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Research Article

STUDIES IN PROCESS DEVELOPMENT OF METFORMIN HCL TABLET DOSAGE FORMULATION

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ABSTRACT

Tablet formulation of Metformin HCL present significant challenges due to its poor inherent compressibility, high dose & highly moisture sensitivity. Process development batches (PDB) were taken and evaluated for satisfactory result during sifting, dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication and compression. Process development 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. Due to unsatisfactory results, changes was done PDB2, in quantity of granulating agent and processing stage. Process development parameter of PDB2 were evaluated & found satisfactory for production run.

Keyword: Process development, Uniformity of mixing, Rugged process, 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 referred 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]. Thus scale-up process is extremely important one. Unfortunately in many case the variety of equipment involved does not facilitate the task of scale-up. During scale-up quality of granules may changes. 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, disintegration time, dissolution rate of active substance , aging of the tablet etc [4-5]. The present work also aim to develop rugged and robust manufacturing process which fulfill all requirement of cGMP.

MATERIALS AND METHODS

Metformin HCL (Shree Maa), Maize Starch (universal starch), Dicalcium phosphate (Enar chemie), PVP-K30 (ISP technology), Sodium benzoate (Navyog pharmaceuticals), Purified Talc (Gujarat mineral industry), Magnesium sterate (Nikita chemical), sodium starch glycolate (Aditya chemical) & purified Water (INH) was used for this Formulation. All raw material used of BP 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 27 station single rotatory (Cadmach), UV-visible spectrophotometer (Shimadzu 1800), six stage dissolution rate test apparatus IP/BP/USP(Tab machine), 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 . During manufacturing temperature NMT 25^{0}c & RH NMT 50% were maintained. After dispensing of required material they were sifted through sifter as shown in table no.1. Metformin HCL, D.C.P & maize starch was dry mixed in RMG at slow speed for time interval 10min . Granulating agent was prepared in steam kettle, maize starch for paste was dispersed in 1/3 quantity of p/w, remaining quantity in steam kettle with boiling, to this sodium benzoate , PVP-K30 & starch mucilage was added with stirring and cool 45 -50 ^{0}c. To dry mix granulating agent was added and mixed slow and high speed till desired consistency of dough mass was formed. Then this material was wet milled with multimill without mesh with impact forward slow speed. Drying in FBD was done at inlet temp 65^{0}c till outlet reaches 38-40^{0}c & LOD 2-3%. w/w for 25min. Sizing was done by passing dried mass through 20 mesh sieve & retention generated passed through 1.5mm mesh of multimill knives forward, slow speed. Lubrication was done in planetary mixer after geometric mixing of sifted lubricant with sized granules into PLM at slow speed for 10min interval.

Compression of batches

Tablet were compressed using 12.7mm FB, round Punch, having break line on upper punch & lower Punches plain on 27 Station single rotatory compression machine. Each 605mg tablet contains 500mg metformin HCl. The specification for tablet was average weight 605mg (±5%) , hardness NLT 3kg/cm^2, thickness 3.60mm (±0.3mm), friability NMT 1%w/w, DT NMT 15 Min, Assay 100% (± 5%), Dissolution NLT 70% of stated amount released in 45 min.

Analysis

Metformin HCL was estimated by using U.V. Spectrophotometer at 232nm (A1%=798) formulation samples was Subjected to U.V spectroscopy. Quantity equivalent to 100mg of metformin HCL was taken for assay. Dissolved this in 70 ml p/w, sonicated & made volume 100ml, filtered it and from filtrate pipette out 10 ml and diluted to 100ml with p/w again pipette out 10ml and diluted it 100 ml with p/w and record absorbance .

RESULTS AND DISCUSSION

The result of PDB1 were shows that consistency of dough formed was during wet mixing, not of desired quality. The LOD obtained after 25min drying was 2%w/w (lower side). The CI, TBD, LBD, %fine & LOD obtained during sizing and lubrication stage was 8.7981%, 0.6029gm/ml, 0.5494gm/ml, 66% & 2%w/w and 6.1730%, 0.6172gm/ml, 0.5791gm/ml, 69.80% & 2.1%w/w respectively. First retention of sizing was 44.97%. While in compression weight variation was reported up to 4%, hardness 2.4- 3.2kg/cm^2 (lower side), friability 1.6232%w/w (not complies). Hence improvement was necessary in PDB2 in quantity of PVP-K30 and increased by 0.035kg & starch for paste was reduced by 0.035kg . Addition of granulating agent & wet mixing was done simultaneously & addition was completed within 4min, desired quality of dough mass formed. The satisfactory LOD

achieved after 25min drying was 2.5%. 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%. The non complies parameter of compression of PDB1 was found complies in PDB2 that is hardness 3.8-5.0 kg/cm^2, friability 0.7071%w/w & other parameter found complies as per release specification of batch. Comparative result of PDB1 & PDB2 was shown in table no 2.

CONCLUSION

From this study it was concluded that the PDB2 formulation and process was rugged and robust hence feasibility of production in large scale must be explored.

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Table 1: Compositions of various process development batches

Ingredient	PDB -1	PDB -2	Role	Mesh
Metformin HCL	10kg	10kg	Active	40
Maize Starch	0.164kg	0.164kg	diluents	60
DCP	0.760kg	0.760kg	Diluents	100
PVP-K30	0.0750kg	0.110kg	binder	100
Maize Starch (Paste)	0.585kg	0.550kg	binder	100
Sodium benzoate	0.008kg	0.008kg	preservative	100
P/W	1.2 lit	1.2 lit	solvent	-
Purified Talc	0.143kg	0.143kg	lubricant	80
Magnesium Sterate	0.150kg	0.150kg	lubricant	80
SSG	0.215kg	0.215kg	lubricant	80
Total Batch Size	12.1 kg	12.1 kg		

P/W=purified water, DCP=Dicalcium phosphate, SSG=Sodium starch glycolate

Table 2: Comparative results of process development batches.

Stage/Equipment	Evaluation Parameter	PDB-1	PDB-2
Sifting(Sifter)	Sieve Integrity Before & After	OK	OK
Dry mixing(RMG)	Uniformity of mixing (10 min)	99.84%	100.09%
Granulating solution preparation	Qty of P/W used	1.2 Lit	1.2 Lit
(Steam Kettle)	Consistency of paste	Not Satisfactory (High Viscous)	Satisfactory
Wet Mixing (RMG)	Mixing Time	4 min Slow, 3 min Fast	4 min Slow, 3 min Fast
	Ampere Reading	10	8
	Dough mass consistency	Highly Sticky dough mass	Excellent
Wet milling (Multimill)	Appearance of granules	Fluppy Granules of irregular size	Granule form almost circular Shape
Drying (FBD)	Drying Time	25 min	25 min
	% LOD	2.0	2.5
Sizing (Sifter/ Multimill)	IST Retention(%)	44.85	32.78
	% Fine	66.00	34.00
	LBD (gm/ml)	0.5494	0.6756
	TBD (gm/ml)	0.6024	0.7246
	CI (%)	8.7981	6.7675
	LOD (%w/w)	1.8-2.0	2.5-2.8
Lubrication (PLM)	Uniformity of mixing (10 min)	98.98%	98.70%
	% Fine	69.80	35.80
	LBD(gm/ml)	0.5791	0.6672
	TBD(gm/ml)	0.6172	0.7097
	CI (%)	6.1730	6.000
	LOD (%w/w)	2.0	2.5-2.8
Compression	Speed of machine	15 RPM	15 RPM
(27station Single rotary machine)	Weight Variation (%)	± 4	± 2.8
	Thickness (mm)	3.55-3.78	3.56-3.77
	Friability (% w/w)	1.6232	O.7071
	Disintegration time	6.0	7.0
	Hardness (Kg/cm^2)	2.4-3.2	3.8-5.0
	Assay (%)	99.60 %	101.39%
	Dissolution (%)	91.92%	90.15%

PDB=process development batch, LOD=Loss on drying ,CI=compressibility index, LBD=loss bulk density,TBD= tap bulk density.

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