International Journal of Pharmacy and Herbal Technology

e-ISSN: 2583-8962 Vol. 2, Issue 4 (October – December, 2024) pp: (2868-2885)

Review on: Formulation, Optimization and In-Vitro Evaluation of Conventional Semi-Solid Dosage Form

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Received Date: November 29, 2024; Published Date: 27 December,2024

Abstract

There is conventional semisolid dosage form in that formulation, optimization & in-vitro evaluation study is carried out. The development of effective and stable dosage form is important for the delivery of therapeutic agent to the skin, in that semisolid dosage form are used like Ointment, Cream, Paste, Gel. In a proper substrate, 1 or more active ingredients are equally shared, were they evaluated for their rheological property, spread ability, viscosity and drug release profile. This study highlighted the need of formulation techniques and in vitro assessments in creating semisolid dosage forms to satisfy clinical requirements and enhance patient acceptance of the product.

Keywords - Dermatological preparation, Evaluation, Semisolid preparation, In vitro Cream, Gel, Ointment, Patient Compliance, Drug release, topical drug delivery.

INTRODUCTION

Regarding pharmaceutical, the dosage form of semisolid substances makes up an important fraction. Drugs which are externally applied via skin, rectal organs, nasal cavity, buccal mucosa, vulva, cornea and pinna wall are carried by them. [1] The development of dermatological dosage forms is essential effective control of various kinds of skin disorders. Creams, ointments, and gels are included in semisolid formulations that are preferred due of their greater patient acceptability and targeted distribution. [2] Improving the physicochemical characteristics of semisolid bases, such as viscosity, spread ability, and retention of moisture, has been the focus of recent developments in formulation science. [3] Some of their special benefits are improved penetration into the skin, regulated delivery of active compounds, and increased patient acceptance. [4]

Percutaneous drug absorption

This method allows medication to be delivered directly through the skin layer, often via topical application like cream, gel, ointment, in this dermatological therapy with drugs, semisolid dose forms typically result in the targeted therapeutic activity at certain areas inside the epidermis. [5] Subcutaneous fatty tissue, epidermis, and dermis of the skin can all be penetrated by drugs, depending on their characteristics and those of their transport base. The viable epidermis or upper dermis is targeted for the majority of dermatological problems, given the fact that some medications are primarily intended to work on the outer skin's layer, hence penetration via the skin as an essential part of medicine treatment. [6]

Penetration Enhancer	Drug Tested
Geraniol, nerolidol	Diclofenac sodium [7]
Propylene glycol	Heparin [8]
Lecithin	Hydrocortisone Acetate, heparin [9]
Cyclodextrin	Hydrocortisone [10]
Oleic acid	Piroxicam [11]
Limonene	Indomethacin [12]
Menthol, Linalool	Propranolol hydrochloride [13]

***Table1*:** *Penetration Enhancers for transdermal drug delivery*

The most important entry sites for drugs into the layer of skin are the follicular area, sweat ducts, as well as the intact layer of corneum in between those elements [14] (see Table.1).

Types of Semisolid dosage forms are

Semisolid Dosage form is:

Cream

Gel

Ointment

Paste

Cream

A cream is a thick, emulsified mixture of organic & aqueous phase used in skincare and pharmaceutical application for its moisturizing and therapeutical property.

They are classified into following two types

O/W cream, here Drops of oil found in water.

W/O cream, here Drops of water found in oil.

These formulations are commonly used in medicine and cosmetics to effectively active substances externally to the skin, Due to their emollient, moisturizing, and therapeutic qualities. [14]

***Figure 1*:** *Preparation of Cream*

Types of Cream

O/W emulsified type	**W/O emulsified type**
Vanishing Cream	Cold Cream

Foundation Cream Emollient Cream
Shaving Cream
Hand Cream
E.g. Cold cream (Calendula herb) it is a skin calming, that herb shows powerful effect on dry & sensitive skin. [15]

Formulation of Cream [16]:

Ingredient	Function	Percentage
Water	Solvent	60-70%
Emollient (e.g. jojoba oil)	Moisturizer	10-20%
Emulsifier (e.g. Glyceryl Stearate)	Stabilize oil and water mixture	3-5%
Thickener (Xanthan Gum)	texture and stability	0.5-2%
Preservative (Phenoxyethanol)	Prevent Microbial Growth	0.5-1%
Fragrance (optional)	scent	0-1%
PH adjuster (citric acid)	PH balance	As needed [17]

***Table 2*:** *Formulation of Cream*

Preparation method of Cream

Equipment Required

Heating Device

Water bath or Hot plate.

Mixing Equipment

Homogenizer or High-Shear mixer.

Thermometer

For temperature Monitoring.

Containers

For mixing and storing the final product.

PH Meter

To measure the pH of the Cream.

Preparations

Preparation of oil phase

Measure ingredients: weight the required quantities of emollients and emulsifiers.
Heat the oil phase: In a heat resistance container, mix the ingredients for the oil phase.
Bring the mixture up to 70–75°C in a water bath until all of the solids have melted and the mixture has reached a homogenous phase. [18]

Preparation of Aqueous phase

Weigh the necessary quantity of distilled water along with any other soluble ingredients (such as glycerin). Heat the aqueous phase (in a different container) to the same temperature as the oil phase (between 70 and 75°C). [19]

Emulsification

After reaching the necessary temperature for both phases, gradually introduce the phase of water into the phase of oil while shaking constantly. To guarantee a stable emulsion, either “high-shear mixer or homogenizer” might be used. Continue stirring constantly for five to ten minutes, or until the emulsion looks stable and homogenous. [20]

Cooling and Stabilization

Once the emulsion cools to a temperature of 40 to 45°C, keep mixing. As a result, separation is avoided and the emulsion is stabilized. (check consistency) Observe the viscosity of the cream while it cools. It should be stable and thick.

Incorporation of Active Ingredient and Preservative

Preservative and any active components that are heat sensitive should be added after the emulsion has cooled. To make sure consistency, gently mix.

Packaging

Transfer into container

While the cream is still warm, carefully transfer it—avoiding solidification—into containers that have been previously sterilized, such as tubes or jars.

Cooling

Before covering the containers to avoid water retention, let the cream set fully at room temp.

Labelling

Include the item's name, the contents, and expiry date on the packaging labels. [21]

Evaluation Method of Cream

Spreadability

"The equipment, consisting of an oak block attached to a spindle at a one end, was used to measure the cream's spreading capacity. [22] Because of the cream's properties and shifting, spread capability was tested using this technique" Other common techniques for evaluating spreadability include:

In-vitro spread ability testing with Franz Diffusion cell

Using Franz diffusion cell, it is useful to test the cream's spreading abilities on a layer of skin. This technique can assess penetration as well as spread ability and allows you to replicate skin application. [23]

Spread ability measure using glass plate method

An application of a specified weight is done on two glass plates that have a fixed amount of cream between them. One measures the length of time the cream spreads under the load. Spread ability is measured by using the following formula:

$$\textbf{Spread ability} = W \times D / T$$

Where, W is a weight applied, D is a distance spread, and T is a time taken [24]

Determination of pH

"Glass electrode, standard electrode, and calibrated Digital pH meter "were fully submerged in the cream to cover the electrode to measure the PH. [25]

Measurement of viscometer

The viscosity of cream is measured at regular intervals, in that the viscometer is used to measure the Viscosity at room temperature that is 45 degrees Celsius. [26]

Microbial Contamination Test

Testing the cream's antimicrobial activity against microbes using specified techniques (e.g. USP procedures) [27]

Stability studies

"In the course of six months, stability tests on the cream formulation were carried out under scenarios: - at 40 ± 1oC that cream examined using an Ultraviolet spectrophotometer as soon as it was prepared (at a zero time) and then once a month for the next six months. [28]"

Homogeneity

When the cream is set in a container then the homogeneity examines the formulation, in the homogeneity test in that they examine the appearance & presence of aggregates. [29]

Gel

A Gel is defined as it is a transparent and non-greasy semisolid preparation whereby aqueous phase is scattered with solid phase. [30] This leads to an object that, although at rest, keeps its shape under the stress. Different procedures, such as the physical or chemical cross-linking of polymers, can result in the formation of gels. [31]

Classification of Gel

Based on Composition

Polymeric Gel

Mostly made up of polymers (that form three-dimensional form).

Natural Gel

Derived from natural source (e.g. Gelatin, pectin).

Synthetic gel

Made from synthetic polymer (e.g. Polyethylene glycol).

Inorganic Gel

Consist of solid inorganic compound in a liquid medium (e.g. Silica). [31]

Based on structure

Hydrogel

Water-based gel that hold large amount of water (e.g. Gelatin, Agar). [32]

Organo gel

Gel that formed with organic solvent instead of water (e.g. Oleo gels).

Aerogels

Gels with very low density and high porosity formed by replacing liquid phase with gas phase (e.g. Silica Aerogels) [33]

Figure 2*: *Gel

Formulation of Gel

Ingredient	Function	Percentage
Water	Solvent	70-90%
Thickener (Carbomer)	Texture and viscosity	0.5-2%
Humectant (Glycerin)	Moisture retention	3-10%
Preservative (Phenoxyethanol)	Prevent microbial growth	0.5-1%
PH Adjuster (triethanolamine)	PH balance	As needed
Fragrance (optional)	Scent	0-1%

Table 3*: *Formulation of Gel

Preparation method of Gel

Equipment Required

Mixing Device

Magnetic Stirrer and High-shear mixer.

Heating Device

Water bath or hot plate.

pH Meter

For checking pH of the gel.

Container

For mixing and storing the final product.

Thermometer

For temperature monitoring. [34]

Preparation

Preparation of Gel Metrix

Determine the necessary quantity of gelling agent by accurately weighing it in accordance with the intended concentration, which is usually between 0.5% and 5% w/w.

Hydration of the Gelling Agent

It is essential to correctly hydrate the material when using gelling agent like carbomer. This can be completed by continuously producing the liquid phase, which is often water, as you sprinkle the gelling ingredient into it. Give it between thirty and sixty minutes to hydrate.

Preparation of liquid phase

Weigh the necessary quantity of filtered water along with any additional ingredients, like humectants. [35]

Heat

In order to dissolve any solids, you might need to heat the liquid phase to between 60 and 70°C if you're employing heat-sensitive gelling agents or other components.

Mixing the Gel

Stir the liquid phase and gradually add the moistened gelling agent. Use a high-shear mixer or magnetic stirrer to ensure complete integration. Once a homogenous gel has been created, keep mixing. It could take anywhere from 10 to 20 minutes, based on the gelling agent being utilized.

Incorporation of Active Ingredient and Preservative

Preservatives and any active medicinal components should be added after the gel has reached a homogeneous texture. For even distribution, gently mix. [36]

Packaging

Transfer to container

Transfer the gel into jars or tubes that have already been sterilized. If the gel remains sufficient liquid to pour readily, this must be done.

Cooling

Before closing the containers, let the gel cool off and solidify fully at room temperature.

Labelling

Include details about the product on the containers, such as the contents and the expiration date. [37]

Evaluation method of Gel

pH Determination

A pH meter that was calibrated and kept at 25 degrees Celsius was used to determine pH, based upon way of the gel is going to be used, there are optimum pH ranges. [38]

Viscosity Determination

To find out the gel's layer and flow characteristics, its consistency is measured using rheometer or viscometer, for the evaluation of gel the Brookfield viscometer. [39]

Spread ability

Through this evaluation, the ease with which the gel covers the skin or surface is evaluated. One simplest technique is to sandwich 2 glass slides with a certain quantity of gel, add a given weight & measure the region that it spreads. [40] The initial and final gel spreading diameter was noted and percentage spread ability measured by using that formula:

Spread ability = D2- D1/D1 x 100

Where,

D1 before load of weight the initial diameter of gel, D2 after load of weight the final weight of gel [41]

Stability Studies

Stability Testing is employed to evaluate a gel's shelf life and formulation purity under several conditions of the environment (light, temperature, humidity). [42]

Ointment

Ointments are preparation that are semisolid & apply externally to mucous membrane to skin. an ointment basis, they often comprise one or more medications that have been dissolved, suspended, or emulsified. They may contain preservatives and an appropriate antimicrobial agent. The ointments are mostly applied to the skin as a moisturize or protective layer. [43]

Figure 3*: *Preparation of Ointment

Different type of Bases of Ointment

Bases of hydrocarbons

Petroleum Jelly.

Bases of absorption

Aloe vera gel.

Bases of H_2O soluble

Glycerine.

Bases of emulsifying agent

Xanthan Gum.

Veggies oil

Sensum oil, almond oil, peanut oil.

Formulation of Ointment [44]

Ingredient	Function	Percentage
Base (Petrolatum)	Provides texture	70-90%
Emollient (soft Paraffin)	Moisturizer	5-15%
Active Ingredient (Hydrocortisone)	Therapeutic action	0.5-2%
Preservative (Phenoxyethanol)	Prevents microbial growth	0.5-1%
Fragrance (optional)	Scent	0.1%

Table 4*: *Formulation of Ointment

Preparation method of Ointment

Equipment Requirement

Mixing Device

Ointment miller or Morter and paste.

Heating Device

Water bath or hot plate.

Container

For mixing and storing the Final produce.

Thermometer

For temperature monitoring.

pH Meter

To check pH of ointment.

Preparation

Selection of base

Choose the ointment base type that best suits the intended application and desired properties (e.g. Hydrophobic, emollient).

Preparation of base

Melt the oleaginous components to a homogenous liquid phase by heating them to between 60 and 70°C if you're using a solid foundation.

Incorporation of Active Ingredient

Weigh the active medicinal components and any other substances precisely.

Mixing

Stir the melting base constantly as you gradually add the active components. Use an ointment mill or mortar and pestle to combine ingredients evenly.

Particle size reduction might be required to improve stability and guarantee even dispersion if the active component is in powder form.

Incorporation of Additional Preservatives

Preservatives and other required additions (fragrance, for example) can be added as needed during mixing.

Cooling and Final Mixing

Stir the blend carefully and let it cool to room temperature once all the ingredients have been thoroughly combined. Determine the appropriate consistency of the ointment. It can be softened out by adding little amounts of an appropriate solvent (like mineral oil) and thoroughly mixing it.

Packaging

Transfer to container

When the ointment remains flexible, grab or put it into previously sterilized bottles or tubes.

Labelling

Identify the product name, components, and expiry date on the containers clearly. [45]

Evaluation method of Ointment

Determination of pH

Measurement of pH of ointment the pH meter is used; after mixing hundred milliliters of sterile water, the ointment solution was ready to use after two hours. Measure the three times pH of solution, & that mean was derived. [46]

Determination of Spread ability

By sandwiching extra sample within two slides that had been pushed to a consistent thickness using a specific weight for a particular period of time, the spread ability is calculated. The spread ability is evaluated the time important to separate the two slides. For the separation of 2 slides it takes short time, [46] it is determined by following formula:

$$\textbf{Spread ability} = W \times L / t$$

Where, W =weight of upper slide, L = length of glass slide, T =separation of slide time takes.

Test of non-irritancy

Ointment applies on a human's skin, and the result was evaluated. [46] A small quantity of product applies on hand during the test, and that results such as redness, erythema, inflammation, etc. Are monitored for 24 hours. As a result, no adverse effect was noticed, and the skin is not irritated. [47]

Consistency

Smooth and no greediness is observed.

Microbial Testing

Determine the level of microbial contaminants and make sure there are no harmful microbes in the ointment. [48]

In Vitro Release Studies

Use diffusion cells to determine the rate at which the ointment's active ingredient is released [49]

Paste

Pastes are a type of semi-solid preparation that is applied topically that function as protective layer on skin. Due to their high-power content, which also make them porous so that perspiration may pass through, the composition has a stiff, thick consistency. Paste is often made by levigating a solid with a percentage of bases to create a paste like substance, then adding the solid straight into a dissolved system. include a significant portion of insoluble solids that have been evenly distributed within an appropriate medium. Pastes are less greasy and more rigid than ointments, which is the main distinction between the two. The active medication is typically dissolved in a separate base to prepare them. [50]

Types of Paste

Emulsion Paste

O/W Emulsion Paste: Suitable for Hydrophilic Drug.

W/O Emulsion Paste: Suitable for Lipophilic Drug. [51]

Powder Paste

Antiseptic Paste: contain antiseptic agent for wound care.

Antifungal Paste: Used to treat fungal infection.

Ointment Paste

Hydrophilic ointment paste: Water-soluble, good for absorbing moisture.
Lipophilic Ointment Paste: oil-Based, useful of occlusive dressings. [52]

Dental Paste

Temporary Filling Paste- Used for temporary dental filling.
Polishing Paste- Used for polishing teeth and dental materials. [53]

***Figure 4*:** *Paste*

Formulation Table of Paste [54]

Ingredient	Function	Quantity
Zinc Oxide	Active ingredient (protective)	20%
White petrolatum	Base (occlusive agent)	30%
Liquid Paraffin	Emollient (moisturizing Agent)	10%
Glycerine	Humectant (hydrating agent)	5%
Purified water	Vehicle	34%
Preservative Paraben)	Antimicrobial agent	1%

Table No. 5: *Formulation of Paste*

Preparation method of Paste

Equipment Required

Mixing Device

Morter and paster.

Heating Device

Water bath or hot plate.

Container

For mixing and storing the final product.

Thermometer

For temperature monitoring.

Sieve

For powder uniformity.

Preparation

Selection of Ingredient

According to the desired pharmaceutical results, identify the active components and choose the right excipients to make the paste.

Preparation of powdered Component

Weight and sieve

Weigh the active substances & the powdered excipients precisely.

Sieve the powders when needed to make sure consistent particle size and get rid of any lumps.

Mixing the Ingredients

Put the active components and the powdered excipient in a clean mortar. For a homogenous blend, thoroughly mix with the pestle.

Incorporation of Additional Ingredient

Preservatives and other ingredients (such as fragrance) should be added as necessary, and the mixture should be evenly distributed over.

Final Mixing

When a paste is excessively thick, it can be thinned out with tiny amount of an appropriate solvent (such as glycerine or water) and well mixed to get the right consistency. Ensure that the paste is lump- and aggregate-free and homogenous.

Packaging

Transfer to container

When the completed paste remains flexible, spoon or pour it into previously sterilized jars or tubes.

Labelling

Indicate the item's name, components, and expiry date on the packing materials clearly.

Evaluation method of Paste

Viscosity Measurement

A Brookfield viscometer is a useful tool for measuring viscosity. After the paste is put in a sample container, the spindle is turned at a predetermined speed. Measured torque needed to rotate the spindle is correlated with viscosity. [55]

Stability Testing

The paste is kept for a particular period of time, usually six months, at high humidity & temp levels. Periodically, characteristics are evaluated, both chemically and physically. [56]

In-Vitro Drug Release

Using Franz diffusion cells, the paste is put in membrane & the release of the medicine into a receptor fluid is measured over time. They evaluate how effectively the drug is released and absorbed through the skin. [56]

Microbial-Testing

Sample of paste are cultivated on selective media to check for microbial contamination. Technique includes total aerobic count and specific pathogenic tests. That ensure the paste is safe for topical application. [57]

Drug Content uniformity

One popular method is High-Performance Liquid Chromatography (HPLC). The concentration of API, in that paste is measured after it has been diluted in an appropriate solvent, filtered, and examined. [58]

The Physiochemical Properties of Cream, Gel, Ointment

Rheological Properties

Gels

Have a viscous characteristic, which make it possible to stretch and then return their original shape when under stress.

Creams

Depending on the ratios of oil to water, they have a creamy, spreadable consistency and varying flow properties.

Ointments

These are viscous and thicker, providing an important resistance to flow. [59]

Composition

Gel

Mainly consisting of an agent that gels dissolved in a solvent, usually water, giving increase in a high-water content.

Creams

Emulsions that combine phases that is oil & water to provide an effective balance of absorption and dehydration.

Ointments

Occlusive and barrier-protective, mainly lipid-based, with minimal water content. [60]

Moisture Content

Gels

High water content; has soothing and cooling properties.

Creams

Lightly moisturizing, with both protecting and hydrating qualities.

Ointments

Low moisture content, occlusive barrier formation; perfect for dry skin types. [61]

Storage and shelf Life

Gels

They contain a lot of H_2o and preservatives, as usually have extended shelf life.

Creams

The number of preservatives and emulsification determine how long a product will last.

Ointments

Can be influenced by external causes, but are more stable due to their low water content. [62]

Advantage of semisolid dosage form

It is used external.

The right dose while using sour medications.

More reliable as a liquid dose format.

First pass metabolism is avoided.

Convenient for unconscious patient. [63]

Disadvantages of semisolid dosage form

May have caused discoloration.

It is difficult to determine the accuracy for the semisolid dose form.

Contamination may result from finger application.

May irritate or trigger allergies in particular people.

A solid dose form is more stable than Physico-chemical.

Large-particle drugs are difficult for the skin to absorb. [63]

Application of semisolid dosage form

Simple to use and effective medication release.

Superior washability in water. [64]

Topical drugs are used to treat skin disorders locally. [65]

Moisture and antibacterial treatment are provided for wounds to promote wound healing. [65]
Applications in Cosmetics: Provides active components for cosmetics and improves skin moisture.

Marketed Preparation for semisolid dosage form

Salicylic acid ointment

Used to encourage exfoliation in the treatment of acne and other skin issues.

Figure 5*: *Salicylic acid ointment

Hydrocortisone Cream

Used to treat skin diseases that cause inflammation and itching.

Figure 6*: *Hydrocortisone Cream

Diclofenac Gel

Used to treat pain due to osteoarthritis topically.

Figure 7*: *Diclofenac Gel

Zinc Oxide Paste

Figure 8*: *Zinc Oxide Paste

FDA Guidelines

The FDA recently established guidelines for semisolid dosage form. These standards include different factors as Equivalency in biological terms, In-vitro evaluation, scaling up & after clearance adjustments, and skin sensation & irritancy studies of general transdermal medicinal material, [65] the primary source of data for developing dosage forms in order to quickly receive their regulatory approval is FDA guidance. [66]

CONCLUSION

Semisolid Formulation largely viewed as suitable for the community**.** In addition to being the greatest visible area of the body, the skin can be very prone to cuts, burns, and other ailments, the topical formulation like creams, gels, and ointments are most preferred for treatment. When semisolid dosage forms are used in medical applications, it is important to understand their release properties, stability, and overall performance through in vitro testing. Formulators can efficiently evaluate how these formulations react under different situations by using techniques including diffusion studies, rheological assessments, and antimicrobial testing. Researchers and formulators can make ensure that their products are safe for patient use as well as effective at releasing active substances by following WHO guidelines. Ultimately, this thorough evaluation strategy helps to create dermatological products of the highest quality that improve therapeutic results and patient care. The Studies highlight the need for a multidisciplinary strategy that involves dermatology, pharmaceuticals, and material science to develop successful semisolid formulations. In order to further increase the effectiveness of dermatological treatments and make sure they satisfy the demands of a variety of patient populations future research should concentrate on investigating novel delivery systems and technologies.

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