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Review Article

LIQUISOLID-PELLETS TECHNIQUE: A RECENT TECHNIQUE FOR ENHANCING SOLUBILITY AND BIOAVAILABILITY OF DRUGS

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ABSTRACT

The current article aims with the introduction of newer solubility enhancing technique as Liquisolid-pellet. The majority of newly invented molecules comes under the biopharmaceutical classification system (BCS) Class II, IV indicating poor solubility and thereby poor bioavailability. Liquisolid Compaq is one of the solubility enhancement techniques used for improving solubility and dissolution of the molecule by incorporating non-volatile solvent followed by carrier and coating agents. However, this technique is only applicable to potent molecules as a higher dose resulted in inconvenience to the patient and difficult to swallow. Another drawback of this method is not suitable for pilot plant scale-up. Liquisolid pellet technique overcoming all limitations of Liquisolid Compaq and offers good compaction, flowability, dose accuracy, less gastric irritations, and better bioavailability. In the Liquisolid-Pellet technique, powdered material received from Liquisolid Compaq is further moistened with granulating fluid to provide enough plasticity. The material is subjected to extrusion using an extruder to generate extrudates. The extrudates are placed under the spheronizer to form spherical particles as Pellets. The pellets are mainly prepared by extrusion-spheronization and hence, articles elaborate details of extruders and spheronizers, their specifications as well as factors, which strongly impart processing. These pellets are filled in capsules according to their dose and utilized as an immediate release or sustained release. The literature related to this review was collected from Science Direct, PubMed, Google Scholar, Google, USPTO, etc. from 1998 to 2020 with the following key-words.

Keywords: Solubility enhancement, Liquisolid technique, Liquisolid-Pellet, Pellet, Extrusion-spheronization, Bioavailability

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INTRODUCTION

Most preference allotted to solid orals owing to their convenience, compliance, uniformity, and stability [1]. Several characteristics of the active ingredient and functional excipients like solubility, dissolution rate, presystemic metabolism, etc. have a strong impact on their bioavailability [2]. Most of the newly invented molecules, around 90 % and 40 % of approved active pharmaceutical ingredients, showed poor solubility in water and ultimately low bioavailability [3]. Hence, one of the simplest attempts to improve the bioavailability is to accelerate their solubility and dissolution rate. Drug permeability is a property that affects oral bioavailability. The outcome of drug design and development introduced the molecules with high lipophilic and molecular weight characteristics, which failed to show good solubility and, ultimately bioavailability [4].

The active ingredient is considered as highly soluble when their highest dose is solubilized in a solvent of 250 ml at the entire pH range (1-7), reported by FDA and BCS. Moreover, the active ingredient is categorized as permeable when its absorption across the intestine will be 90 percent. BCS reported that there is a definite relationship between dissolution and bioavailability observed outside and inside of the body, termed as IVIVC. Rely on solubility and permeability, active ingredient categorized into four classes and out of them, class II and IV is a good candidate for improving the bioavailability [5-7]. Several techniques have been implemented for improving the solubility and bioavailability depicted in table 1 [8].

Table 1: Several approaches for enhancing the bioavailability of drugs

Approaches	Techniques	References
Enhancing solubility and dissolution	Micronization	[9]
	Nanonisation	[10]
	Supercritical fluid recrystallization	[11]
	Spray freezing into liquids	[12]
	Using surfactants	[13]
	Using salt form	[14]
	Using precipitation inhibitors	[15]
	Solid Dispersion	[16]
	Using cyclodextrins	[17]
Enhancing permeability	Microemulsions, Self-micro emulsifying drug delivery system (SMEDDS), self-nanoemulsifying drug delivery system (SNEDDS)	[18] [19]
	Solid lipid nanoparticles (SLN)	[20]
	Nanostructured lipid carrier (NLC)	[21]
	Liposomes	[22]
	Penetration enhancers	[23]
Enhancing stability	Enteric coating	[24]
	Using metabolism inhibitors	[25]

Liquisolid compaq technique

The Liquisolid concept was first demonstrated by Spireas and his team described that the active ingredients mostly exist as powder and hydrophobic. Their solubility was improved by incorporating a liquid that is non-volatile to make it available as a solution or suspension [26-27]. Excipients functioning as a carrier and having good adsorption characteristics with porosity should be preferred

and added to the above solution or suspension. Moreover, the incorporation of a coating agent in solution or suspension improved the flow behavior of powder and make it available as directly compressible to formulate as tablets [28].

The non-volatile solvent should be selected based on the highest solubility of the active ingredient in the solvent. Greater solubility of active ingredient resulted in improved dissolution and bioavailability [29]. One of the limitations of the Liquisolid technique is that it applies only for a minimum dose of drugs. Active ingredients are having a weight of more than 400 mg found to be poor candidates, as they required a large amount of solvent for solubilization. The addition of more amount of solvent needs an excess quantity of carrier and coating agent. This ultimately resulted in a higher weight of the finished product, which is difficult to swallow. Hence, this method is not suitable for high doses [30].

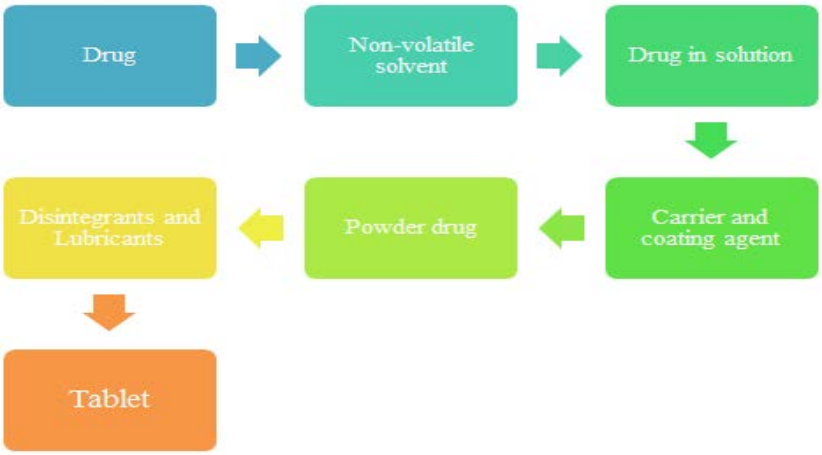

Fig. 1: Manufacturing steps involved in liquisolid technique

Liquisolid pellet technique

Mathew Lam *et al.* 2019 developed the Liqui-pellet, a new solubility enhancing technique for enhancing oral bioavailability of BCS class II/IV drugs. Liqui-pellet comes from combining the concept of the Liquisolid Compaq technique with pelletization technology. Firstly, it was postulated that the Liqui-pellet was different from the Liquisolid technique from the definition point of view [31]. The Liqui-pellet cannot be considered as the Liquisolid Compaq technique, as it is based on the concept of powdered material, which is moist and not as freely flowable. Whereas, Liqui-pell*et al.* so showed good flowability characteristics and available in the form of pellets. Liqui-pellet technique overcomes the limitations of Liquisolid Compaq, where a higher dose can also be suitable for improving the solubility and final weight is quite low [32].

Matthew Lam and his coworkers provided further clarification in 2020, that the Liquisolid-pellet were different from the Liqui-pellets. Spireas in his patent, described that the Liquisolid powders should be flowable by adding more carriers, which in turn reduces load factor and makes the final dosage form, which was very bulky. As it contains a high load factor, a wet mass system, which is a non-flowable powder, should be produced, which was different from the Liquisolid system, which is a flowable powder. Hence, on that basis, differentiated the terms, the Liqui-pellet uses the Liqui-mass system, whereas Liquisolid-pellet uses the Liquisolid system [33].

Fig. 2: Advantages of liquisolid-pellet technology

Formulation components of the liquisolid-pellet technique

1. Selection of drug candidate:

Drugs with low oral bioavailability are a good candidate for this technique. Drug candidates classified as class II/IV as per BCS is to

be chosen for enhancement of bioavailability. E. g. Carbamazepine, Naproxen and Ritonavir, etc. [34-36].

2. Selection of Non-volatile solvent (NVS):

They possess inertness, high boiling point, and lower viscosity. Generally, the less viscous liquid should be preferred as it requires a minimum amount of carrier and coating agent to generate free-flowing powder as well as minimizes tablet weight. E. g.

Polyethylene glycol 200/400/600, propylene glycol, Polysorbate 20/80, Span, Labrafil, Labrasol and Kolliphor EL, etc. [37-40].

3. Selection of Carrier material:

Carrier material should be incorporated for compression enhancing. These materials are porous with enough soaking tendency. Several derivatives of cellulose, starch, lactose are used as carrier material. Carrier material should be selected based on its absorption capacity and inertness with drugs.

4. Selection of coating material:

Coating material should be having good flow characteristics and possess high adsorptive property. Various grades of silica are widely used for coating. They are primarily utilized for adsorption behavior and thereby providing the material as freely flowable [39-40].

5. Additional excipients:

Liquisolid-Pellet system requires additional excipients used as Disintegrants, directly compressible excipients, and lubricants, etc. [41-43].

Manufacturing process for liquisolid-pellet technique

The manufacturing process involved in the Liquisolid-Pellet technique involves the utilization of both processes as the Liquisolid technique followed by extrusion-Spheronization. According to the solubility of the drug, non-volatile solvents should be chosen. The active ingredients should be rapidly dispersed in a non-volatile solvent, which results in the formation of liquid medication or as a drug solution. This drug solution was sonicated for about 10-15 min until a clear homogenous solution is obtained. Microcrystalline cellulose should be mixed with solution or suspension as a carrier, which is also a filler and binder for further process of extrusion-Spheronization. Finally, cross povidone is incorporated as a disintegrating and coating agent, which gives, moisten powder material as Liquisolid system [44].

The prepared Liquisolid mixture is then further gradually wetted with solvent so that enough plasticity is generated for extrusion-Spheronization. The wet mass is then rapidly undergoing extrusion using an extruder through a desired mesh. The extrudates obtained is then quickly transferred to Spheronization, so that good quality of pellets will be formed. The formed pellets are then dried in a fluidized bed dryer for about 10-20 min. The dried pellets are further compressed to form tablets or filled in capsules [45].

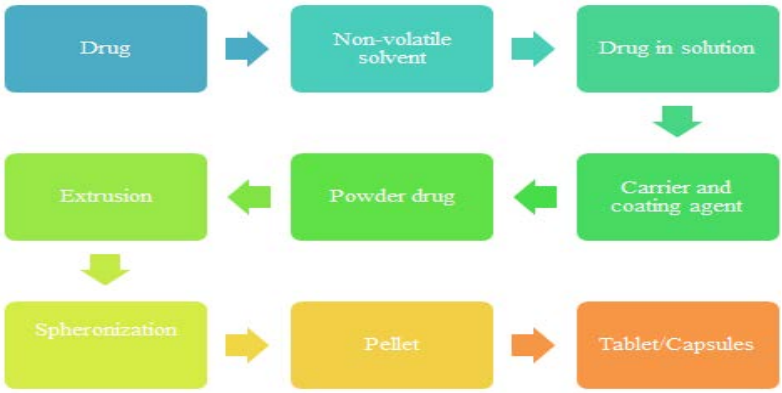

Fig. 3: Manufacturing steps involved in liquisolid-pellet technology

Extrusion-spheronization

Extrusion-spheronization is the most widely used technique for the manufacturing of pellets. Pellets are defined as ''small, free-flowing, spherical units made up of fine powders or granules of bulk drugs and excipients by involving mostly extrusion and spheronization.'' The prepared pellets can be utilized for rapid release or controlled release. One of the big advantages of extrusion-spheronization technology is that a large number of active ingredients can be loaded in pellets as compared with other techniques for pellets production [46].

Manufacturing of pellets via extrusion-spheronization

The process of extrusion-spheronization involves several steps as,

a. The material utilized for processing should be dried completely for further mixing to get uniformity in powder dispersion.

b. Then the material is wetted to create enough plastic wet load or mass.

c. The obtained wet mass further undergoes extrusion to generate rod-shaped particles.

d. These rod-shaped particles further spheronize so that spherical particles are generated.

e. The spherical particles are further dried and screen to achieve the desired particle size [47].

Types of extruders

Extruders are generally composed of 2 portions; the delivery and die system. The delivery system responsible for the movement of material and mixing of the material, whereas die systems helps in generating the material in the desired shape. Based on the feed mechanism, extruders are classified as follows.

1. Screw feed extruder containing axial, dome, and radial type

2. Gravity feed extruder consisting of cylinder roll, gear roll, and radial type.

3. Piston feed or Ram extruder

4. Screen or Basket extruder

5. Roll extruder [48]

Screw feed extruders

Make use of the screw for creating pressure required to propel the material so that it will flow. Rely on the design, solid substances move via several openings, thereby resulted in similar strands, which are commonly known as extrudates. They composed of single or twin helical screws revolving in a barrel and hence shifted the solid material from the hopper to the die. The die system is consisting of a thin steel plate with several holes and available in the form of an axial or radial screw feeder.

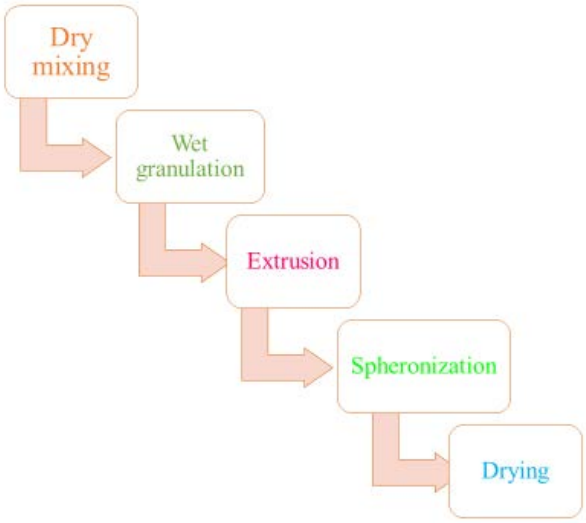

Fig. 4: Steps involved in manufacturing of pellets

Table 2: Types of screw extruder and their specifications

S. No.	Screw extruder	Description	Advantages	Features	Reference
1	Axial	Mostly employed in pellet formation with size ranges from 400 µ to 2000 µ. Provides a minimum output of 250 g and a maximum of 150 kg/h.	Axial mesh with feed hopper and pressing cams and a screws Available as a screen along with hopper and compressing cams with a screw. Rotates at 20-100 rpm. Available at touch screen with traceability Easy to operate and clean.	Build the main part with stainless steel 316 grade and rest with 304. The maximum product recovered up to 100 %. Created low fines after the operation Available in several axial meshes as 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1 and 1.2 mm.	[49]
2	Dome	The Dome extruder presses 300-1200 µ of particle sizes. Providing an output of a minimum of 100 to 200 g and max. of 6 kg/h.	Operated at 40-100 rpm. Available as pressing cams with screw and hopper.	Similar to axial	[49]
3	Radial	Capable of producing an extrudate of 400 to 1500 µ particles.	Operated at speed of 20-100 rpm.	Similar to axial.	[49]

Gravity feed extruders

They composed with moving gear and cylinder, which further merged into roll extruders. They utilize rollers, which create pressure on the material and generates extrudate. These extruders generated extrudate by exerting pressure on the wetted mass by utilizing two rollers. The cylinder type extruder with two rollers available in the form of a cylinder as solid and other with a hollow cavity to generate dies. Whereas gear type extruders are also containing rollers with gear. The third type of extruder is radial in which arms are rotated so that wetted mass passed with pressure. Due to the presence of a rotating blade, they tear the wetted material and capable of generating extrudate. These are differentiated from gravity and screw extruder in the aspect of not using compression before extrusion.

Ram extruder

This type of extruder is based on the concept of utilizing a ram or plunger alternatively to screw. In this type of extruder, the piston displaces and drive the material towards the die at the opposite end [50].

Screen or basket extruder

Screen or sieve type extruders composing a chamber that grip the material and enabled them to extrude. The spinning section pushes the material through a porous screen or sieve, thereby producing tiny or long extrudates. The formation of these extrudates relies on the presence of moisture content. Whereas basket extruder differs from the screen extruder as it is placed horizontally and vertically, respectively.

Roll extruder

It is also known as Pellets mill, worked by suppling materials between a ring die or plate and roller. The designing of the roll extruder consisting of a ring die plate that revolves inside of the cylindrical die chamber and each one revolving on a fixed plane. Every part which is capable of spinning is in the same directions. The substances are added to the interior surface of the die and hence rollers compress them outsides.

Impact of factors on extrusion-spheronization

Moisture content

The amount of water or moisture available in the solid materials determines the effective processing of extrusion as well as the quality of pellet formation. Enough amount of moisture content is desirable during extrusion as a lower amount resulted in the generation of dust particles during spheronization. If the moisture content is beyond their limits, then it also affects the process by forming agglomerates. The moisture content in the material also affects the density of spherical particles, its surface characteristics and the torque of an extruder [52]. Lustig-Gustafsson *et al.* reported that the quantity of water necessary for pellet formation depended on the active ingredient and its particle size [53].

Types of spheronizers

Table 3: Spheronizer and its features

S. No.	Types	Salient features	Reference
1	Micro spheronizer	Applicable only for small labs and trial purpose	**[51]**
2	Multi bowl spheronizer 250	Design with the intention of laboratory-scale indicating minimum quantity. Capacity: ranges from 1 g to 1 kg Used along with screw extruder 20 and mini screw extruder	**[51]**
3	Model 380 spheronizer	Implemented for producing smooth and spherical pellets Capacity: ranges from 0.5 kg to 4 kg	**[51]**
4	Model 500 spheronizer	Implemented for producing smooth and spherical pellets Capacity: ranges from 1 kg to 11 kg	**[51]**
5	Model 700 spheronizer	Produces smooth and regular pellets Capacity ranges from 5 kg to 25 kg.	**[51]**
6	Model 700 spin spheronizer	Applicable for continuous production due to the presence of dual drum	**[51]**

Granulating fluids

The most widely used solvent for granulation is distilled water. Additionally, alcohol or a mixture with water is also recommended. Dreu *et al.* observed that the quality of pellet formation changes according to the addition of granulating fluids as tested using water and a combination of water/alcohol. The mechanical and structural characteristics of pellets strongly dependent on the type of granulating fluids. This is mainly due to the affection of contraction driving and counteracting forces during drying conditions [54].

Excipient

The excipients incorporated as carrier and coating agent as well as for further processing conditions of extrusion, have a strong impact on pellets formation. Fielden *et al.* evaluated lactose powder when used in two different grades as coarse and fine during extrusion showed variability in the formation of the spherical shape of pellets. Levis *et al.* evaluated several grades of microcrystalline cellulose as single ultra-fine (A), in combination with SLS (B) and another PH-101 grade (C). The material labeled as A and B showed better yields than C in the formulation of indomethacin pellets [55]. Rojas *et al.* reported that MCC II exhibiting good pellet formation properties with good flowability, enough mechanical strength, and less friability [56]. Sometimes, MCC is not used during extrusion-spheronization as it tends to retards the release of the poorly water-soluble active ingredients, not compatible with active moiety and adsorption tendency. Hence, alternatively cellulose derivatives, HPMC, HPC, PEO, cross-linked PVP as well as some synthetic polymers [52].

Extruders

The selection of extruder is important for availing good quality of pellets. The displacement forces observed in the Ram extruders are found to be better than in gravity feed extruders. The pressure or strength needed to eject the wetted material through ram extruder decreased upon the addition of water. Hence, lowering the water content resulted in increasing ejection, thereby influencing the quality of spherical units. Small size pellets are generally achieved using a screen extruder as compared with ram extruders. In the case of roll type extruders, criteria for deciding discharge flowing speed, the pressure applied on the screen, and roller torque rely on the spacing available between roller blade and screen as well as roller turning speed. An axial type screw extruders are capable of generating highly dense particles comparatively with radial screw extruders. Sonaglio *et al.* developed paracetamol pellets by using an axial and radial type of screw extruder and reported that alterations in temperature and time required for extrusion [57] found to be higher in an axial type.

Extrusion screen

The die aperture present in the screen or plate is available in various designs. The type of desired products depending on the selection of the screen or the plate. When a thick plate or screen is employed, it generates dense products. The thin screens or plates are generally straight. The aperture size ranges from 0.5 to 1.5 mm and is considered as standard.

Extrusion speed

The cumulative yield of any extruder depends on its speed. Generally, higher yield is expected from any kind of extruders but excessive high speed affects the quality of spherical particles.

Extrusion temperature

Fielden *et al.* evaluated the effects of fluid and MCC by using thermal methods. The studies indicated that water or fluid utilized as granulating fluids is available in the free form and easily converted into the vapors by the process of evaporation, thereby sometimes affects the final products [58].

Friction plate

It is one of the most important segments of spheronizer having a furrowed surface that is responsible for providing frictional forces [59]. There are two different types of furrow geometry observed as cross-hatch and radial, which work effectively. The more controlled action was observed in the radial disc, but not found to be suitable for giant diameter discs. The most widely used disc in spheronizer is square cross-hatched square design, in which developing surfaces are overlaid with a grid of truncated tomb. The material of extrudates with a diameter up to 0.8 mm is carried out using a 2 mm pitch plate and for 3 mm diameter, 3 mm pitch plate is recommended.

Disk speed and load

During spheronization, disk speed and load should be remaining optimum to achieve better output. If the speed remains low, then extrudates will not densify and spherical units not formed. Whereas excessive speed than recommended resulted in higher pressure on the granular materials, lower porosity, increased breaking tendency of granules, pressing of particles. Particularly the revolving speed for disks having less than 500 mm diameter should be operated at about 200 to 1000 rpm. The optimum speed relies on the properties of the material being used and their particle size. Generally, for smaller particles, higher speed is chosen and for larger ones, lowers speed. It is recommended that, during the initiation of Spheronization, velocity is kept higher and later will be slower. The quantity of load incorporated is dependent on machine capacity and size. A machine with 380 mm diameter, the material is approx. 4 liters, also depends on the density of that material.

Product-related parameters

The materials subjected to Spheronization must have enough plasticity to permit distortion to take place during striking. Some of the extrudates bearing high cohesive forces, which takes a longer time to break and increased processing time. [51]

Other factors

The rheology of the material can be altered by using binders, lubricants, or by modifying mixing time. In critical cases, Mixer Torque Rheometer found very useful for measuring the rheology of the material easily and immediately. A sufficient quantity of binders must be added, which provides robustness to the granules and

minimizes the formation of dusty particles during spheronization. Excessive binder concentration resulted in the hardening of granules and created difficulties in spherical units [60, 61].

CONCLUSION

Oral drug delivery is mostly preferred in pharmaceutical developments due to its several advantages. Dissolution is the rate-limiting steps towards achieving oral absorption and bioavailability. Liquisolid Compaq is such a technique utilized for the enhancement of poorly soluble active ingredient by incorporating non-volatile solvent. However, this technique can't utilize for drug candidates above 400 mg of dose, as higher dose resulted in large size of the dosage form, which is difficult to, administered as well as difficult to scale up in the Pharmaceutical industry. Hence to provide the benefits of this technique and overcoming its limitations, the Liquisolid-Pellet technique is introduced. Liquisolid-Pellet technique has no such restrictions of dose of drugs and highly scales up and more beneficial. This technique generated good quality of pellets using the concept of Extrusion-Spheronization, so before proceeding to this technique, researchers have to understand the impact of various factors affecting extrusion-spheronization.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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