Review
Sciences of Pharmacy

Method and Critical Aspect of Semisolid Mixing

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[The author informations are in the declarations section. This article is published by ETFLIN in Sciences of Pharmacy, Volume 1, Issue 1, 2022, Page 18-26. https://doi.org/10.58920/sciphar01010020]

Received: 30 May 2022
Revised: 17 June 2022
Accepted: 22 June 2022
Published: 26 June 2022

Editor: Marline Abdassah Bratadiredja

Keywords: Semisolid mixer, critical aspect of semisolid mixing, semisolid manufacturing.

Abstract: Semisolid preparations are widely used to deliver drugs through the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and outer ear lining. They can prevent the first-pass metabolism, reduce side effects, provide immediate local effects, and increase patient compliance. However, an improper manufacturing process will produce a system with bad characteristics, one of which is the mixing process. Several conditions that need to be considered, such as vacuum, temperature, humidity, pressure, stirring speed, stirring time, shear stress, the volume of the mixture, and type of impeller, can affect the consistency, size, and dispersion of particle size, homogeneity, porosity, reactivity, and other characteristics that affect the quality of the semisolid system. Therefore, this article discusses the critical aspects of semisolid mixing, the types, principles, and specifications of several mixer tools and impellers, and how they affect the characteristics of semisolid systems. This review concludes that each type of semisolid preparation requires an impeller and mixer with the specifications and mixing conditions that suit the needs in maintaining the stability and quality of the semisolid system.

Introduction

Semisolid preparations are intended for systemic or local use that has specific applications that rely on the flow's nature, the dispersion system's shape, and its consistency (1, 2). Semisolid preparations can be in the form of gels, pastes, creams, and ointments. Semisolid preparations can be used as drug carriers delivered through the skin, rectal tissue, cornea, nasal mucosa, buccal tissue, vagina, urethral membrane, and outer ear lining (3, 4). Semisolid preparations are generally used for topical delivery, which can avoid the first-pass metabolism, reduce side effects, provide immediate local effects, and increase patient compliance (5, 6). Some semisolid systems can also control drug release, maintain stability, and improve the drug's pharmacokinetic profile (7-9). These advantages indeed correlate with the quality of the system. One critical factor that can affect the quality and support the formation of semisolid systems is the mixing process (10, 11).

Each type of semisolid preparation has critical parameters in the mixing process. The improper mixing process can damage the system. Several conditions that need to be considered, such as vacuum, temperature, humidity, pressure, stirring speed, stirring time, shear stress, the volume of the mixture, and type of impeller, can affect the consistency, size, and dispersion of particle size, homogeneity, porosity, reactivity, and other characteristics that affect the quality of the semisolid system. Each mixer for semisolid preparations has different principles and condition controls to support the desired specifications of semisolid preparation. Besides, the type of impeller used is strongly influential on the characteristics of semisolid preparations. Using an appropriate impeller, semisolid preparations can reach nano-size and even form a multi-coated system (12-14). However, improper use of impellers can result in the consistency of permanently diluted preparations (15). Therefore, this article discusses the critical aspects of semisolid mixing, types, principles, and specifications of several mixer tools that have been used in semisolid mixing and how they affect the characteristics of semisolid systems.

Methodology

This review employed literature originating from Scopus and PubMed by using the keywords 'mixing method for semisolid', 'semisolid mixer', and 'mixer for semisolid'. The selected literature included research on mixers used in semisolid mixing. We excluded reviews, non-English, and literature in which the use of mixers was not for semisolid preparations. A flowchart of the methodology can be seen in Figure 1.

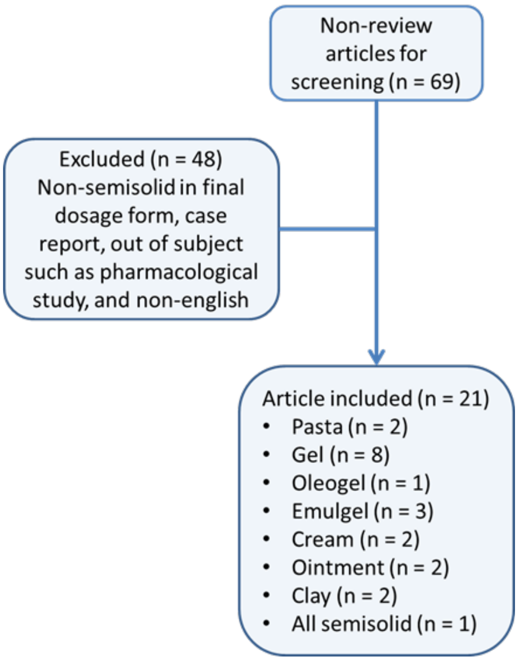

Figure 1. The flowchart of the methodology.

The included articles were then categorized based on their year of publication (see Figure 2). The articles used were published between 2013 and 2020, with the most articles published in 2019.

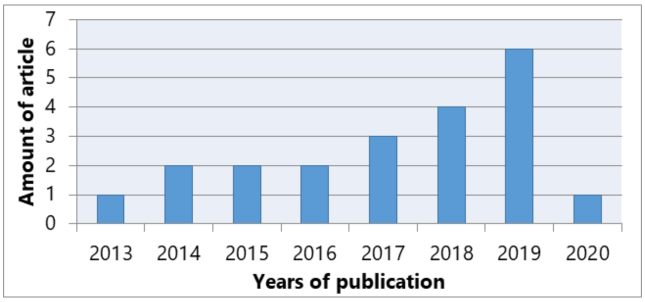

Figure 2. Distribution of articles based on the year of publication.

Critical Aspects of Semisolid Mixing

The method used in mixing semisolid preparations can affect its stability, especially in ointments containing steroid drugs. In a study conducted by Kitagawa et al., it was shown that the viscosity of white petrolatum-based ointments, drug dispersion, white petrolatum components, accumulation in the skin, and permeation of the drugs were influenced by the mixing method used. White petrolatum's structure can be affected by shear stress, so the mixing procedure can change the rheological properties causing the instability of the dispersion and reduce the permeation of the drug from the white petrolatum-based ointment (16).

In addition to the methods used, temperature and humidity are critical in the mixing process and the quality of semisolid preparations. Temperature and humidity can affect the adhesivity and strength of the gel. Relatively higher humidity can reduce water loss from the hydrogel paste due to the presence of hydrophilic groups. The interconnected hydrogel bonding structure can absorb and maintain large amounts of water from relatively high humidity. Therefore, the high-water content will support the diffusion rate of molecules or ions involved in the matrix's chemical interactions (crosslinking). With a higher water content, the rheology is excellent, the glass transition will be lower, and the adhesivity and cohesiveness will increase. In contrast, if the relative temperature is higher, it can eliminate water in the hydrogel, the gel strength will be higher, and the adhesivity will be lower (17).

In cream preparations, the size of the droplet is very influential on the stability of the preparation, where the more significant the size of the dispersed phase droplet will accelerate the phase separation based on specific gravity (18). The size of the droplet is influenced by the stirring process, where the speed, temperature, and duration of stirring are critical factors. The formulation with the smallest globule size showed better drug release and physical stability, while the yield stress impacted the cream's spreadability and adhesivity. The higher the yield stress, the lower the adhesivity of the cream (19).

Stirring in the open air can increase its porosity in semisolid preparations that form a matrix system. This phenomenon can have positive and negative effects depending on the intended use of the semisolid preparation. Applying polymers as fused agents for ligaments, joint or bone fractures in osteoporosis sufferers is certainly not desirable to have a large porosity because they can affect their tensile strength (20).

As explained earlier, each semisolid has critical parameters in the mixing process. The selection of appropriate mixing methods and tools is needed. The following is an explanation of the principles of the mixer for semisolid preparations.

Principal of Semisolid Mixer

Centrifugal Force

The principle of centrifugal force is rotating the sample away from the center of the axis of rotation. The centrifugal force induces hydrostatic pressure in a gradient way in a tube that is oriented perpendicular to the axis of rotation, giving rise to a large buoyancy force that pushes low-density particles inward. The element or particle is denser than the fluid moving outward under the influence of the centrifugal force (21).

High-speed or Supersonic Mixing

Mixing with this method relies on a very high paddle rotation speed. The heat generated can reduce the viscosity of semisolid preparations to speed up the mixing process (22). Materials that can be mixed using this method are only thermally stable. Long stirring time can cause segregation or agglomeration (23).

Melt-mixing

The principle of melt-mixing is the mixing process carried out at the material's melting point. At this point, the viscosity of the material will decrease and facilitate the movement of particles to be homogeneous (20).

Microfluidizing

This method's working principle is that a high-pressure pump forces the product into the interaction space through a reservoir system at speeds up to 400 m/s. Then the product is cooled and collected through an external reservoir system (24, 25).

Radial and Flow Mixing

Radial mixing is the process by which particles or granules of material roll due to plate friction. In contrast, flow mixing is the process of flowing particles or granules of material due to the impulse of a twisted plate pattern. Statically and continuously, this process will produce a homogeneous mixture (26, 27). An illustration of the principle of radial and flow mixing can be seen in Figure 3.

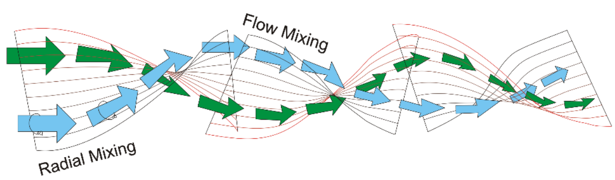

Figure 3. An illustration of the principle of radial and flow mixing.

Shear Mixing

Shear mixing is stirring with a variation of tip rotor speed that can reach 50 m/s, shear rates of up to 100,000 dt^{-1}, highly localized energy dissipation rates near the mixing head, and relatively higher power consumption than conventional mechanical vessels, which are associated with centrifuge force resulted from the relative motion between the rotor and the stator with a narrow distance (ranging from 100 to 3000 µm) (28).

Turbulent Mixing

Turbulent mixing uses a strong force that causes changes in flow velocity. This makes the mixture fragmented, destabilized, and mixed (29, 30).

Mixers Used in Semisolid Preparation

Each mixer has a principle, scale, and specific uses in mixing semisolid preparations (see Table 1).

Coaxial Jet Mixer

This type of mixer can be modified and used for sustainable production and can produce gel-shaped polymeric mixtures with sizes reaching nano. The system can run automatically for 24 hours (34). The momentum coefficient is said to be the most critical factor for jets mixing enhancement (49). Mouthpieces with rectangular and triangular vortex generators of varying sizes inserted in the nozzle varied the mixing intensity. The tabs lowered the formation length of the quasi homogenous mixture by around 10 jet diameters. The triangular tabs outperformed the rectangular ones (50).

Handmixer

Hand mixers can mix semisolid and liquid products on yohurt or food. Only at the lowest speed can 100 grams of preheated hydrocolloid be mixed homogeneously within minutes (44).

High Shear Mixer

Research by M. Balashanmugam et al. showed that speed and stirring time affect the particles' fragmentation (51). This type of mixer can also form emulsions that have non-ideal plastic behavior, form solids at low pressure, and break at high pressure, depending on the stability of the material used against the temperature and mechanical force applied. This rheological behavior is associated with forming three-dimensional tissue from aggregate protein microspheres formed by thermal denaturation of globular proteins in water droplets from oil (W/O emulsion) (12). However, using the appropriate apparatus can produce small-scale emulsions (5 grams) with the same drop size and size distribution as industrial-scale products (38).

High-speed Mixer

For lab scale, this mixer reportedly can be used well in mixing oleogel formed from whey protein airgel (33). Research conducted by M. E. Mohamed et al. shows that the high-speed mixer can produce more clay modifications than magnetic stirrers. However, this mixer produces heat caused by mixing at high speeds, so this mixer is intended only for materials that are stable to thermals (22).

Table 1. Mixers used in semisolid dosage preparation.

No	Mixer	Scale	Principal	Application	Ref(s)
1.	Static mixer	Laboratory - industry	Flow division or radial mixing	Pasta, hidrogel	(20, 31)
2.	High-speed mixer	Laboratory - industry	High-speed mixing	Oleogel and organoclay	(22, 32)
3.	Coaxial Jet Mixer	Industry	Turbulent mixing	Nanogel	(33)
4.	Modified mixer	Industry	Thixomixing	All semisolid	(34)
5.	Vortex mixer	Laboratory	Centrifugal force	Paste, gel	(31, 35)
6.	High shear mixer	Laboratory - industry	High shear mixing	Paste (wet granulation), emulgel, viscous emulsion (mayonnaise), and bitumen.	(36-39)
7.	*Ointment slab* dan ointment spatula	Laboratory	Manual hand mixing	Ointment	(16)
8.	*Vacuum mixer*	Industry	Shear mixing	Hydrogel	(17)
9.	Twin screw extruder	Industry	Melt-mixing and shear mixing	Cream	(19)
10.	Planetary mixer	Industry	Shear mixing	Ointment, gel	(16, 40, 41)
11.	Rotating roller mixer	Laboratory	Radial mixing	Hydrogel	(42)
12.	Stand food mixer	Laboratory - industry	Shear mixing	Emulgel	(43)
13.	Magnetic stirrer	Laboratory	Shear mixing	Gel	(41)
14.	Handmixer	Laboratory	Shear mixing	Gel and cream	(44)
15.	Mortir	Laboratory	Manual hand mixing	Ointment	(40)
16.	Twin roll mixer	Industry	Radial and shear mixing	Gel	(45)
17.	Rotating mixer	Industry	Radial and shear mixing	Gel	(46)
18.	Mechanical stirrer	Laboratory	Shear mixing	Emulgel	(47)

Homomixer or Turboemulsifier

This mixer is not recommended in the manufacture of hydrogels because the very high mixing intensity will cause the preparation to lose its viscosity permanently (15).

Magnetic Stirrer

Magnetic stirrers are often used in the dissolution process, including in making gels. Mixing the components of the gel material using a magnetic stirrer can produce a homogeneous gel at 10 minutes, depending on the mixture's volume (42).

Mechanical Stirrer

The mechanical stirrer is the tool most often used in laboratories to mix materials in liquid or semisolid form. This mixer can homogenize the mixture at a suitable speed. Within a few minutes of stirring, a small-scale semisolid preparation can be obtained (48).

Microfluidizer

The average diameter of a droplet can decrease due to increased pressure. High-shear mixers produce the largest droplets with an average particle diameter of around 16 μm operating at pressures between 1000 and 5000 psi, while microfluidizers operating at pressures from 7500 to 20,000 psi produce droplets emulsions with diameters. Average particles range from 0.6 to 0.4 μm (18).

Mortar

This method can produce homogeneous ointments, but there are limits, especially for large amounts of liquid to be included in the base or preparation of ointments in large quantities (41, 52).

Novel Modified Mixers

Akbarzadeh et al. have made a novel mixer with the principle of thixomixing. This mixer can make a mixture of semisolid carbon fiber in the form of a microstructure. This mixer has two main parts: the rotor and the stationary part with a distance of 2 mm. The rotor was previously heated at temperatures reaching 600 oC to produce good carbon fiber. This type of mixer cannot be used for thermolabile substances. Using conventional sharp impellers can also damage the texture of carbon fiber, so it is recommended to use impellers with blunt surfaces. This mixer is recommended for mixing semisolid-containing metal (35).

Ointment Slab and Ointment Spatula

Mixing and reduction of the insoluble drug are better than the mortar method. The first step is to rub the powder with a little ointment base to form a concentrated ointment base containing a fine homogeneous powder, concentrated ointment, then gradually diluted with the rest of the ointment base rubbed with a spatula. Spatula must be made of long, thick, and flexible stainless steel. Still, the limitation is that some drugs (salicylic acid, iodine acid, mercury salt, etc.) can react with steel, so a rubber or hardwood spatula can be used (52).

Mixing ointments using this method produces homogeneous ointments and does not reduce thixotropic behavior on an ointment base, such as mixing ointments containing white petrolatum and salicylic acid, their viscosity decreases during repetition but does not reduce thixotropic behavior compared to mixing using planetary mixers (16).

Planetary Mixer

The use of planetary mixers must be considered in mixing ointments because they affect viscosity and thixotropic behavior, as in ointments containing white petrolatum and salicylic acid, when mixed with planetary mixers, the viscosity decreases, and thixotropic behavior is almost lost (16).

Gel mixing can be done using a planetary mixer, such as using a type of planetary centrifugal deaeration mixer with a speed of 400 rpm within 10 minutes can produce a homogeneous gel, and mixing efficiency is also higher than using a magnetic stirrer (42).

Rotating Mixer

Research conducted by A. Sivaraman et al. showed that this mixer could produce gels with good flow properties and maintain the gel's viscoelastic properties depending on the type of polymer used (47).

Rotating Roller Mixer

Besides vortex, rotating roller mixers can be used for mixing biological compounds in the form of semisolid liquid. Rotating a roller mixer for 24 hours at room temperature can homogenize the hydrogel (43). A rotating roller mixer is a shaker with a rotating roll, usually homogenizing in a closed state to maintain sample sterility (53).

One of the advantages of this mixing method is that the mixing is carried out in an ointment container (closed system) so that only a small amount of scattering occurs during the mixing process. This tool does not require an impeller, so it does not need to be washed. It can avoid cross-contamination through mixing and exposure during instrument cleaning (especially for antineoplastic drugs). Mixing time is also shorter compared to using a mortar (41).

Rotation Hybrid Mixer

This equipment consists of the leading rotary head mounted on a vertical axis for rotational motion and a second rotor mounted on a bearing on the main head for the rotation of the sample movement, which is centrifuged by pseudo-planetary motion. This motion creates a large enough centrifugal force that removes tiny air bubbles from the material and mixes them at the same time [1]

Stand Food Mixer

Emulgel mixing can be done using a food mixer stand. With a speed of 2800 rpm for 2 minutes, this tool can produce a homogeneous emulsion. To produce an emulgel, it is necessary to warm up the system at a temperature of 90 ° C for 30 minutes (44).

Static Mixer

Static mixers have been reported to reduce the pores of the paste, which will generally form more when using other types of mixers (20). Static mixers can homogeneously mix gel components in the form of biological compounds at a micro-scale. The double syringe delivery systems mix with a 1: 1 mixing ratio with an installed static mixer with eight turns and cone-shaped outlet geometry. The static mixer is usually made from silicon tubes (inner: 2.5; 3; and 4 mm) where the inner guidance cannula (outer: 0.7; 0.8; 1.3; 1.65; 1.9 and 2, 15 mm), with 8 or 12 windings, 2.5 mm in diameter, and 1 mm wall thickness (31).

Twin Roll Mixer

Research conducted by D. Qiao et al. shows that stirring using this mixer can produce gels in nano size (46).

Twin-screw Extruder

In the research of Mendonsa et al. (2019), the making of the cream was carried out by mixing the oil phase into the water phase, which had been melted in a twin-screw extruder (TSE), and the flow rate of the oil phase and the water phase was set at 4.8 mL/min. This mixing method generally consists of dispersive and distributive mixing. Here, the staggering angle and disk width of the mixing element have an impact on the homogeneity of the mixing process, as well as higher dispersive mixing with a higher screw extruder speed will result in a greater extruder shear force (19).

The oil phase must completely melt before the water phase is added so as not to produce a non-homogeneous product due to re-neutralization, which will also affect the texture and rheology of the cream. The mixing temperature can impact adhesivity, yield stress, and prolong the residence time of the mixture in the extruder. Long residence time is caused by low conveying ability, which can cause high torque values. However, during the extrusion process, the torque (shaft) in the barrel can be maintained up to 3-4% (19).

Vacuum Mixer

Mixing hydrogel material using a vacuum mixer with a speed of 80 rpm and a vacuum level of -0.08 MPa for 5 minutes produces a homogeneous hydrogel paste with the strength or cohesiveness of the hydrogel paste increases with the length of mixing time (17). The study reported by Chung, I. G., et al. (2011) showed that the increase in vacuum conditions led to an increase in the porosity of the semisolid slurry (54).

Vortex Mixer

A vortex mixer is usually used for homogenizing biological compounds in semisolids (gels) or liquids with small volumes (31). Vibration causes striations or lamellae that develop in a short period through the dissipation of turbulent energy (55).

Impellers Used in Semisolid Mixer

The impeller is an essential part of the mixer. Impellers can affect the shape and size of the stirred material particles. Some materials, such as fiber, are not suitable for sharp impellers because they can damage the fiber, but sharp types of impellers can be used well to reduce size. Here are some impellers that can be used in the stirring process.

The flow pattern produced by the impeller is divided into three parts, namely radial velocity (pushing fluid towards the vessel wall), axial velocity (flow pattern leads vertically, up or down), and tangential velocity (moving fluid in a circular motion on a horizontal vessel) (56). Here are some impellers that can be used in the stirring semisolid.

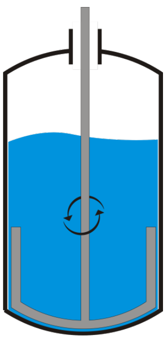

Figure 4. The illustration of the anchor blade.

Anchor Blade

An anchor blade is used on vessels and hemispherical kettles with a bowl-shaped base equipped with jacketed cooking kettles to prevent the mixture from being scorched due to heating. The impeller is mounted on a shaft and operated at a low speed of tens of rpm (56). An illustration of the anchor blade can be seen in Figure 4.

Sigma Z Blade

This blade type is commonly used on planetary mixers and sigma blade mixers. Sigma Z blade is intended to mix, whip, and knead, so the effect is the same as the screw blade (56). An illustration of the sigma blade can be seen in Figure 5.

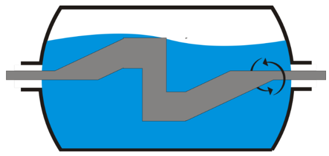

Figure 5. The illustration of the sigma Z blade.

Paddle Blade

The simplest type of impeller is the paddle blade. It consists of one or two pairs of rotating flat blades mounted on a shaft and operated at low to high speed (56). An illustration of the paddle blade can be seen in Figure 6.

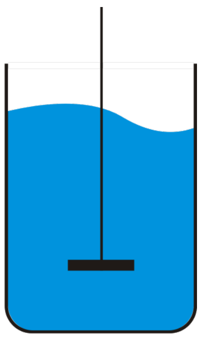

Figure 6. The illustration of the paddle blade.

Screw Blade

For example, a screw blade can be used in semisolid mixing in a TSE. The screw blade rotates in a TSE barrel. Usually, the screw is segmented and assembled on the shaft, and the torque transmitted to the shaft is a limiting factor for the amount of power. TSE design parameters such as the ratio of outer and outer (OD) screw (ID) and screw depth in the channel determine the available free volume and torque (57).

Lower screw speeds are used by Mendonsa et al. (2019) in making creams, which are 50 and 70 rpm. At this speed, the residence time of the mixture in the extruder will increase. With increasing residence time, heat energy input is higher in physical mixtures with low-shear environments; the increased thermal energy results in good product expansion. In contrast, the high screw speed will result in a lower residence time with an increase in the shear rate, reducing the material's viscosity in the extruder. However, it is easier in terms of diffuse power, whereas the amount of torque will decrease after a gradual increase in screw speed due to a decrease in filled length in the extrusion device (19).

Turbine Blade

This impeller consists of four or more flat or curved slats. Usually mounted vertically on the shaft and operated at high speeds up to hundreds of revolutions per minute. Impeller diameter of one-third to half of the vessel diameter, and its application involves the mass transfer or phase disperse. Turbine blades at some level can act as centrifugal pumps. The resulting flow is radial and axial flow. Axial flow in turbines can be increased by pitched blades (56).

Helical Ribbon Impeller

Helical ribbon impellers are equipped with one or more helical ribbons (56). A helical ribbon impeller is effective for mixing high-viscosity liquids (more than 1,000,000 cP) but is rarely applied at low viscosities because of higher costs (58). This impeller is most effective for liquids with high viscosity than turbines, anchors, and paddles. Turbine, anchor, and paddle can produce circumferential and inadequate mixing of high viscosity due to a lack of axial flow to sweep entire vessels (56).

Conclusion

Each type of semisolid preparation has different critical factors and conditioning requirements in the mixing process. The difference in vacuum condition, temperature, humidity, pressure, stirring speed, stirring time, shear stress, the volume of the mixture, and type of impeller can affect the consistency, size and dispersion of particle size, homogeneity, porosity, reactivity, and other characteristics that affect the quality of the semisolid system. So it is crucial to consider the type of mixer that will be used based on the needs of the semisolid preparation.

Declarations

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Acknowledgment

The author expressed his gratitude to Mrs. Prof. Dr. rer. nat. Anis Yohana Chaerunisaa, Apt., as a lecturer in drug stability, has provided material and instruction in writing this review article.

Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

Ethics Statement

Not applicable.

Funding Information

Not applicable.

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How to cite: Sutoro, M., Falya, Y., Damayanti, R.H.. Method and Critical Aspect of Semisolid Mixing. Sciences of Pharmacy. 2022; 1(1):18-26