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Research

Design of experiment for fluphenazine hydrochloride 2.5 mg table using extra granular material - magnesium stearate with novel technology

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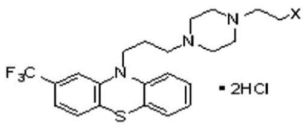
Abstract

The scope of this study is to Design of experiment (DOE) for Fluphenazine Hydrochloride 2.5 mg mg table using extra granular material- Magnesium Stearate with novel technology, Fluphenazine HCl is poorly soluble in water and other common vehicles used for the parenteral adm inistration of drugs. Certain organic solvents may at least partially dissolve fluphenazine HCl. However, when a water-miscible organic solvent containing fluphenazine HCl at near its saturation solubility is diluted with aqueous infusion fluid, the drug tends to precipitate or adsorb to internal surfaces of the infusion set. Oral dosage is easy for intake and unit dose form.

Keywords: Fluphenazine, Mg stearate, Organic solvents, Schizophrenia.

INTRODUCTION

Drug Profile: *Fluphenazine is an antipsychotic medication used to treat schizophrenia and psychotic symptoms such as hallucinations, delusions, and hostility.*



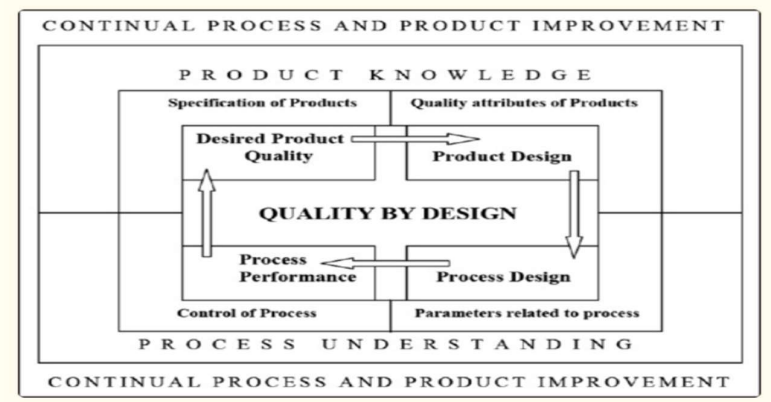
Fluphenazine, X= CH_2-CH_2-OH

Trifluperazine, X=CH_3

Molecular formula: C22 H26 F3 N3 O S, Melting Point: 268-274° C : 271 ° C

Fuphenazine Hydrochloride: is the hydrochloride salt of fluphenazine, a phenothiazine with antipsychotic activity and potential antineoplastic activity. Fluphenazine blocks postsynaptic dopamine D2 receptors in the limbic system, cortical system and basal ganglia, resulting in a reduction of schizophrenia-associated hallucinations and delusions. In addition, as a serotonin antagonist, this agent may inhibit lymphocyte and myeloma cell proliferation by blocking 5-hydroxytrptamine type 1B (5-HT type 1B) receptors for serotonin.

Product development: QbD principles, when implemented, lead to a successful product development, subsequent prompt regulatory approval, reduce exhaustive validation burden, and significantly reduce post-approval changes. The key elements of QbD viz., target product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement are discussed to understand the performance of dosage forms within design space.



Selection of Manufacturing Process: Commonly used methods for manufacturing of tablet dosage forms are:

Wet Granulation: This method commonly used if dose of drug is high along with poor flow property. This method also provides more uniform mixing so as to prevent blend uniformity related issues.
Dry Granulation: This method is used when the API used is heat and moisture sensitive. This method Improve tablet disintegration since it does not involve the use of water so it increases water-uptake ability of the disintegrant.

Direct Compression: This method involves fewest processing steps as compare to other
Process. It is also useful for moisture and heat sensitive APIs. API is having poor flow properties hence wet granulation method was selected for further development.
Quality target product profile for test product was decided based on Reference product information, Literature and requirement of dosage form.

Design of the Drug product is: Components of Drug Product, Manufacturing Process Development, Compatibility

Selection of excipients: Identical excipient types to the reference product were selected for our product development. The selection of excipient grade was based on previous formulation experience, regulatory requirement and knowledge about the excipients that have been used successfully in approved product manufactured by wet granulation method.

Microcrystalline Cellulose Ph.Eur : Microcrystalline cellulose is a purified, partially depolymerized Cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet. Microcrystalline grade (Flocel 102) was selected based on the acceptable flow properties. Microcrystalline cellulose (Flocel 102) complying as per Ph.Eur from supplier Gujarat micro wax was used in the formulation

Sodium Croscarmellose : Sodium croscarmellose is an internally cross-linked sodium carboxymethylcellulose for use as a superdisintegrant in pharmaceutical formulations.

Pre-gelatinized starch Ph.Eur: Partially Pre-gelatinized starch is a modified starch used in oral solids formulations as binder, diluent and disintegrant. The selected grade provides binding properties when used in

combination with Povidone. Pregelatinized starch (Unigel-270) complying as per Ph.Eur from supplier Universal starch was used in the formulation.

Magnesium Stearate : Magnesium stearate is capable of forming films on other tablet excipients during prolonged mixing, leading to a prolonged drug liberation time, a decrease in hardness, and an increase in disintegration time.

MATERIALS AND METHODS

Material Manufacturer		
Material	**category**	**Manufacturer**
Fluphenazine HCl USP	API	Aspen
Microcrystalline cellulose EP	Diluents	Roquette
Croscarmellose sodium EP	Disintegrate	DFE Pharma'
Pregelatinized starch USP	Binder	Colorcon
Magnesium Sterate USP	Lubricant	DFE Pharma'
Purified water	Solvent	Inhouse

Equipments

Equipment	Equipment Number	Make and Model
Vibrator sifter	PRO-0028	Russell Finex
Rapid Mixer Granulator	PRO-0017	Tapasya
Multi-mill	PRO-0027	Shiv Shakti Multi Mill Machine
FBP	PRO-0032	Fab india
Blender	PRO-0019	Pharma fab
Compression Machine	PRO-0023	Killan
Metal Detector	PRO-00189	METTLER TOLEDO
DE duster	PRO-0123	Prim pharma
Stirrer	PRO-0121	JKM Engineers
Coating Machine	PRO-0016	Neocota
Balance	PRO-0019	Mettler Toledo
Hardness tester	PRO-0028	Erweka Tester
Friability Tester.	PRO-0237	Pharmaceuticalsky
DT apparatus	PRO-0118	Effem Technologies
Moisture Analyser	PRO-0035	METTLER TOLEDO

Manufacturing formula: During process development, the manufacturing steps and critical process parameters: The method of manufacture is a wet granulation followed by drying, milling, lubrication, compression.

Material	**Function**	**Manufacturer**	**%per dosage form**	**Mg per solid dosage form**	
Sifting material					
Fluphenazine HCl USP	API	Aspen	2.5	10	10
Microcrystalline cellulose EP	Diluents	Roquette	57.25	223	223
Croscarmellose sodium EP	Disintegrate	DFE Pharma'	3.00	24	24
Pregelatinized starch USP	Binder	Colorcon	36.50	140	140
Dry mixing				397	
Purified water	Diluent		Quantity Sufficient		
Extra granular material					
Magnesium Sterate USP	Lubricant	DFE Pharma'	0.75	3.00	3.00
				400	400
Quantity of microcrystalline cellulose to be adjusted to get a constancy weight based on assay on dried basis as % w/w LOD of Fluphenazine HCl USP					

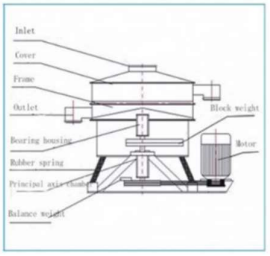
Tablets 400 mg evaluated for final manufacturing involves the following steps:

Dispensing: Dispensing the right materials to the right batches prior to the manufacturing process is a key activity in life sciences and other process industries.

Sifting: Sieving & filtering is the process to eliminate impurities or grade the material. Pharmaceutical industries are the most hygienic among others. All the machines used in pharma industries are made with high-quality stainless steel, food grade rubber items and requires clean environment.

Dry mixing: Mixing is an important part of pharmaceutical production. Operations can include dissolving solids and powders, preparing emulsions, combining raw materials, enabling chemical reactions, and milling active pharmaceutical ingredients (APIs)
Granulation is a process of producing granules generally. In pharmaceutical manufacturing, granulation process implies the techniques that are, used to combine powdered particles to form relatively bigger ones called granules.

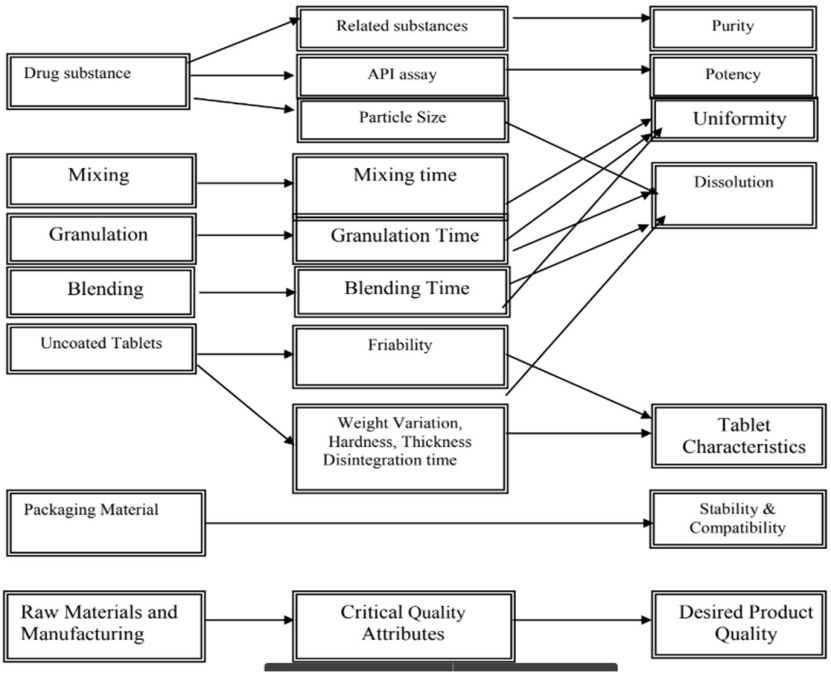
Mesh Used for sifter



Dry Mixing
Granulation: Drying was done in Fluidized bed dryer at 600C to obtain a LOD 1– 3%.
Fluid bed drier (FBD), Lubrication, Compression: Compress the lubricated granules in compression area using 51 station double rotary compression machine equipped.

Pictorial diagram of manufacturing flow
Wet Granulation

Diagram 1: Depicts our approach to reach the desired product quality. The selection of raw materials and the design of the manufacturing process determine the properties of the drug product need to reach the desired quality.



Dry Mixing	E23011	E23012
Purified water	70	80
Impeller speed	50	50
Amperage	5	7
Kneading time	5	5

Chooper speed during Kneading	slow	slow
Amperage	2	3
Discharge wet mass 15 micron	15 mm	15 mm
LOD	6%w/w	7 % w/w

Drying: Dry the wet mass at an inlet temperature 60 in FBD and dries till LOD gets 3- 7 % w/w used moisture balance for the water content. Water content shall be per for:

Drying	**E23011**	**E23012**
Inlet temperature	55-63	49-52
Bed temperature	29-43	30-34
Outlet temperature	25-31	29-32
Air flow CFM	351-420	374-900
Total drying time	180 minute	220 minute
% LOD- Oven gets 3- 7 % w/w	5.29 % w/w	6.23 %w/w
% LOD- moisture analyser gets 3- 7 % w/w	6.01 % w/w	4.89% w/w

Siting and Milling: Sift the dried granules through mesh #20 micron and mill the retention using Co mill at 1000-2500RPM in forward direction. All retention shall be sifted with 60 micron mesh. If required repeat the procedure.

Sifting	**E23011**	**E23012**
Mesh	#20 micron	#20 micron
Co-mill RPM	1850	2200
Screen	#60 micron	#60 micron

Sifting of the Extra granulator material: Sift magnesium stearate though mesh # 80 and collect in the clean container.

Sifting extra Granulator	**E23011**	**E23012**
Mesh	#80 micron	#80 micron

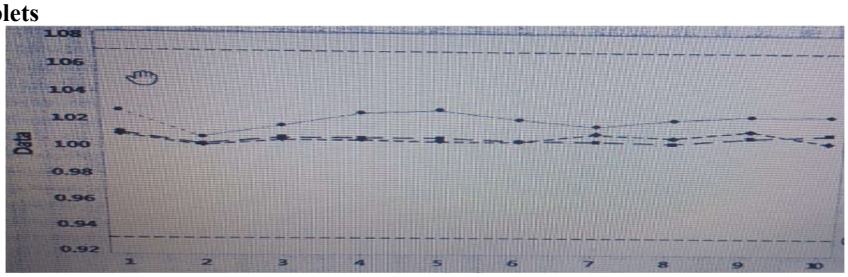
Pre lubrication and Lubrication: Load the sifted milled granule in the blender for 20 minute at 15 RPM and add the extra granulator material Magnesium Stearate USP in to blender and blend for the 10 minute.

Lubrication	**E23011**	**E23012**
Mesh	#80 micron	#80 micron
Blender RPM	15	15
Blending time	20	20
Description	White to off white granule	White to off white granule
Blend Uniformity Results		
1	97.5	99.7
2	100.1	99.1
3	100.3	99.8
4	99.1	99.1
5	101.9	98.1
6	98.2	99.2
7	100.2	99.8
8	99.4	98.7
9	98.0	99.1
10	97.2	99.6
Minimum	97.5	98.1
Maximum	100.2	99.7
Mean	100.1	99.8
% RSD	0.6	0.5

All the results meets the pre determine specification and quality attributed. It is concluded blend can be used for the compression machine with specified punches and dies. Load the blend in to hopper of compression machine. Following critical parameter for the compression:

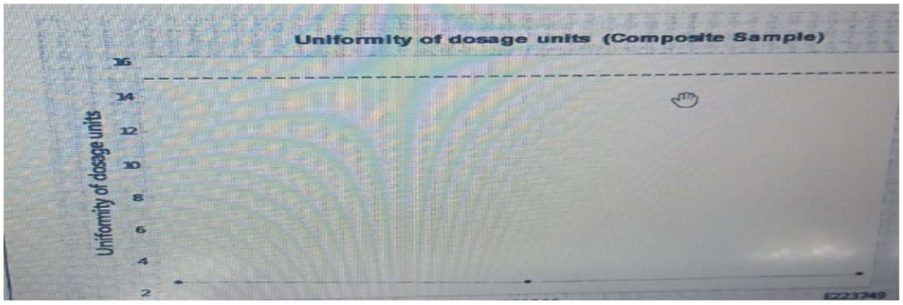
Parameter	Control parameter	E23011	E23012
Description	Round tablet with white to off white colour with break line	Round tablet with white to off white colour with break line	Round tablet with white to off white colour with break line
Weight of 10 tablets	1.90 to 2.10	1.95	2.09
Hardness	12Kp-15 kP	12	14
Disintegration	NMT15 minutes	8 minute	7 minute
Friability	NMT 1.0%	0.15	0.12
Turret Speed	5-25	22	20
Die fill	3-7	4.50	3.90
Upper penetration force	2-3	2	2
Main compression force	25-35	30.3	34

Weight of 10 tablets



Individual Weight of 10 tablets

Content Uniformity



Rational for the selection of the critical parameters

1. Sieving: Mesh size aperture present in liner inch. Sieving is essential to devoid of foreign particles present if any
2. Pre lubrication, blend uniformity is important to make ensure that the active ingredients are homogeneously mixed.
3. Final blend: assay water Assay, Bulk density and particle size shall be carried out. To ensure the potency of the blend meets the defined criteria

CONCLUSION

Drug product without primary pack No significant change observed for description, assay and related substances with reference to initial results. Drug product without primary pack under dark control: No significant change observed for description, assay and related substances with reference to initial results. Drug product with Primary pack: No significant change observed for description, assay and related substances with reference to initial results. Photostability results for product (Praziquantel tablets USP 600 mg) with and without primary pack and dark control complies with shelf life specifications and no significant change is observed. Hence, no special storage condition is required for product.

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