of beater & chopper till desired consistency of dough mass was formed if required P/W was added. Drying in FBD was done at inlet temp 60^{0}c till outlet reaches 38-40^{0}c & LOD 2.5-3.5 %. w/w for 30 min. Sizing was done by passing dried mass through 16 mesh sieve & retention generated passed through 1.0mm mesh of multimill knive forward, slow speed direction. Lubrication was done in planetary mixer after geometric mixing of sifted lubricant expect magnesium sterate with sized granules into PLM at slow speed for 5 min interval. Then magnesium sterate was added and again mixed for 2min at slow speed.

Compression of Batches:

Tablet were compressed using 9.5mm stranded concave circular plain punches (both upper & lower) on 16 Station single rotatory BB type compression machine. Each 280mg tablet contains 100mg nimusulide. The specification for tablet was kept as average weight 280mg (±5%) , diameter 9.5mm((±0.3mm%) hardness NLT 2kg/cm^2, thickness 3.70mm (±0.2mm), friability NMT 1%w/w, D.T. NMT 15 Min, Assay 100% (± 10%).

Analysis:

Results and discussion:

The result of PDB1 were shows that dough mass formed during wet mixing was sticky. The LOD obtained after 30min drying at 60^{0}C was 3.5-4.5 % w/w (beyond limit). The CI, TBD, LBD, %fine & LOD obtained during sizing and lubrication stage was 9.9897%, 0.629gm/ml, 0.510gm/ml, 40% & 3.2-4.3%w/w and 8.980%, 0.641gm/ml, 0.580gm/ml, 43.10% & 3.4-4.4 %w/w respectively. First retention of sizing was 45.85%. While in compression lamination was observed tremendously due-to this tablets was not formed as per specification. Hence improvement was done in PDB1. Probable reason for lamination was excessive moisture content. Hence improvement was done in inlet air drying temperature and was increased by 10^{0}C along with drying time by 5min interval. Also quantity of P/W reduced by 500ml for preparation of granulating agent. As per this recommended process changes PDB2 was taken and the satisfactory LOD achieved after 35min drying was 2.5-3.5%.w/w. The CI, TBD, LBD, %fine & LOD obtained during sizing and lubrication stage was 6.7675%, 0.7246gm/ml, 0.6756gm/ml, 34% & 2.5% w/w and 6.000%, 0.7097gm/ml, 0.6672gm/ml, 35.80% & 2.5% w/w respectively. First retention obtained during sizing was 32.72%.

Table No: 1 Compositions of various process development batches.

Ingredient	PDB -1	PDB -2	PDB-3	Role	Mesh
Nimusulide	1.7857kg	1.7857kg	1.7857kg	Active	40
Maize Starch	2.6696kg	2.6696kg	2.6696kg	Diluents	200
Maize starch (paste)	0.1785kg	0.1785kg	0.1785kg	Binder	200
S.S.G.	0.1785kg	0.1785kg	0.1785kg	Disintigrant	200
Gelatin	0.0090kg	0.0090kg	0.0090kg	Binder	100
Talc	0.0357kg	0.0357kg	0.0357kg	Glident	200
P/W	5.0 Lit	4.5 Lit	4.5 Lit	Solvent	-
Colloidal silicon dioxide.	0.0357kg	0.0357kg	0.0357kg	Lubricant	20
Magnesium Sterate	0.0357kg	0.0357kg	0.0357kg	Lubricant	100
S.S.G.	0.0714kg	0.0714kg	0.0714kg	Disintigrant	20
Total Batch Size	5.0kg	5.0kg	5.0kg		

P/W = purified water, SSG=Sodium starch glycolate

The non complies parameter of compression of PDB1 was found complies in PDB2 that is hardness 3.8-5.0 kg/cm², friability 0.7071%w/w & other parameter found complies as per release specification of batch. Problem of lamination was get completely rectified. To develop rugged and robust manufacturing process and formulation another batch, PDB3 taken as per same process and formulation changes. Comparative result of PDB1, PDB2 & PDB3 was shown in table no 2.

Conclusion:

From this study it was concluded that the PDB2 & PDB3 formulation and process was rugged and robust hence feasibility for production run at large scale must be explored.

Table No 2: Comparative Results of process development batches.

Stage/Equipment	Evaluation Parameter	PDB-1	PDB-2	PDB-3
Sifting(Sifter)	Sieve Integrity Before & After	OK	OK	OK
Dry mixing(RMG)	Uniformity of mixing (5 min)	97.97%	101.01%	99.98
Granulating solution preparation (Steam Kettle)	Qty of P/W used	5.0 Lit	4.5 Lit	4.5 lit
	Consistency of paste	Satisfactory	Satisfactory	Satistifactory
Wet Mixing (RMG)	Mixing Time	2 min Slow, 3 min Fast	2 min Slow, 3 min Fast	2 min Slow, 3 min Fast
	Ampere Reading	6	7	6
	Dough mass Consistency	Sticky dough mass	Excellent	Excellent
	Additional P/W added	Nil	Nil	Nil
Drying (FBD)	Drying Time and inlet air Temp.	30 min & inlet air Temp. 60^0c	35 min & inlet air Temp. 70^0c	35 min & inlet air Temp. 70^0c
	% LOD	3.5-4.5	2.5-3.5	2.8-3.9
Sizing (Sifter Multimill)	I^{ST} Retention(%)	45.85	35.98	36.90
	% Fine	50.00	34.00	32.90
	LBD (gm/ml)	0.590	0.585	0.550
	TBD (gm/ml)	0.629	0.690	0.645
	CI (%)	9.9897	5.7675	5.9089
	LOD (%w/w)	3.2-4.3	2.5-3.6	2.7-3.6
Lubrication (PLM)	Uniformity of mixing(5+2 min)	99.90%	101.23%	99.76
	% Fine	48.10	32.80	30.98
	LBD (gm/ml)	0.600	0.578	0.560
	TBD (gm/ml)	0.641	0.672	0.667
	CI (%)	8.980	5.700	5.000
	LOD (%w/w)	3.4-4.4	2.5-3.4	2.5-3.8
Compression (27 station Single rotary machine)	Speed	15 RPM	15 RPM	15 RPM
	Weight Variation (%)	NA	± 3.20	3.40
	Thickness (mm)	NA	3.65-3.74	3.58-3.70
	Friability(%w/w)	NA	O.4602	0.5830
	Disintegration time	NA	4.0	4.0
	Hardness (Kg/cm^2)	NA	4.0-5.0	4.2-5.5
	Assay (%)	NA	102.09 %	98.90

PDB=Process development batch, LOD=Loss on drying, CI=Compressibility index, LBD=Loss bulk density, TBD= Tap bulk density.

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