Nwoko Valentine E. / Vol 4/ Issue 2/ 2014 / 77-84.

International Journal of

Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

TOOLS, CRITICAL PROCESS PARAMETERS, STRATEGIES TO OPTIMIZE THE SEMI SOLID DOSAGE FORMS MANUFACTURING PROCESS AND PROCESS VALIDATION

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ABSTRACT

The objective of present study was to document the requirements for manufacturing of semisolid dosage forms. These guidelines also brief about some issues associated with tools, strategies, critical process parameters and strategies of the manufacturing and validation processes specific to semisolid dosage forms. Studies about the effect of manufacturing processes and formulation excipients on the rheology of semisolids have contributed significantly toward their characterization. The development of computer-assisted instruments also has contributed substantially to their characterization and thereby to improving their quality. Moreover, some of the guidelines established by regulatory agencies, especially by FDA, are major steps toward the standardization of these dosage forms. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization).

KEY WORDS: Process, Tools, Parameters, Validation.

INTRODUCTION

Semisolids constitute a significant proportion of pharmaceutical dosage forms. They serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining [1]. A semisolid dosage form is advantageous in terms of its easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules. Semisolids are available as a wide range of dosage forms, each having unique characteristics [2]. *Ointments* are semisolid preparations for external application to skin or mucous membranes.

Their composition softens but does not melt upon application to the skin. Therapeutically, ointments function as skin protectives and emollients, but they are used primarily as vehicles for the topical application of drug substances. *Creams* are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base, usually oil in- water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are water-washable and are cosmetically and aesthetically acceptable. *Gels* are semisolid systems that consist of either suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. *Pastes* are semisolid dosage forms that contain one or more drug substances incorporated in a base with large proportions of finely dispersed solids.

A wide range of raw materials is available for the preparation of a semisolid dosage form. Apart from the usual pharmaceutical ingredients such as preservatives, antioxidants, and solubilizers, the basic constituents of a semisolid dosage form are unique to its composition.

The choice of suitable raw materials for a formulation development is made on the basis of the drug delivery requirements and the particular need to impart sufficient emolliency or other quasi-medicinal qualities in the formulation. In general, semisolid dosage forms are complex formulations having complex structural

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elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug, as well as other characteristics, such as viscosity [3].

ADVANCES IN THE FORMULATION OF SEMISOLID DOSAGE FORMS

The formulation of a suitable semisolid dosage form involves the selection of an appropriate drug carrier system, with a special emphasis on the drug's physicochemical properties and required therapeutic application. Drug delivery by means of semisolid dosage forms has seen new challenges in the past few years in terms of altered drug-release profiles as well as the enhanced stability of active pharmaceutical ingredients (APIs).

An ideal topical formulation can be produced using a simple, flexible process. Most topical formulations developed today, however, are complex and, therefore, require tightly controlled processing parameters. Following are five critical process parameters (CPPs) and additional strategies [4].

Critical Manufacturing Parameters, for a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because dispersed matter can distribute differently depending on to which phase a particulate Substance is added. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed.

Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation prior to packaging is critical and should be specifically addressed in process validation studies Five critical process parameters: temperature, rates of heating and cooling, mixing methods and speeds, mixing times, and flow rates. Following are additional strategies to optimize the manufacturing process for topical dosage forms [5].

USE PROCESS-CONTROL TOOLS

Although preserved topical products do not require the strict process controls involved in sterile manufacturing, a well understood and controlled process is crucial. Emulsions, for example, can be difficult to process because they are inherently thermodynamically unstable. The use of manufacturing vessels with programmable logic controllers (PLCs) is one tool that can provide more reliable and accurate control of the pressure/temperature and mixing speed and times [6].

ADD INGREDIENTS IN THE OPTIMAL PHASE AND ORDER

Generally, topical formulations comprise one or more phases. Emulsions, for example, primarily comprise an aqueous phase and a hydrophobic phase. Adding ingredients in the correct phase contributes to overall stability. For example, some polymers, such as microcrystalline cellulose/sodium carboxymethyl cellulose, must be dispersed and hydrated prior to adding other ingredients.

Most ingredients have an optimal method of incorporation into a formulation. Preservatives, such as parabens, should be added just prior to emulsification to reduce time in contact with water-soluble surfactants at elevated temperatures. Polymers (e.g., carbomers) and gums (e.g., Xanthan gum) must be added slowly to avoid formation of fish eyes and other partially hydrated, undispersed material. These problems can be avoided by using eductors (e.g., Tri-Blender and Quadro Ytron dispersers) or by preparing a slurry of polymer or gum in a medium of low or no solubility (e.g., glycerin or glycols for certain gums or oils for carbomers). These thickeners act as emulsion stabilizers to keep oils or creams suspended in water and prevent separation. Such thickeners can be shear sensitive, however, so they must be processed with care.

As an example, DPT Labs was tasked with manufacturing a formulation that was a fatty-acid-based emulsion neutralized using an amine. With the amine in the water phase upon emulsification, the product immediately gained viscosity, requiring a higher mixing speed. As the product cooled, the formulation hit a critical temperature in which it rapidly thinned out and began splashing out of the mixing tank. DPT resequenced the product and added the amine post-emulsification. This change maintained the quality of the product and eliminated negative effects on the formulation and potential danger to staff [7].

PROTECT APIS FROM DEGRADATION

The manufacturing process must be designed to protect APIs from physical degradation. Some APIs, such

as retinoic acid compounds, are sensitive to both UV light and oxygen. These APIs can be protected by using yellow or amber light that is free from harmful low-wavelength UV rays and by using nitrogen, argon, or another inert gas to purge the product of oxygen.

IDENTIFY EQUIPMENT CONSTRAINTS

The manufacturer must be able to perform all processes using its current equipment capabilities. The scale-up path for a 1:10 batch size from the pilot or clinical size to commercial level must exist with similar equipment. Guidance from FDA's Scale-Up and Postapproval Changes Semisolids (SUPAC-SS) Working Group provides the basis of comparison for the design and operating principles of equipment [4].

CONSIDER REGULATORY REQUIREMENTS

Satisfying regulatory requirements for the scale-up or transfer of a process can be challenging. To scale up a process used for clinical batch manufacturing or transfer a commercial process to a new manufacturing site, the equipment must at least be of the same materials of construction and employ the same type of mixing, as defined in the SUPAC-SS guidance [4].

CONSIDER AN OUTSOURCING PARTNER

The manufacturing process can influence a topical product's stability and performance. If a formulation is transferred to a contract manufacturer, changes in mixing speeds, temperature controls, and order of ingredient addition may be needed. Outsourcing formulation development and manufacturing to a contract development and manufacturing organization (CDMO) allows technology transfer, scale-up, and manufacturing to take place at one location, which ensures project continuity [8].

UNDERSTAND CRITICAL PROCESS PARAMETERS TEMPERATURE

Processing at the right temperature is critical for successful manufacturing. Too much heating during processing can result in chemical degradation. Insufficient heat can lead to batch failures, and excess cooling can result in the precipitation of solubilized ingredients. An example of the need for good temperature control is the emulsification step of a traditional oil-in-water emulsion. If the temperature of the water phase is much cooler than that of the oil phase, the melted constituents of the oil phase may solidify upon introduction into the aqueous phase and never properly form the emulsion, possibly even resulting in solid matter in the batch.

HEATING AND COOLING RATES

Heating too slowly can result in poor yields from evaporative loss. Heating too rapidly may burn areas of the batch in contact with the heating surface, which raises the potential for burnt material in the batch. Rapid cooling can result in precipitation/crystallization or increased viscosity. The successful consistency of ointments, for example, depends on proper rates of heating and cooling [9].

MIXING METHODS AND SPEEDS

It is essential to determine the required amount of shear and the optimal mixing methods and speeds. Emulsification typically requires high shear or homogenization to obtain the optimal droplet size and dispersion, while the mixing of a gel may require low shear in order to preserve certain physical characteristics, such as viscosity. Proper mixing speeds must be obtained for each phase at every batch scale. Optimal hydration depends on the amount of shear imparted to initially disperse the polymer into the medium. If the process involves only very low shear mixing, a polymer may never be completely dispersed and hydrated, which may result in an out-of-specification viscosity. Equipment, such as a recirculation loop, may also be used to correct uniformity without changing mixing speed or time, as shown in Figure 1. Mixing of gels require low shear .Obtaining proper mixing speeds for each phase at very batch scale.

MIXING TIMES

Optimizing mixing time requires identifying the minimum time required for ingredients to dissolve and the maximum mixing time before product failure (e.g., when viscosity begins to drop). For polymeric gels, particularly acrylic acid-based types, over-mixing, especially high shear, can break down the polymer's structure. In an emulsion, over-mixing may cause the product to separate prematurely, resulting in a drastic decline in viscosity.

FLOW RATES

Optimizing flow rate involves determining the amount of shear or throughput needed. For example, a water-in-oil emulsion may require a slower addition speed than a traditional, oil-in-water emulsion, and the flow rate must be modified appropriately. Care must be taken for any product using a pump. Overhearing can occur if the formulation is pumped too quickly. If pumping is too slow, the formulation will experience extra time in an in-line homogenizer, thus also exposing the formulation to additional shear [10].

Two processes that require experimentation to optimize flow rates are the use of a powder education system and an in-line homogenizer. Theoretical calculations can determine the number of times a sample will pass through either, but actually performing the experiments is necessary to achieve optimal results.

Raw material dispersers and in-line homogenizers require proper flow rates for optimal usage. If the product is not flowing through a disperser at the proper rate, there will not be enough suction for properly incorporating the powders. Suction can be tested by measuring the vacuum being pulled at the inlet of the disperser with a

vacuum/pressure gauge. Monitoring the flow rate when using an in-line homogenizer is necessary in order to calculate the theoretical number of times the product passes through it.

PROTECTION FROM DEGRADATION

Active Pharmaceutical ingredients have physical degradation pathways .It is important for the manufacturing process must be properly designed to protect from degradation [11].

- Use of Yellow/Amber light
- Use of Argon, Nitrogen or other inert gas to purge the product of Oxygen and protect.
- Retinoic acid compounds are sensitive to both UV light and oxygen

ADDITION OF POLYMERS AND GUMS

Addition of polymers (Carbomers) and gums (Xanthan) must be performed in a very controlled manner if adding directly to batch .Likewise there are other alternate methods of incorporation are: Eductors such as Tri – Blenders and Quadro Ytron dispersers and preparation of slurry of polymers or gum in a medium of low or no solubility [13].

ORDER of ADDITION OPTIMIZATION

Fatty acid based emulsion, neutralised by amine .With the amine in the water phase upon emulsification, the product immediately gains viscosity .As the product is cooled, the formulation hit a critical temperature in which it rapidly thinned out and began mixing out of the tank. The product is re-sequenced to add the amine post – emulsification

PROCESS VALIDATION OF OINTMENT/*CREAM* FORMULATION

Why need of process validation for ointment/cream?

- Product bio burden high?
- Multiple components?
- More adequate preservative system?
- All have Newtonian flow behavior?
- ***History***: Zinc oxide rash cream that was heated to a relatively high temperature solely by the action of rotating mixing plate.

Processes that must be validated in pharmaceutical manufacturing [6] **are:**

- Cleaning
- Sanitization
- Fumigation
- Depyrogenation
- Sterilization
- Sterile filling
- Fermentation
- Bulk production
- Purification
- Filling, capping, sealing
- Lyophilization Process Validation
- Documented evidence, a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specification and quality characteristics.

Process validation

- Why enforce it?
- When is it performed?
- Who performs it?

Why?

- Makes good engineering sense.
- Results in fewer product recalls and troubleshooting assignments in manufacturing operations.
- Results in more technically and economically sound products and their manufacturing processes.

When?

Development stage	**Batch size**
Product design	1X batch size
Product characterization	1X
Formula selection	1X
Process design	1X
Product optimization	10x batch size
Process characterization	10X
Process qualification	10x
Process demonstration	100X batch size
Process validation program	100x
Product / process certification	100x

Who?

- Formulation development
- Process development
- Pharmaceutical manufacturing
- Engineering
- QA
- QC
- API operations
- Regulatory affairs
- **IT operations**

ORDER OF PRIORITY

A. Sterile products and their processes(High Risk)

1) LVP
2) SVP
3) Ophthalmic, other sterile products and medical devices

B. Non- sterile products and their processes (Low Risk)

1) Low dose/high potency tablets and capsules/ TDDS
2) Drugs with stability problems
3) Other tablets and capsules
4) Oral liquids, *topical ointment and cream*
5) Diagnostic aids

Validation Protocol **[6]**

- Written plan describing the process to be validated, including production equipment.
- How validation will be conducted
- Objective test parameter
- Product characteristics
- Predetermine specification
- Factors affecting acceptable result

Protocol for validation of *manufacturing process*

- Purpose and prerequisite for validation
- Presentation of the whole process and sub processes including flow diagram and critical step analysis
- Validation protocol approvals
- Installation and Operation qualification
- Qualification reports including method, procedure, release criteria, calibration of test equipment, test data, summary of result
- Product qualification test data from pre validation batches
- Test data from formal validation batches
- Sampling plan - where, when and how the samples to be taken
- Evaluation of test data, conclusion
- Any need for requalification and revalidation
- Certification and approval
- Summary report of finding with conclusion
- Copies of product stability

Components Included in cGMP Process Validation

All should be validated.

- Facility
- Environment
- People
- Analytical laboratory
- Raw materials
- Equipment
- Procedures
- Process

Process Validation Option

- Prospective Process Validation- performed before the process is put into commercial use
- Retrospective Validation- done for established products whose manufacturing processes are considered stable
- Concurrent validation- in process monitoring of critical processing steps and end product testing of current production

Revalidation

- change in critical component(raw material)
- change or replacement in a critical piece of equipment.
- change in a facility and/or plant
- significant increase or decrease in batch size
- sequential batches that fail to meet product and process specifications

Unit Operation for semisolid System [5]

- *Five* unit operation

1) Mixing of liquid
2) Mixing of solid
3) Mixing of semisolid
4) Dispersing
5) Milling and size reduction of solid and semisolid

Filling and Packaging Operation [4]

- The following critical aspects must be evaluated and controlled during large-scale validation and manufacturing runs

1. Proper control of product temperature to aid product flow and maintain product consistency before and during filling and packaging operations
2. Proper agitation in holding tanks and filling order to main product uniformity and homogeneity during filling and packaging operation
3. The use of air pressure and inert atmosphere to achieve product performance and stability in the primary container.

Product testing

- Validation testing of bulk and finished product must be based on *testing standard release criteria* and *in process testing criteria*
- Routine QC release testing should be performed on a routine sample.
- These samples should be taken separately from the validation samples.

Validation sampling and testing typically is 3 to 6 time the usual QC sampling

Validation Batch: Bulk Sampling

- Take 10 sample from the mixture, tank, or during product transfer to the storage/filling vessel.
- The samples must represent the top, middle and bottom of the vessel
- If sampling from the mixture/tank using an specific equipment, samples should be taken immediately adjacent to blades, baffles, and shafts where product movement during mixing may restricted.

The bottom of the tank and any potential dead spots should be sampled and examined for unmixed material, if possible.

Sampling Plan

Samples must be representative of each filling nozzle.

For single filling size

- Take a minimum of **3** fill containers from each of the beginning, middle and end of the filling run.
- The total number of samples must be not less than 10.
- All samples must be tested.

Multiple filling size

Take minimum 3 samples each at the beginning and end of the filling size

OTHER SAMPLING PATTERN

• Ten equidistant points across the filling run must be sampled.

The beginning and end of filling must be represented.

• Samples should be taken in triplicate.

Monitoring Output [10-12]

1) **Particle size Consideration**

Controls of particle morphology and particle size are important parameters to attain high quality drug product manufacture and control procedure. Particle size distribution for most disperse system should be in the range of 0.2-20 microns.

2) **Viscosity**

The Viscometer- Calibrated to measure the apparent viscosity of the disperse system at equilibrium at a given temperature to establish system reproducibility

Consistency type	Approximate viscosity in cps at 25°C	Pharmaceutical example
Soft, spreadable	100,000-300,000	W/O, O/W CREAM
Plastic flow, spreadable	300,000-1,000,000	Ointment

3) **Content Uniformity**

Most important parameter governing product stability and process control of the disperse system.

In ointment/cream formulation are more dependent on particle size, shear rate, and mixing efficiency in order to attain and maintain uniformity of the active drug component(usually the internal phase).

Monitoring Output	Acceptance Criteria (n = 10)	Sampling Plan
Content Uniformity	UPL & LPL within 90 – 110% LA	3 – 4 units from beginning, middle and end of filling cycle; total = 10 units
	RSD ≤ 4.2%	
● The average result of 10 individual results must meet the release limit for assay. ● The usual sample size for testing ranges between 0.5 and 1.5 g per sample assay.		

4) **Preservative effectiveness**

Incorporating a USP antimicrobial preservative testing procedure or microbial limit test into formal validation of aqueous dispersion.

Determination of bio burden for validation and production batches can also be used to establish appropriate validated cleaning procedure for the facilities and equipment used in manufacture of disperse system.

DESIGN of EXPERIMENTS

DoE is used in determining critical process parameters [12]

Batch	Emulsification RPM	Time of Emulsification	Temperature of Emulsification	High Shear on cool down	Temperature switch on CMM	CMM speed	Initial Viscosity	1 week viscosity
1	High	‘‘x’’ minutes	75 – 80^{0}C	Low	Low	‘‘x’’rpm	110,000	70,000
2	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**Low**	**Medium**	**‘‘x’’rpm**	**100.000**	**80,000**
3	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**Low**	**High**	**‘‘x’’rpm**	**100,000**	**70,000**
4	High	‘‘x’’ minutes	75 – 80^{0}C	Medium	Low	‘‘x’’rpm	120,000	110,000
5	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**Medium**	**Medium**	**‘‘x’’rpm**	**70,000**	**60,0000**
6	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**Medium**	**High**	**‘‘x’’rpm**	**60,000**	**50,000**
7	High	‘‘x’’ minutes	75 – 80^{0}C	High	Low	‘‘x’’rpm	120,000	120,000
8	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**High**	**Medium**	**‘‘x’’rpm**	**100,000**	**70,000**
9	**High**	**‘‘x’’ minutes**	**75 – 80^{0}C**	**High**	**High**	**‘‘x’’rpm**	**90,000**	**70,000**

1. Mixing of Liquids

Equipment: *Kettle and tank fitted with agitator*

Process variables	Properties affected by variables	Monitoring Output
▪ Capacity of unit		
▪ Shape and position of agitation system	▪ Appearance of liquid	▪ Potency
▪ Order of agitation		▪ Appearance
▪ Rate of addition	▪ Viscosity of liquid	▪ pH
▪ Fill volume		▪ Specific gravity
▪ Mixing speed of agitator		▪ Viscosity
▪ Temperature of liquid and time		

2. **Mixing and Blending of Solid**

Equipment: *Blade mixture and tumbler*

Process variable	Property affected by variable	Monitoring output
▪ Capacity of unit		
▪ Mixing speed of unit	▪ Particle size of solids	▪ Potency
▪ Shape of unit and Position of mixing elements within unit	▪ Blend uniformity	▪ Particle size analysis
▪ Product load		▪ Content uniformity
▪ Order of addition of solids to unit mixing time		

3. Mixing and Blending of semisolid

Equipment: *Blade mixture and kinder*

Process variable	Properties affected by variable	Monitoring Output
▪ Type and capacity of unit		▪ Potency
▪ Shape of unit and position of mixing elements within unit	▪ Homogeneity	▪ Content uniformity
▪ Product load	▪ Specific gravity	▪ Viscosity
▪ Temperature		
▪ Agitation speed	▪ Viscosity	▪ Density
▪ Mixing time		

4. Dispersing

Equipment: *Homogenizers, Colloid mill, or ultrasonic device*

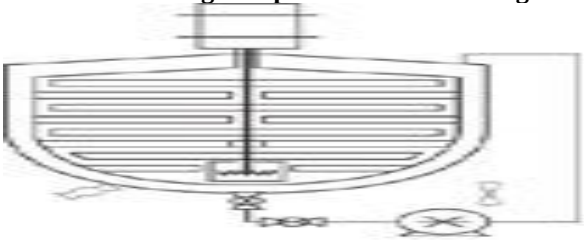
Process variables	Properties affected by variables	Monitoring output
▪ Bore opening/ power setting		▪ Potency
▪ Pressure/rotor speed/power consumption	▪ Particle size of solids	▪ Particle size distribution
▪ Feed rate	▪ Viscosity of liquid	▪ viscosity
▪ Temperature		
▪ Dispersion time		▪ Specific gravity
▪ Order of mixing		

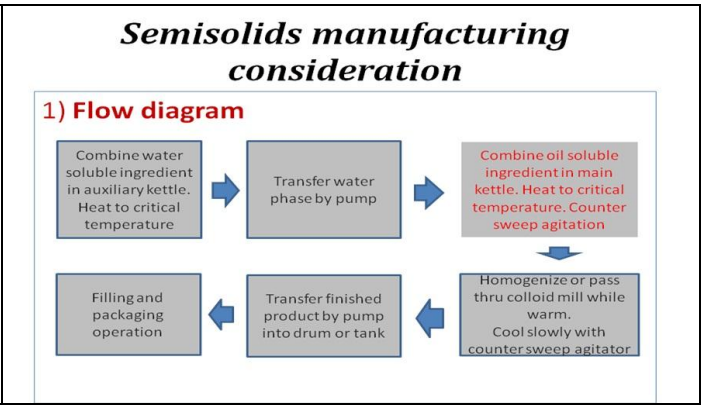
5. Size Reduction of Solid and Semisolid

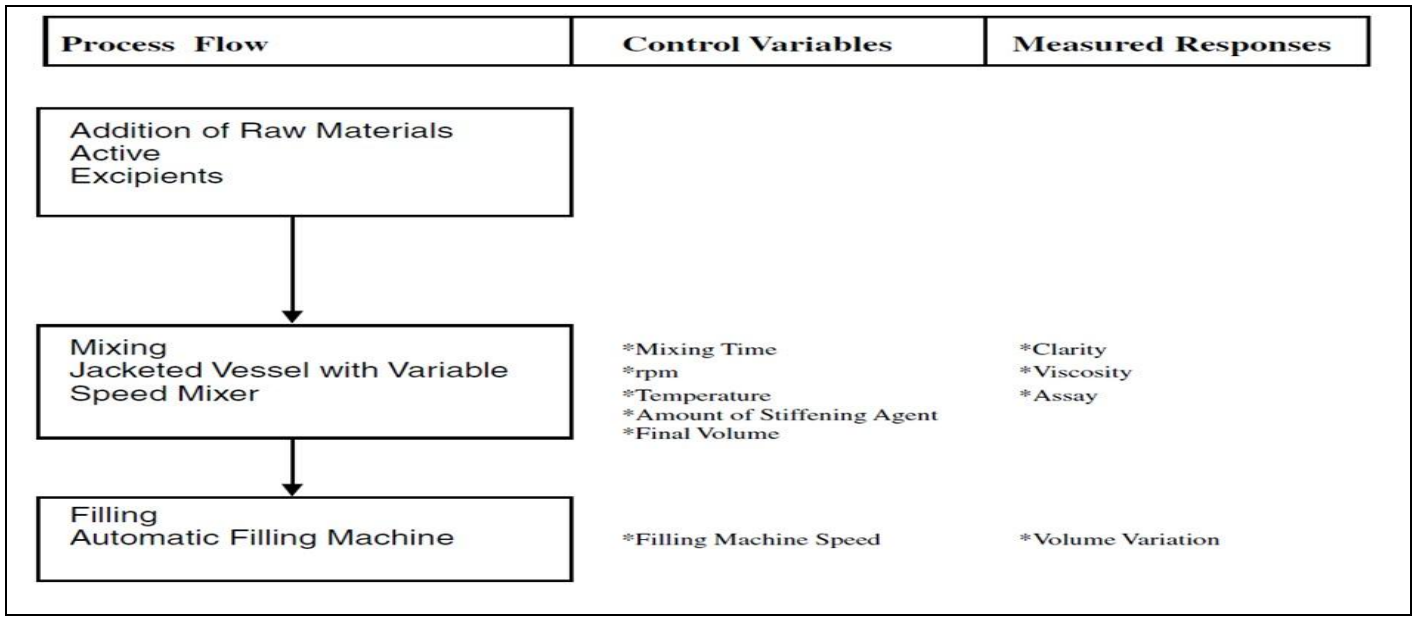
Equipment: *end-runner mill, hammer mill, ball mill, colloid mill, micronizer*

Process variable	Properties affected by variables	Monitoring output
▪ Mill type		▪ Potency
▪ Mill size	▪ Particle size	▪ Particle size analysis
▪ Mill speed/air pressure	▪ Bulk density	▪ Density/surface area
▪ Product load	▪ Dissolution rate of solid	▪ Dissolution rate/ flow rate of solid
▪ Feed rate		
▪ Inert atmosphere		

Fig 1. Diagram of mixer with recirculation loop. When top, middle, and bottom active uniformity samples differed by more than 15%, DPT added a recirculation loop during mixing. The loop produced a far more uniform product without increasing the speed or time of mixing







5) **Dissolution Testing**:

It is primary used as a quality control procedure to determine product uniformity. Secondary as a means of assessing the in vivo absorption of the drug in terms of a possible in vitro/vivo correlation.

For cream/ointments, the Franz in vitro flow through diffusion cell has been modified by using silicon rubber membrane barrier to stimulate percutaneous dissolution unit for testing purpose

Validation Report : Standard Format [4]

1. Executive summary
2. Discussion
3. Conclusions & recommendation
4. List of attachment

- Topic should be presented in the order in which they appear in the protocol.
- Protocol deviation are fully explained & justified.

The report is signed & dated by designated representatives of each unit involved in water system validation[12].

CONCLUSION

There are many different physical forms that can effectively deliver a drug topically .The method of processing which we choose to prepare these drugs formulations are many and must be controlled as tightly as possible. Rigorous experimentation and feasibility batch studies are critical in developing a commercial manufacturing process.

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