INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

SEMI SOLID DOSAGE FORMS MANUFACTURING: TOOLS, CRITICAL PROCESS PARAMETERS, STRATEGIES, OPTIMIZATION AND RECENT ADVANCES

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ARTICLE INFO

Article history
Received 10/11/2017
Available online
06/12/2017

Keywords
Process, Tools,
Parameters,
Validation,
Vertical [TM],
Nano-particles.

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 exipients 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. 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). Semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. Novel semisolids are non-greasy since they are made up of water washable bases. Hence they cause less irritation to skin and are superior to conventional semisolid dosage form. The major conclusion drawn from such detailed study of semisolids in –process shortfalls provides a better vision and encounter while designing and developing new formulations.

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*Please cite this article in press as **Md. Amman Maqbool** et al. Semi Solid Dosage Forms Manufacturing: Tools, Critical Process Parameters, Strategies, Optimization And Recent Advances. Indo American Journal of Pharmaceutical Research.2017:7(11).*

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]. Topical semisolid dosage forms are normally presented in the form of creams, gels, ointments, or pastes. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity increasing agents, anti microbial agents, antioxidants', or stabilizing agents. The objective of this compiled data is to provide a clear and in-depth knowledge of about various tools, strategies, critical process parameters and strategies of the manufacturing and validation processes specific to semisolid dosage forms.

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 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].

Advantage of semi-solid dosage form:

- It is used externally
- Probability of side effect can be reduce
- Local action
- First pass gut and hepatic metabolism is avoided.
- Patient compliance is increased, the drug termination is problematic cases is facilitated as compared with other routes of drug administration.

Disadvantages of semi-solid dosage form:

- There is no dosage accuracy in this type of dosage form
- The base which is used in the semi-solid dosage form can be easily oxidized.
- If we go out after using semi-solid dosage form problems can occur.

Different type of semi-solid:

Ointment:

Ointments are homogenous, semi-solid preparations intended for external application to the skin or mucous membrane. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purpose and where a degree of occlusion is desired.

Hydrophobic ointments:

Hydrophobic (lipophilic) ointments are usually anhydrous and can absorb only small amounts of water. Typical bases used for their formulation are water-insoluble hydrocarbons such as hard, soft and liquid paraffin, vegetable oil, animal fats, waxes, synthetic glycerides and polyalkyl siloxanes.

Water-emulsifying ointments:

Water-emulsifying ointments can absorb large amounts of water. They typically consist of a hydrophobic fatty base in which a w/o agent, such as wool fat, wool alcohols, sorbitan esters, mono glycerides, or fatty alcohols can be incorporated to render them hydrophilic. They may also be w/o emulsions that allow additional quantities of aqueous solutions to be incorporated. Such ointments are used especially when formulating aqueous liquids or solutions.

Hydrophilic ointments:

Hydrophilic ointment bases are miscible with water. The bases are usually mixture of liquid and solid polyethylene glycols (macrogols) [4].

Creams:

Creams are homogeneous, semi-solid preparations consisting of opaque emulsion systems. Their consistency and rheological properties depend on the type of emulsion, either water-in-oil (w/o) or oil-in –water (o/w), and on the nature of the solids in the internal phase. Creams are intended for the application to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes, especially where an occlusive effect is not necessary.

Gels:

Gels are usually homogeneous, clear, semi-solid preparations consisting of a liquid phase within a three-dimensional polymeric matrix with physical or sometimes chemical cross-linkage by means of suitable gelling agents.

Hydrophobic gels:

Hydrophobic gel (oleogel) bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic gels:

Hydrophilic gels (hydrogel) bases usually consist of water, glycerol, or propylene glycol gelled with suitable agents such as tragacanth, starch, cellulose derivatives, carboxyvinyl polymers, and magnesium aluminium silicates.

Pastes:

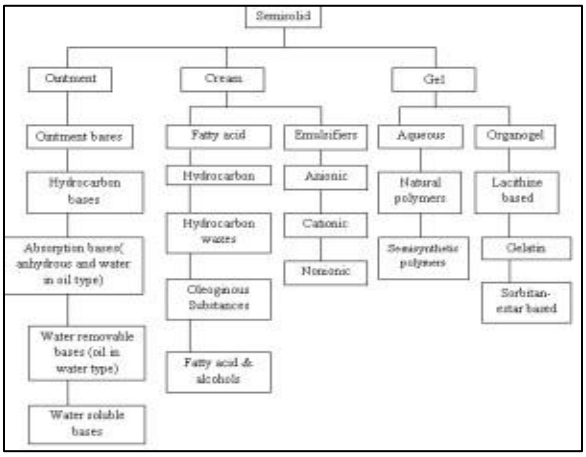
Pastes are homogeneous, semi-solid preparations containing high concentrations of insoluble powdered substances (usually not less than 20%) dispersed in a suitable base. The pastes are usually less greasy, more absorptive, and stiffer in consistency than ointments because of the large quantity of powdered ingredients present. Some pastes consist of a single phase, such as hydrated pectin, and others consist of a thick, rigid material that does not flow at body temperature. The pastes should adhere well to the skin. In many cases they form a protective film that controls the evaporation of water.

Poultices:

A poultice is an ancient form of topical medication also known as a cataplasma. It is a soft mass of vegetable constituents or clay, usually heated before application. Kaolin poultice BP is prepared by mixing and heating dried, heavy kaolin and boric acid with glycerine. After cooling, the aromatic substances are incorporated with stirring. The product is spread on a dressing and applied hot to the skin.

Novel Advances in Semisolid Dosage Forms:

Some basic raw materials required for the development of any kind of semi=solid dosage form is depicted in Fig. 1.



(Fig 1: Basic raw materials used in the development of various semisolid dosage forms)

Ointment:

For topical:

Vectical (TM):

Psoriasis is a chronic skin disorder that affects 2 to 3 percent of the U.S. population. It is characterized by thick, red, scaly patches of skin and caused by an abnormally high growth rate of skin cells that form thick, dry scales (plaques).

Vectical (TM) Ointment is indicated for the topical treatment of mild to moderate plaque psoriasis in patients 18 years and older [5] Vectical (TM) Ointment contains calcitriol, the naturally-occurring, active form of vitamin D3, and is one of the only vitamin D3 products shown in clinical trials to be well-tolerated even when used on sensitive skin fold areas [6].

New treatment for faecal incontinence using zinc-aluminium ointment:

The study shows that the zinc-aluminium based ointment decreases faecal incontinence significantly compared with placebo [7].

A novel wound healing ointment: A formulation of *Hypericum perforatum* oil and sage and regano essential oils based on traditional Turkish knowledge**:** These are used against inflammatory disorders and for healing of skin wounds in traditional Turkish medicine. A new ointment formulation was developed to provide more efficient wound healing activity.

Creams:

Creams containing microspheres:

Microspheres are white powders that under a microscope show every particle to be spherical. In cosmetics, microspheres are used for: enhanced feel, optical blurring, absorption/ delivery of materials. Microspheres can alter the tactile qualities of a cosmetic like initial contact, application, after feel etc.

Lamellar faced creams:

They are liquid paraffin in water emulsion prepared from cetrimide/ fatty alcohol like mixed emulsifiers and ternary system formed by dispersing the mixed emulsifier in require quantity of water. The cationic emulsifying wax showed phenomental swelling in water and this swelling was due to electrostatic repulsion which can be suppressed by addition of salt and can be reduced by changing surfactant counter ion [8].

Cream containing liquid nanoparticles:

For enhanced penetration of topical drugs, occlusion of skin is the prime criterion. This requirement can be achieved easily by the incorporation of large quantities of fats and oils, especially liquid and semisolid paraffin. However, such formulations have the limitations of poor cosmetics properties characterized by a greasy feel and glossy appearance [9].

The development of a water-in-oil cream containing small particles of solid paraffin was studied. A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid paraffin particles with a mean size of 200 nm (nano dispersion). However, this nano dispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were served as a lubricant for nanoparticles, thereby preventing a rough feel during application.

Gel:

The word ‘‘gel’’ is derived from ‘‘gelatin,’’ and both ‘‘gel’’ and ‘‘jelly’’ can be traced back to the Latin gelu for ‘‘frost’’ and gelare, meaning ‘‘freeze’’ or ‘‘congeal”. The USP defines gels (sometimes called jellies) as semisolid systems consisting of either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid. Most topical gels are prepared with organic polymers such as carbomers which impart an aesthetically pleasing, clear sparkling appearance to the product and are easily washed off the skin with water. In a typical polar gel, a natural or synthetic polymer builds a three dimensional matrix throughout a hydrophilic liquid. Typical polymers used include the natural gums Tragacanth, carrageenan, pectin, agar and alginic acid; semi synthetic materials such as methylcellulose, hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose, and carboxy methyl cellulose; and the synthetic polymer, carbopol may be used. Gels are compatible with many substances and may contain penetration enhancers for anti-inflammatory and anti-nauseant medications [10].

Nanosphere gel:

Tyrosine-derived nanospheres have demonstrated potential as effective carriers for the topical delivery of lipophilic molecules. Gel formulation containing nanospheres was developed for effective skin application and enhanced permeation. Carbopol and HPMC hydrophilic gels were evaluated for dispersion of these nanospheres. Sparingly water soluble diclofenac sodium (DS) and lipophilic Nile Red were used as model compounds.

Controlled release gel:

Drug delivery to nasal or ocular mucosa for either local or systemic action faces many obstacles – these routes are protected by effective mechanisms. Gel formulations with suitable rheological and muco adhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact time.

It was possible to control the release of uncharged drug substances by including surfactants that form micelles in the gel. This release depended on lipophilic interactions between the drug and the polymer and/or the micelles. Controlled-release formulations of charged drugs could be designed by mixing the drugs with oppositely charged surfactants in certain ratios. In this way, vesicles in which the drug and surfactant constituted the bilayer formed spontaneously. The vesicle formation was affected by the presence of polymer, and very small vesicles that gave a slow release rate were formed when a lipophilically modified polymer was used. The gels were also evaluated in the Ussing chamber using porcine nasal mucosa. The rate of transport of drugs through the mucosa could be controlled by the rate of release from the formulation. Furthermore, the Ussing chamber could be used to evaluate the potential toxicity of formulations [11, 12].

Amphiphilic gels:

Amphiphilic gels can prepared by mixing the solid gelator like sorbitan monostearate or sorbitan monopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature Amphiphilic gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a 3D network throughout the continuous phase. The gels demonstrated thermoreversibility. Gelation temperature and viscosity increased with increasing gelator concentration, indicating a more robust gel network. At temperatures near the skin surface temperature, the gels softened considerably; this would allow topical application.This study has demonstrated the formation/preparation of stable, thermoreversible, thixotropic surfactant gels (amphiphilogels) with suitable physical properties for topical use.

Hydrophilic gels:

Hydrophilic gels are bicoherent systems composed of the internal phase made of a polymer producing a coherent three-dimensional net-like structure, which fixes the liquid vehicle as the external phase. Intermolecular forces bind the molecules of the solvent to a polymeric net, thus decreasing the mobility of these molecules and producing a structured system with increased viscosity. The physical and chemical bonds binding the particles of the internal phase provide a relatively stable structure, which can originate by swelling of solid polymers, or by decreasing the solubility of the polymer in a solution. An important group of gels used in pharmacy are hydrophilic gels, or hydrogels, usually made of hydrophilic polymers, which under certain conditions and polymer concentration, jellify. Attention of pharmaceutical research now concentrates primarily on hydrophilic gels, as this dosage form seems to be prospective for the development of modern drugs based on systems with prolonged and controlled release of active ingredients.

Non aqueous gels:

Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol dicaprylate/dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three dimensional gel network, with suitable mechanical characteristics for use as a vehicle for topical drug delivery. Molecular conformation of the solvent was found to influence the molecular interactions associated with formation of ethylcellulose gel networks.

Bioadhesive Gels:

Chitosan bioadhesive gel was formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers like saponin, sodium deoxycholate, ethylendiamine tetra-Acetic Acid (EDTA) and lecithin. The gels contained 4000 Iu/dl insulin, 2 or 4% of low and medium molecular weight of chitosan, and lecithin or EDTA. Drug release was studied by a membraneless diffusion method and bio adhesion by a modified tensiometry test.

Mucoadhesive nasal gels:

Venlafaxine Hydrochloride, were prepared using polymers like carbopol 934 and sodium alginate and characterized in terms of viscosity, texture profile analysis, ex vivo drug permeation profiles and histopathological studies. The results show that values of viscosity, hardness and adhesiveness increase while those of cohesiveness decrease with corresponding increase in concentration of the polymers. Ex vivo drug permeation profiles showed that formulation containing 5% sodium alginate provided a better controlled release of the drug than the other formulations over a period of 12 h.Mucoadhesive nasal gel of venlafaxine hydrochloride is a novel dosage form which delivers the drug directly into systemic circulation and provides controlled release of the drug [13].

Thermosensitive sol-gel reversible hydrogel:

They are the aqueous polymeric solutions which undergo reversible sol to gel transformation under the influence of environmental conditions like temperature and pH which results in *in situ* hydrogel formation. Common procedural steps followed for the preparation of Thermosensitive sol-gel reversible hydrogel is given in Fig. 2.

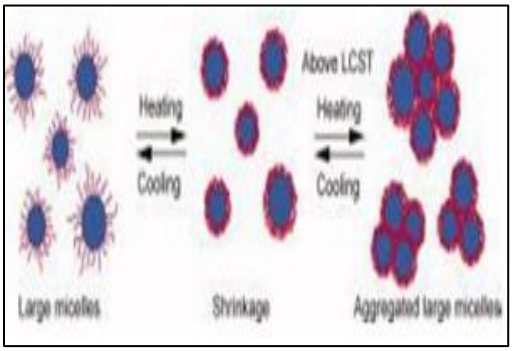


Fig 2: Thermo sensitive sol - gel reversible hydrogel.

Advantages of thermo sensitive sol-gel reversible hydrogels over conventional hydrogels are:

a) It is easy to mix pharmaceutical solution rather than semisolids
b) Biocompatibility with biological systems
c) Convenient to administer
d) The pharmaceutical and biomedical uses of such sol-gel transition include solubilization of low molecular- weight hydrophobic drugs.
e) Release can be in a controlled fashion.
f) Helps to deliver labile bio macromolecule such as proteins and genes.
g) Immobilization of cells
h) And tissue engineering [14].

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 [15].

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 re-sequenced 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 [16].

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 constrains

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 Post approval Changes Semisolids (SUPAC-SS) Working Group provides the basis of comparison for the design and operating principles of equipment [17].

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.

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 [18].

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 as shown in Fig.3. 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. The successful consistency of ointments, for example, depends on proper rates of heating and cooling [19].

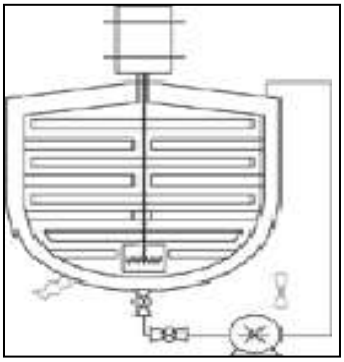


Fig. 3: Diagram of mixer with recirculation loop.

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. 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 [20]. Two processes that require experimentation to optimize flow rates are the use of a powder ejection 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 [21].

- 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.

DESIGN OF EXPERIMENTS

The major process parameters useful for design of experiments is provided in Table 1.

Table 1: DoE is used in determining critical process parameters.

Batch	Emulsification RPM	Time of emulsification	Temp. of emulsification	High shear on cool down	Temp. switch on CMM	CMM speed	Initial viscosity	1 week viscosity
1	High	X minutes	75-80^{o} C	Low	Low	X rpm	110000	70000
2	High	X minutes	75-80^{o} C	Low	Medium	X rpm	100000	80000
3	High	X minutes	75-80^{o} C	Low	High	X rpm	100000	70000
4	High	X minutes	75-80^{o} C	Medium	Low	X rpm	120000	110000
5	High	X minutes	75-80^{o} C	Medium	Medium	X rpm	70000	60000
6	High	X minutes	75-80^{o} C	Medium	High	X rpm	60000	50000
7	High	X minutes	75-80^{o} C	High	Low	X rpm	120000	120000
8	High	X minutes	75-80^{o} C	High	Medium	X rpm	100000	70000
9	High	X minutes	75-80^{o} C	High	High	X rpm	90000	70000

Process validation:

Documented evidence, a high degree of assurance that a specific process will consistently produce a product that meets its pre-determined specification and quality characteristics.

Table 2: Development stage and batch size.

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 validation	100X

Processes that must be validated in pharmaceutical manufacturing are

- Cleaning
- Sanitization
- Fumigation
- Depyrogenation
- Sterilization
- Sterile filling
- Fermentation
- Bulk production
- Purification
- Filling, capping, sealing
- Lyophilization

Validation protocol

- 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

Unit operation for semisolid system [22]

Five unit operation

- Mixing of liquid
- Mixing of solid
- Mixing of semisolid
- Dispersing
- Milling and size reduction of solid and semisolid

Mixing of liquids

Equipment: Kettle and tank fitted with agitator

Mixing and blending of solid

Equipment: Blade mixture and tumbler

Mixing and blending of semisolid
Equipment: Blade mixture and kinder

Dispersing
Equipment: Homogenizers, Colloid mill, or ultrasonic device

Size reduction of solid and semisolid
Equipment: end-runner mill, hammer mill, ball mill, colloid mill, micronizer

Filling and packaging operation
The following critical aspects must be evaluated and controlled during large-scale validation and manufacturing runs
- Proper control of product temperature to aid product flow and maintain product
- Consistency before and during filling and packaging operations
- Proper agitation in holding tanks and filling order to main product uniformity and homogeneity during filling and packaging operation
- 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 ime 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
- **Particle size Consideration**:

Control 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.

- **Viscosity**:

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

- **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).

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.

Dissolution testing

It is primary used as a quality control procedure to determine product uniformity. Secondary for 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

- Executive summary
- Discussion
- Conclusions & recommendation
- 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.

CONCLUSION

Many kind of formulations can be designed by semi solid dosage form and for the same in depth problems occurred in various steps must be controlled. To prepare a successful product batch studies and testing should be done in a broad level. Extensive future research studies should be conducted for more precise and accurate product.

Conflict of Interest:

All authors have no conflict of interest.

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