BP702T.INDUSTRIAL PHARMACYII(Theory)

UNIT-IPILOTPLANTSCALEUPTECHNIQUES

INTRODUCTION:

- ThePilotplantisaHybridDevelopmentfacilityandManufacturingunit,whichintegrates followings;
  - Development,
  - Earlydevelopmentactivities,
  - Clinicalsupplymanufacture,
  - Technologyevaluation,
  - Scaleup and
  - Transfertoproductionsites,
- A ***pilot plant*** can also be defined as the pre-commercial production system which includes new production technology and produces small volumes of new technology-based products (Fig 1).
- ***Scale-up***istheprocess ofincreasingthebatchsizeoraprocedureforapplyingthesame process to different output volumes.
- ThePilotplant studiesmust include;
  - Current GoodManufacturingPractices(cGMP) environment,
  - Highlytrainedandskilledstaffs,
  - Equipment support,
  - Facilityofthrough andcloseexamination oftheformula.
- Thefactors thatmust bedetermine forsuccessful productscale upare;
  - The requirements,
  - Training,
  - Thereportingrelationships,
  - Responsibilityof personnel.
- Thepilotplant,productionandprocesscontrolmustbeevaluated,validatedandfinalized during the scale up.
- Thepilotplantplaysanimportantroleinthetechnologyevaluation,scaleupandtransfer activities of new products.

Pilotplant scale up activities:

- The*majoractivities* takesplaceduringscaleup inearlydevelopmentphaseare;
  - Technicalaspectsofprocessdevelopment,
  - Technical aspectsofscaleup,
  - Organisationresponsibility
  - Determinationofresponsibilityoftechnologytransfer team,
  - Technologytransfer documentation,
  - FDApre-approvalinspectionpreparation.

Majortechnicalaspects:

- Thescale upof pilotplant includes*major technicalaspects*that are;
  - In earlydevelopment,

- Identificationofcriticalcomponents,
- Control ofcriticalcomponents,
- Identificationofformulation variables,
- Control offormulationvariables,

- Simulatingthepilotplantequipmentwithmanufacturingareasequipment.
- Identificationofcritical processparameters.
- Identification of operatingranges forthepilot plantequipment
- Collectionofdata ofProductandprocess.

ObjectivesofPilot plantscaleup:

- Avoidanceof theproblems associatedwith the scale-up.
- Productionandprocess controls guidelinespreparation.
- To identifythecritical features ofthe process
- Preparationand providingof MasterManufacturing Formula formanufacturing.
- Evaluation and Validation forprocess and equipment.
- Examinationof theformula to assessthe batch stability.

***SignificanceofPilotPlant*:**

- Standardizationofformulae.
- Reviewofrangeofrelevantprocessingequipment.
- Optimizationand controlofproductionrate.
- Informationon infrastructureofequipment during thescale up batches.
- Informationof batches physical spacerequiredfor equipment.
- Identificationof critical featurestomaintainqualityofaproduct.
- AppropriaterecordsandreportstosupportGMP.

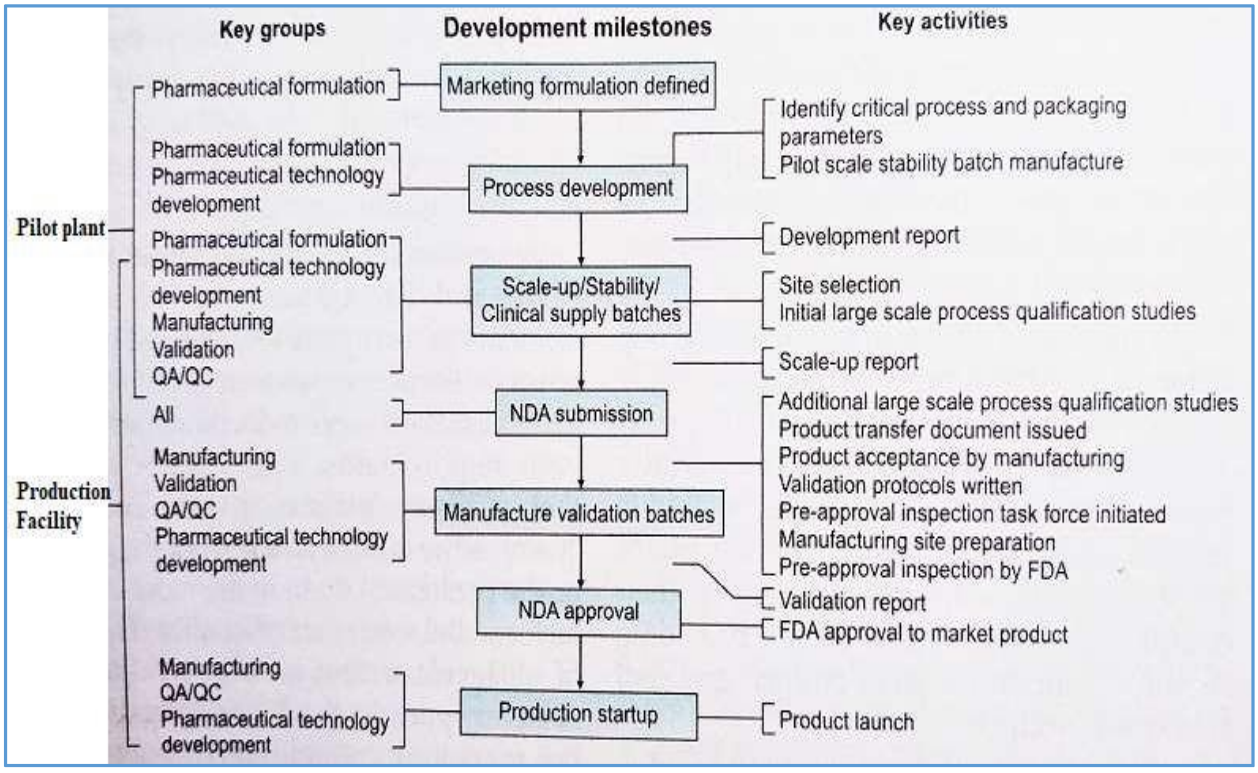

Fig1.Thelayout of the relationship betweendifferentactivitiesduring technologytransfers from the pilot plant to the production facility.

GENERAL CONSIDERATIONS:

Reporting Responsibility:

- The objective of the reporting responsibility in Pilot plant is to facilitate the transfer of a product from the laboratory into production.
- The effectiveness of Pilot plant is determined by the ease with which the new product or process is brought into routine production.
- This could be possible if a good relationship exists between the pilot plant group with other groups (Research & Development, Processing, Packaging, Engineering, Quality Assurance, Quality Control, Regulatory and Packaging) of the company.
- The formulator who developedthe productcan taketheproductinto theproduction.
- Theformulatorcontinuestoprovidethesupporttotheotherdepartmentsevenafterthe transition into the production has been completed.

Personnel requirements:

- TheQualificationrequiredfor apersontowork inpilotplantorganization are;
  - Goodtheoreticalknowledgeonblending
  - Pharmaceuticalindustryexperiences.
  - Abilitytodevelopgood relationships withotherpersonnel.
  - Goodcommunication skill(Writingand speaking).
  - PracticalExperiencesin productionareasabout formulation,processandequipment.
  - Shouldbe ableto understandtheintentof theformulatorandperspective ofproduction personnel.
  - Musthaveminimum knowledgeonEngineering, ElectronicandComputer.
  - MusthaveknowledgeonPhysical,Chemical,BiochemicalandMedicalattributesof dosage form.
  - Mustbeawareon theprincipleofGMPPractices.
- Theindividualresponsibilitiesshouldbeclearlyunderstoodbytheindividuals,whichmustbe recorded.

Space requirements:

The spacerequired in pilot plant isdividedinto4areas thatare asfollows;

- Administrationandinformationarea:
  - Adequateofficeand deskspaceshould be provided forboth scientists and technicians.
  - Thespaceshould beadjacentto the workingarea.
- Physicaltestingarea:
  - This area should provide permanent bench top space for routinely used physical-testingequipment.
- Standardequipmentandfloorspace:
  - Thesufficientspecifiedspacemustbethereforfreeinstallation,operationandeasy maintenance of the equipment.
- Storagearea:
  - Storage area for in process materials, finished bulk products, retained samples, experimental production batches, packaging materials (segregated into approved and unapproved areas).

- Controlled environment space allocated forstorageofstabilitysamples.
- SeparateprovisionsforAPIandexcipientsfurthersegregatedintoapprovedand unapproved areas according to GMP.

Training:

- The various departmentsthat areresponsible for complianceof GMPare;
  - Engineering
  - Quality control
  - Material handling
  - Warehousingand distribution
  - Purchasing.
- Dependingoncomplexityofthejob,eachpersoninvolvedinmanufacturing,Processing, packaging and holding of a drug product, must receive the GMP and other specific training.
- Theemployeethose needtrainingaredividedintothe followingcategories;
  - Newemployees.
  - Thoseemployees whoareassigned witha newjob.
  - Thoseemployee whoseperformance atask falls below requiredstandard.

Theemployeeget trainedonfollowingactivitiesas pertheGMPandFDAguidelinesthat are;

- Technicalenvironment
- Dealingwithpotentordangerouschemicals
- Workingwithsystemofweightsandmeasures
- Checkingofmanufacturingsteps, containers,equipment and dryingracks.
- Identificationof packaging.
- Properstockrotationsystem.
- Rawmaterialinspection.
- Qualityvalidation.

Reviewof theFormula:

- The objective of each ingredient and its contribution to the final product manufactured on small scale equipment must be thoroughly understood.
- Themodificationin formulationduringthescaleupispossibletobedoneinphase IIItrial,so that sufficient time could be available for generation of meaningful long term stabilitydata in support of a proposed New Drug Application (NDA).

Rawmaterials:

- Onemajor responsibilityof aPilot plant is the approval and validation of activeand excipient raw materials used in the Pharmaceutical products.
- This is because the raw materials used during the small scale formulation trials may not be representative of the large volume shipment of material due to change in raw materials propertieslikeparticlesize,shape,morphology,bulkdensity,staticcharges,rateofsolubility, flow property and colour.
- Analternativesuppliermust bearranged asstand bybasis whichmustvalidatethebatches for manufactured products.

RelevantProcessingEquipment:

- The selection criteria for one equipment to produce effective product within the proposed specifications are equipment must be economic, simple (In installation, handling, cleaningand maintenance), efficient and most capable of consistently producing a product.

- Thesizeoftheequipmentshouldbesuchthatexperimentaltrialscanberunthatare meaningful and relevant to the production sized batches.

ProductionRate:

- For determination of production rate, size and type of equipment required, the immediate and future market requirement must be considered.
- Theselectionofprocessandequipmenttoproducebatchesatafrequencyneedfollowing considerations that are;
  - Thetimerequiredtoclean theequipmentbetweenthe batches.
  - Theproduct loss intheequipment duringthemanufacture.
  - The numberof batchesthat needtobetested before release of product.

ProcessEvaluation:

- Thingsthat shouldbecriticallyexaminedduringthe ProcessEvaluation are;
  - Order ofaddition ofthe components includingadjustment of theiramount.
  - Mixingspeedant time.
  - Rateaddition ofgranulatingagent,solvents and drugsolutions.
  - Heatingand coolingrates.
  - Filtersizeforliquids.
  - Typeandnature offiltermediausedfor liquids.
  - Screeningsizeforsolids.
  - Dryingtemperatureand time.
  - Fan speed.
- Thebasisforprocessoptimizationandvalidationistheknowledgeoneffectofabovementioned parameters on the in process and finished product quality.
- Theobjectiveofprocessvalidationtoensuretheselectedprocesscouldbeabletoproduce quality products at various critical stages of production.
- Thisispossiblebycriticallymonitoringthewithinthebatchvariationofmeasurable parameters like content uniformity, moisture content and compressibility.
- Somemeasurablechange in the materials may take place during the processes like milling,mixing, heating, cooling, drying, sterilizing, compacting and filling, should be evaluated.
- Theprocessremainsvalidatedonlyifthereisnochangeintheformula,qualityofthe ingredients and equipment configuration.
- The manufacturing process and quality control information should be reviewed on an annual basis and should be followed by re-validation to ensure that changes have not occurred.

Preparation ofMasterManufacturingProcedure:

TheMaster ManufacturingProcedureincludes followings;

- TheProcessor ManufacturingDirection.
  - Processdirectionshould bepreciseandexplicit.
  - Must bewritteninasimplemannerwhich shouldbe easilyunderstood bythe operator.
- TheChemicalWeightSheet.
  - Identificationofchemical required.
  - Quantities ofchemical to be added.
  - Order ofchemicals to beadded.
  - ThenameandIdentificationnumberoftheingredientmustbementioned.

- The SamplingDirection.

- Time of samplingof finished product.
- Mannerof samplingoffinishedproducts.

➢ TheBatchrecorddirection.
- The batch record directions should include specification for addition rates, mixing times, mixing speeds, heating and cooling rates and temperature.

➢ TheIn-Process Specification.
- Mustmention a simpleand easyaccessspecificationfor easyunderstandingofoperators.

➢ TheFinishedProduct Specification.
- The druginthedosespecified.
- The self-lifeof the product.
- The capabilityof the process.
- Thereliabilityof the testmethods.
- The stabilitykinetics ofthe product.

The periodic revalidation, GMP and monitoring of finished product test results via control charts are essential to maintaining consistent product quality.

GMPConsideration:

➢ ThechecklistoftheGMPitemsthatshouldbeapartofthescale-upornewproductor process introduction including following;
- Equipment qualification.
- ProcessValidation.
- Regulatoryschedulepreventivemaintenance.
- Regularprocess reviewand revalidation.
- Relevantwritingstandardoperatingprocedures.
- The useofcompetent,technicallyqualified personnel.
- Adequate provisionfortrainingofpersonnel.
- Awell-definedtechnologytransfersystem.
- Validatedcleaningprocedures.
- Arrangementofmaterialtoavoidcross contamination.

TransferofAnalyticalMethods to Quality Assurance:

➢ Analyticalmethodsdeveloped inresearchmust betransferredto theQA department.
- Transferprocessincludes thefollowingaspects;
- Review theprocessto make surethatthe properanalyticalinstrument isavailable.
- Personnelshouldbetrained toperform the test.
- Reliabilityofthetestshouldbechecked.
- At lastassayprocedureshould bereviewedbeforetransfer.

PILOTPLANTSCALEUPCONSIDERATIONSFOR SOLIDS:

➢ The followingpointsto becarefullyconsiderduringscalingup thesoliddosageforms;
- Batchsizefrom intermediatetolarge scale production.
- Eachstage of operation.
- Differenttypesofequipment.
- Useof sophisticated instruments with larger volume load.
- Varioussizes ofequipment.

MaterialHandling:

Thehandlingofmaterialsisquitedifferentandnecessarytohandlecarefullyinmediumand large scale production from the laboratory scale (Mostly poured by hand or scooped).

- The characteristics of materials like density, size, shape and static charge must be taken into consideration while adopting the processing steps like;
  - Liftingand tiltingofdrums,
  - Vacuum loadingsystem,
  - Screwfeedingsystems,
  - Meteringpump systems.
- Anymaterialhandlingsystemmustdelivertheaccurateamountoftheingredienttothe destination.
- Thecrosscontaminationmustbepreventedifasystemusestransferofmaterialsformore than one product step.
- Thisisaccomplished byuse ofvalidatedcleaningprocedure forthe equipment.

ChemicalWeighing:

- Theincorrectingredientsandquantitiesmayleadtocrosscontaminationandmisbranded brand during chemical weighing.
- Acentralweighingdepartmentshouldhaveforalltheprocessingareasduetofollowing advantages;
  - Centralizationof responsibility,
  - Avoidanceofduplicating weighing facility,
  - Lowerlabour cost.
- A chemical weighing department should be designed to provide supervision, checkers, lightening, dust collection, adequate sanitation, proper weighing equipment, supply of sink and drain board, cabinets, vacuum supply system, printing scale facility and meters forliquids.
- Forweighingofdyeandhigh potentdrugs, aseparate roommust be equipped.

Tabletblending andGranulation:

Blending andGranulation:

- Powdersto beusedforencapsulationortobegranulatedmustbewell blendedtoensuregood drug distribution.
- Inadequateblendingatthisstagecouldresultindiscreteportionsofthebatchbeingeither high or low in potency to avoid drug content variation.
- Steps should also be taken to ensurethat all theingredients arefreeof.
- The lumps and agglomerates can be removed by doing screening or milling of the ingredients should be done to avoid flow problems, non-reproducible compression and encapsulation process, to facilitate content uniformity of the product.
- In blending, segregation and mixing operation takes place which depends on particle size, shape, hardness and density.

DryBlendingandDirectCompression:

- Different blenders used in blending are V- blender, double cone blender, Ribbon blender, Slantconeblender,Binblender,Orbitingscrewblenders,verticalandhorizontalhighintensity mixers.

- The factors affect the optimization of blending operation of directly compressible materialsare;
- The order ofaddition of components to theblender.
- Themixingspeed–Planetarytypemixer,TumblingMixer,ConeTypeMixer.
- Themixingtime–ItaffectscompressibilityofFinished Material.
- The use ofauxiliary dispersion equipment withthe mixer – Use chopper cell inTwinShellMixer.
- The mixingaction– Determinedbythe Mechanicsofthe Mixer.
- Theblender loads Optimumworkingvolume andnormal workingrange.

Slugging(DryGranulation):

- Thedrypowdercannot becompresseddirectlydueto poor flowandcompressionproperties.
- The sluggingis donebyusingthe TabletPress of15tonnes.
- Aftercompression,slugsarebrokendownbyHammerMillwithsuitableparticlesize distribution.
- Thegranulationbydrycompactioncanalsobeachievedbypassingpowdersbetweentwo roller which put pressure of 10 Tonnes per linear inch.

Wet Granulation:

- Themostcommon reasonsgiventojustifygranulatingare;
  - Toimpart good flow properties to the material,
  - Toincreasetheapparentdensityofthe powders,
  - To change theparticlesize distribution,
  - Uniformdispersionofactive ingredients.
- Traditionally, wet granulation has been carried out using Sigma blade mixer and Heavy-duty planetary mixer.
- Wet granulation can also be prepared using tumble blenders equipped with high-speed chopper blades.
- More recently, the use of multifunctional "processors" that are capable of performing all functions required to prepare a finished granulation, such as dry blending, wet granulation, drying, sizing and lubrication in a continuous process in a single equipment.
- Thefactors that affecting theFluidized BedGranulator are;
  - ProcessInletAirTemperature,
  - Atomization AirPressure,
  - Air Volume,
  - LiquidSprayRate,
  - Nozzle Position andNumberof SprayHeads,
  - Product and Exhaust Air Temperature,
  - FilterPorosity.

Drying:

- Themostcommonconventionalmethodofdryingagranulationcontinuestobethe circulating hot air oven, which is heated by either steam or electricity.
- The important factors to consider as part of scale-up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays.
- Ifthegranulation bed istoo deep or too dense, the drying process willbe inefficient, and ifsoluble dyes are involved, migration of the dye to the surface of the granules.

- Dryingtimesatspecified temperatures andairflowratesmust beestablishedforeachproduct, and for each particular oven load.
- Fluidizedbed dryers areanattractive alternative to thecirculatinghot air ovens.
- The important factors considered as part of scale up fluidized bed dryer are optimum loads, rate of airflow, inlet air temperature and humidity.
- The parameters to be considered for drying process by using Tray Dryer for scale up areAir flow,Airtemperature,Depthofthegranulationonthetrays,Monitoringofthedryingprocess bytheuse of moistureandtemperatureprobes and Dryingtimesatspecifiedtemperatures and air flow rates for each product.
- The Parameters to be considered for the drying process by using a Fluid Bed Dryer for scale upareOptimumload,AirFlowRate,InletAir TemperatureandHumidityoftheincomingair.

ReductionofParticle size:

- Compression factors that may be affected by the particle size distribution are flowability, compressibility, uniformity of tablet weight, content uniformity, tablet hardness, and tablet color uniformity.
- First step in this process is to determine the particle size distribution of granulation using a series of "stacked" sieves of decreasing mesh openings.
- Particle size reduction of the dried granulation of production size batches can be carried outby passing all the material through an oscillating granulator, a hammer mill, a mechanical sieving device, or in some cases, a screening device.
- As part of the scale-up of a milling or sieving operation, the lubricants and glidants, which in the laboratory are usually added directly to the final blend, are usually added to the dried granulation during the sizing operation.
- This is done because some of these additives, especially magnesium stearate, tend to agglomerate when added in large quantities to the granulation in a blender.

Facilities:

- Toavoidcrosscontaminationinscaleupandtofacilitatethecleaningofequipment effectively, following facilities must be available that are;
  - Presenceofseparateroomwithavailabilityofmore space,
  - Musthavegranulation asunit operation,
  - Musthavewashinganddrainage facilities,
  - Must have cold,hotwaterandsteamsupplysystem,
  - Platformshouldbewith stainlesssteelor non-dust materialsystem,
  - Aircondition systemis encouragingbutifabsent,windowmust be screened,
  - Useof a multifunctionalprocessingsystem.

GranulationHandling and FeedSystem:

- The handling of the finished granulation in the compression area is either by Hand scooping for small scale or by sophisticated automated handling system with vacuum or mechanical system for large scale.
- The properties of material like size, size distribution and flow property affects the tablet properties like drug content uniformity, tablet weight, thickness and hardness.
- For efficient cleaning, sophisticated material handling systems like long lengths transfertubes, valves, vacuum and pneumatic pumps should be used.

Tablet Compression:

- Thetabletpressperformsfollowingfunctionsduringthecompressionare;
  - Fillingofanemptydiecavitywithgranulation.
  - Pre-compressionof granulation.
  - Compression ofgranules.
  - Ejectionofthe tablet fromthediecavityand take-offof thecompressed tablet.
- The prolonged trial runs at press speeds is generally adopted to find out the potential compression problems like stickingto the punch surface, tablet hardness, capping, and weight variation detected.
- High-speedtablet compression dependson theabilityof the press to interact withgranulation.
- Duringselectionofhighspeedpress criteria thatshouldbeconsideredare;
  - Granulationfeedrate.
  - Deliverysystem should not change the particle size distribution.
  - Systemshouldnotcausesegregationofcoarseandfineparticles.
  - Itshouldinducestaticcharges.
- The die feed system must be able to fill the die cavities adequately in the short period of time that the die is passing under the feed frame.
- Thesmallerthetablet, the moredifficult itisto get a uniform to fill high press speeds.
- Forhigh-speedmachines,induceddiefeedsystemswithavarietyoffeedpaddlesandvariable speed capabilities, are necessary.
- Compression of the granulation usually occurs as a single event as the heads of the punchespass over the lower and under the upper pressure rollers.
- This causes the punches to penetrate the die to a pre-set depth, compacting the granulation to the thickness of the gap set between the punches.
- The rapidity and dwell time in between this press event occurs is determined by the speed at which the press is rotating and by the size of compression rollers.
- Largerthecompressionsroller,themoregraduallycompression forceisappliedandreleased.
- Slowingdown the press speed orusinglarger compression rollers can often reduce cappingin a formulation.
- Thefinaleventistheejectionof compressedtabletsfromthediecavity.
- During compression, the granulation is compacted to form tablet, bonds within compressible material must be formed which results in sticking.
- High levels of lubricant or over blending can result in a soft tablet, decrease in wettability of the powder and an extension of the dissolution time.
- Bindingtodiewallscanalsobeovercomebydesigningthedietobe0.001to0.005inch wider at the upper portion than at the centre in order to relieve pressure during ejection.

Tablet Coating:

- Many changes in Sugar coating (Carried in conventional coating pans), due to new developments in coating technology (Conventional sugar coating pan changed to perforated pans or fluidized-bed coating columns), changes in safety and environmental regulations.
- The development of new polymeric materials has resulted in a change from aqueous sugar coating to aqueous film coating.
- The tablets must be sufficiently hard to withstand the tumbling to which they are subjected in either the coating pan or the coating column.

- Some tablet core materials arenaturallyhydrophobic, and in these cases, film coating with an aqueous system mayrequirespecial formulation of the tabletcore and/or the coatingsolution.
- A film coating solution may have been found to work well with a particular tablet in a small lab coating pan but may be totally unacceptable on a production scale.
- Tofacilitatetheefficientcoating the tabletshouldnotbedesignedasflatsurfaceorsharpe edges.

Encapsulation ofHardGelatinCapsules:

- The High Speed equipment is used to prepare the capsule by using the processed powder blend with following particle characteristics like particle size distribution, bulk density, compressibility to promote good flow property.
- Thisfacilitatesthe formationofcompactsoftherightsizeandofsufficient cohesivenesstobe filled into capsule shells.
- Fillingofcapsule isdonebytwofilling systems;
  - ZanasiorMartelli formslugs inadosator.
  - Hofliger-KargMachine
- Weight variation in capsules maycome due to poor flow characteristics, improper lubrication and plug sticking to the dosator plunger surface.
- Overlay lubrication may create problems in weight variation, disintegration, dissolution and Bioavailability.
- The characteristics of granulation and the finished products are greatly influenced bythe type and size of equipment used for blending, granulating, drying, sizing and lubrication.
- For better encapsulation, need of controlled environmental conditions that are Controlled humidity(RH 45 to 55 %) system in processing and encapsulation (RH 35 to 65 %) room and appropriate temperature condition of 15 to 25 ℃.

PILOTPLANTSCALE UPCONSIDERATIONS FORLIQUID ORALS:

- ThephysicalformofadrugproductthatcanbeincorporateddemonstratesNewtonianor Pseudoplasticflow behaviour.
- Itconformstoitscontaineratroom temperature.
- Liquiddosage formsmaybe dispersedsystems orsolutions.
- In dispersed systems therearetwo or more phases,where onephase is distributedinanother.
- Asolution refersto twoormoresubstancesmixedhomogeneously.

Stepsof liquidmanufacturingprocess:

- Planningof material requirements.
- Liquidpreparation.
- FillingandPacking.
- Quality assurance.

Criticalaspectsof liquidmanufacturing

- PhysicalPlant.
- Heating,ventilationand aircontrollingsystem.

- The effect of long processing times at suboptimal temperatures should be considered in terms of consequences on the physical or chemical stability of ingredients as well as product.

Solution:

- Theparameters to beconsideredare for scaleup of solutions are;

- Impellerdiameter.
- Tank size (diameter).
- Numberof impellers.
- Impellertype.
- Mixingcapabilityofimpeller.
- Rotationalspeedofthe impeller.
- Heightofthefilledvolumein the tank.
- Numberof baffles.
- Transfer system.
- Clearancebetween ImpellerBladesandwallofthemixing tank.
- Filtrationequipment(shouldremovedesiredmaterialsbutshouldnotremoveactiveor adjuvant ingredients).
- Passivation of Stainless Steel (Pre-reacting the SS with acetic acid or nitric acid solutionto remove. the surface alkalinity of the Stainless Steel).

Suspension:

- Theparameters tobeconsideredarefor scale upof suspension are;
  - Versator (Toavoidairentrapment).
  - Wettingof suspendingagent.
  - Additionand dispersion of suspending agents.
  - Selection oftheequipmentaccordingto batchsize.
  - Timeand temperature requiredforhydration of the suspending agent.
  - Mixingspeeds(High speedshould notbeusedas itleadstoair entrapment).
  - Meshsize(Mustbeabletoremovetheforeignparticulatesandsieveselectedbased on production batch size trials).

Emulsion:

- Theparameters to beconsideredare for scaleup of emulsion are;
  - Homogenizing equipment.
  - Temperature.
  - Mixingequipment.
  - Phase densities.
  - In-processor finalproduct filters.
  - Phase volumes.
  - Screens,pumps and fillingequipment.
  - Phase viscosities.

PILOTPLANTSCALEUPCONSIDERATIONSFOR SEMI SOLIDS:

- The followingparameters areto beconsidered duringthe scaleup ofsemisolid products;
  - Mixingspeed.
  - Mixingequipment(Couldbeabletomovesemisolidmassfromoutsidewallstothe centre and from bottom to top of the kettle).
  - Motors(Drive mixingsystemwithappropriate handlingsystemat itsmost viscous stage).
  - Heatingand coolingprocess.
  - Componenthomogenization.

- Product transfer.
- Addition of activeingredients.
- Workingtemperature range.
- Shearduringhandlingand transferfrom manufacturingtoholdingtank tofillinglines.
- Transfer pumps (Easily must move viscous material without applying excessive shearand free of entrapped air).

➢ Followingparametersmustbeconsiderduringchoosingthe sizeand typeofpump,
  - Pumpingrate.
  - Pumpingpressurerequiredshouldbe considered.
  - Productcompatibilitywiththepumpsurface.
  - Product viscosity.

SUPAC(SCALE UPAND POSTAPPROVALCHANGES)GUIDELINES:

➢ SUPAC represents the changes recommended by the US FDA at the time of scale up or approval of NDA / ANDA.

➢ In the process of developing a new drug product, the batch sizes used in the earliest human studies are small and the size of the batches is gradually increased (Scale-up).

➢ The scale-up process and the changes made after approval in the composition, manufacturing process, manufacturing equipment, and change of site have become known as Scale-Up and Post approval Changes, or SUPAC.

***TheSUPACGuidelinesdefine*;**

➢ Thelevelofchanges–Minor,ModerateandMajorChanges.

➢ Test – Application test,*in vitro* dissolution and*invivo*

➢ Filing– Annual report,changesbeingeffected supplement and Prior Approval Supplement.

➢ Thelevel ofchanges mayimpact onformulation andqualityperformanceinfollowinglevels;
  - Level1: unlikelytohavedetectableImpact.
  - Level2: couldhave significant impact.
  - Level3: likelytohave significant impact.

➢ Theseguidelinesprovide recommendationsforpostapprovalchanges in;
  - The components or compositionchange,
  - Thesite ofmanufacturechange,
  - Thescale-upofmanufacturechange
  - Themanufacturing(process and equipment) change.

A) Thecomponents or compositionchanges:

➢ Thissection focuses on changesinexcipients in thedrug product.

➢ SUPAC-MR - Excipientcriticalor non-critical tothe Modifieddrugrelease.
  - Changesinnon-releaseandreleasecontrollingexcipients.

➢ SUPAC-SS- Changes in preservativein semisolid formulations.

➢ SUPAC-IRChangesforimmediate-releasesolidoraldosageforms.

B) Thesitechangesof manufacture:

➢ Changes in location of the site of manufacture, packaging operations and/or analytical testing laboratory.

➢ Donotincludeanyscale-upchanges,changesinmanufacturing(includingprocessand/or equipment), or changes in components or composition.

- Current GoodManufacturingPractice(CGMP) inspection.

LevelI Changes -

Classification-Single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., Temperature and humidity) and controls, and personnel common. Test Documentation- Application/ compendia requirements in chemistry, dissolution and *in vivo*Bioequivalence - None.

FilingDocumentation- Annualreport.

LevelIIChanges-

Classification–Samecontinuouscampus,Commonpersonnel,Nootherchanges. Test Documentation–

- Application/compendialrequirements
- NotificationofLocationof newsite
- Updatedbatchrecords
- SUPAC – MR - Multi-point dissolution profiles(15,30,45,60 and 120 min)USP buffer media at pH 4.5-7.5 forextended release). Three differentMedia (e.g., Water, 0.1N HCl, andUSP buffer media at pH 4.5 and 6.8for delayed release)until 80% ofDrug Released.

FilingDocumentation- Annualreport.

LevelIIIChanges-

Classification–Differentcampus,Differentpersonnel. Test Documentation–

- Application/compendialrequirements.
- NotificationofLocationofnewsite.
- Updatedbatchrecord.
- SUPAC-IR:Multi-pointdissolutionprofileintheapplication/compendialmedium.
- SUPAC - MR: Multi-point dissolution profiles (15, 30, 45, 60 and 120 min) USP buffermedia at pH 4.5-7.5 for extended release). Three different Media (e.g., Water, 0.1N HCl, and USP buffer media at pH 4.5 and 6.8 for delayed release) until 80 % of Drug Released.

FilingDocumentation- Annualreportpriorapproval of supplement.

C) Changes in BatchSize(Scale-Up/Scale-Down):

- Post-approval changes in the size of a batch from the pivotal/pilot scale bio batch material to larger or smaller production batches call for submission of additional information in the application.
- Scale-downbelow 100,000 dosageunitsis not covered bythisguidance.

LevelI Changes -

Classification-Changeinbatchsize,uptoandincludingafactorof10timesthesizeofthe pilot/biobatch. TestDocumentation–Updatedbatchrecordsapplication/compendialrequirementsstability. Filing Documentation- Annual report (long term stability data).

LevelIIChanges-

Classification-Changesinbatchsizebeyond afactoroftentimesthesizeofthepilotorbiobatch, No other changes.

TestDocumentation–

- Chemistry Documentation Application/ compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

- DissolutionDocumentation-CaseB testing.
- *InVivo*Bioequivalence-None.

FilingDocumentation-Changesbeingeffectedsupplement;annualreport(long-termstability data).

D) ManufacturingChanges:

Manufacturingchangesmayaffectbothequipmentusedinthemanufacturingprocessandthe process itself.

i) Equipment-

LevelI Changes:

Classification- Alternate equipment of the same design and principles as automated equipment.
TestDocumentation–Updatedbatchrecords,Application/compendialrequirementsandstability.
FilingDocumentation-Priorapprovalsupplementwithjustificationforchange;annualreport (long-term stability data).

LevelII Changes:

Classification-Changetoequipmentofdifferentdesignandprinciple.
TestDocumentation–Updatedbatchrecords, Application/compendialrequirements and stability.

- SUPAC–IR - Multi-point dissolution profiles inmultiplemedia.
- SUPAC – MR - Multi-point dissolution profiles in multiple media.

FilingDocumentation-AnnualreportandchangesbeingEffectedSupplement.

ii) Process-

LevelI Changes:

Classification- Alternate equipment of the same design and principles as automated equipment.
TestDocumentation–Updatedbatchrecords,Application/compendialrequirementsandstability. Filing Documentation- Annual report.

LevelII Changes:

Classification- This category includes process changes including changes such as mixing timesand operating speeds outside of application/ validation ranges.
TestDocumentation–Updatedbatchrecords, Application/compendialrequirements and stability.

- SUPAC-IR - Multi-pointdissolution profile.
- SUPAC- MR -Multi-point dissolution profilesinmultiple media.
- SUPAC– SS-*In vitro*releasetest Documentation.

FilingDocumentation-Changesbeingeffectedsupplement;annualreport(longtermstability data).

LevelIII Changes:

Classification- Changes in the type of process used (e.g. wet granulation to direct compression).
TestDocumentation–Updatedbatchrecords,Application/compendialrequirements,stability, bio-study and IVIVC.

- SUPAC-IR - Multi-pointdissolution profile.
- SUPAC- MR -Multi-point dissolution profilesinmultiple media.

FilingDocumentation-Priorapprovalsupplementwithjustification;annualreport(long-term stability data).

INTRODUCTIONTOPLATFORMTECHNOLOGY:

Platformtechnologies:

- Platform technologies are systems that distribute the system out into different levels of abstraction. This is done in orderto differentiate between core –platform– functions, and the application layer that sits on top of, and draws upon, these underlying common services.

PharmaceuticalPlatformtechnologies:

- Pharmaceutical Platform technologiesare considered a valuable tool to improve efficiency and quality in drug product development. The basic idea is that aplatform, in combination with a risk-based approach, is the most systematic method to leverage prior knowledge for a given new molecule.Platform technology is becoming a popular industry approach for bioprocessing.

Importanceplatformtechnology:

- Platformcompanies move faster than their traditional counterparts. When your core products and services frequently change, it forces your employees and your organization to embrace change quickly.

Types ofplatformtechnology:

- Operatingsystems providethebasicservicesrequiredto usehardware.
  - ComputingPlatforms.
  - DatabasePlatforms.
  - StoragePlatforms.
  - Application Platforms.
  - MobilePlatforms.
  - WebPlatforms.

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