Review Article

Liqui-Pellets: A Magnificent Solubility Improvement Approach

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ABSTRACT

Inconsiderate of the decisive benefits that the liqui-solid automation provides, particularly to conflict poor bioavailability of water-insoluble drugs (BCS class II drugs i.e., low solubility and high permeability). As there are a few evaluative limitations it is necessary to employ the technique of Liqui-pellets for class II drugs. Liqui-pellets are a new oral dosage form that increases the rate of drug release in the gastrointestinal tract, increasing the bioavailability of water-insoluble drugs. A product that combines the liquid-solid principle with pelletization technology is referred to as a "liquid pellet". This article mainly summarizes about in-depth information regarding the introduction, advantages, disadvantages, potential applications of liquid-pellets, material and methods i.e., extrusion-spheronization, characterization of liquid-pellets. Finally, this article provides conclusion to overcome certain drawbacks there are poor compatibility, poor flow- ability, high lipid load factor inability and an in ability to produce a high dose dosage form of a tolerant size for consuming. These are the crucial difficulties which inhibits this automation form being materialistically attainable.

Objectives:

- To improve solubility and dissolution rate for poorly water-soluble drugs.
- To enhancing the bioavailability of poor bioavailable drugs (BCS class II).
- Able to achieve high liquid load factor maintaining excellent flow properties.

Methodology: Extrusion-Spheronization: In liqui-pellet formulation is formulated by using different liquid vehicles like PEG 200, PG, tween 80 and coating material like aerosol 300 and main ingredient i.e., carrier like avicel pH 101,102.

Conclusion: The perspective of innovative technique in the field of pharmaceutical industry, the liquid-pellets can successful in which improves the solubility and bioavailability and drug release rate in GIT.

Keywords: Liqui-pellets, liqui-mass system, poorly water-soluble drugs, extrusion-spheronization, dissolution improvement, pelletization

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INTRODUCTION

Liqui-pellets are a next-generation revolutionary oral dosage form that increases the rate of drug release in the gastrointestinal tract, improving the bioavailability of water-insoluble drugs. The poorly water-soluble drugs face so many hurdles it leads to poor drug release and poor bioavailability (i.e., BCS class II drugs). This is the crucial problem challengingly pharmaceutical industry [1]. Around 60-70 percent of medications on the market are insoluble in GIT fluids, which is determined by BCS, and around 30-40 percent of drugs in development are classified as water insoluble or poorly water-soluble drugs [2, 3].

Liqui-pellets arise from collaborating to liqui-solid theory with pelletization technology. The size ranging from 1mm to 2 mm [4]. It is basically contrasting from liquid-solid technology. So, it does not suit under the precision of liqui-solid system, in consequence it is known as liquid-pellet alternative of liquid-solid pellet. Converting liquid lipophilic medications into powder is how powdered medication is manufactured, drug suspensions, or weakly water-soluble drug solutions in a suitable non-volatile liquid vehicle into a dry, non-adherent powder, free flowing, and readily blendable powder combination by integrating specific carriers and coating materials [5].The admixture for the liqui-solid formulations is under liqui-solid system, which is largely used and define term in liqui-solid technology. Liqui-pellets formulation is not a liqui-solid formulation because it does not belong to the liqui-solid systems [4]. The main purpose of a liquid-pellet formulation is to increase the bioavailability of BCS class II medications. In BCS class II drugs usually the drug dissolution rate i.e., Rate Limiting Step (RLS) for bioavailability [4, 6, 7]. In a multidose unit, the pellet delivery mechanism has even more options. Liqui-pellets can be made to administer medication in either an explosive or sustained manner. The pH of the microenvironment can even be changed in unprinted data to improve the drug release rate [8, 9]. Already earlier studies [4, 6, 7, 8, 9] reveal

favorable results in terms of materialistic production, quality control and also necessary for proper coating such as:

- Resistance to friability
- Narrow size distribution
- Smooth surface structure

Coating liquid-pellets for pediatrics use has several advantages, including longer, delayed, and gastro-retentive release, as well as flavor masking. Water and tween 80 (liquid vehicles) were discovered to have a significant effect on the medication dissolution rate in liqui-pellets in prior studies. Increasing the tween 80 concentration while decreasing the water content improves the medication release rate in this case [(7)]. It is possible to optimize the drug release profile using this information. As a result, this fundamental understanding is crucial in the formulation of liqui-pellet. Aerosol 300 is utilised as a coating ingredient in liquid-pellet formulations to accomplish a variety of activities. Carrier, such as Avicel pH 101, is the key ingredient used in liqui-pellet composition (Micro Crystalline Cellulose).

Based on the foregoing, liqui-pellets are a novel emerging technology that improves the solubility of poorly water-soluble pharmaceuticals by enhancing the rate of dissolution in the gastrointestinal tract. Therefore, the aim of the investigation regards the liqui-pellets technique is a pharmaceutical automation and inventive technique to improve the bioavailability of BCS class II drugs [10].

Advantages of Liqui-Pellets:

Liqui-pellets technique is unique and outstanding technique which is desirable upon comparison to other solubility enhancement techniques. Because it has a wide range of excellent characteristics, which include:

- Being simple technique, Cost effective
- Safer due to more expected drug absorption and drug release [1, 11].
- It uses green technology & may possibly resolve issues with polymorphism if API kept in liquid state
- Reduces the risk of dose dumping
- Small uniform size of pellets permits a more expectable drug dispersion and transportation in the GIT [12]. Small size of pellets shows better dissolution rate in GIT it leads to better bioavailability due to better drug absorption.
- The medicine in a liqui-pellet form is freely disseminated in the GIT, reducing the possibility of high drug concentration at the local site as well as toxicity and adverse effects [13].
- Liqui-pellets that can hold a large volume of liquid medication while maintaining great flowability & possible for versatile modifications makes liquid-pellets an exciting and interesting dosage form [14].
- It reduces the inter and intra patient variability
- Liqui-pellets are combined to administer incompatible bioactive substances at the same time.
- All liqui-pellets formulations are loaded with a homogeneous dose to the maximum extent possible.

Disadvantages Of Liqui-Pellets:

- Liqui-pellets are difficult to compress into tablets because they are excessively stiff.
- It demands highly sophisticated and specialized equipment and also requires high cost of manufacturing.
- Controlling the production process is difficult due to the large number of process variables.

Potential Applications of Liqui-Pellets:

1. Pediatric use: The small pellets can be sprinkled on yoghurt or other foods. Which easier for small children to swallow. The pellet can be coated to vary the taste from bitter to pleasant.
2. Geriatric use and for patients with swallowing difficulty: Liqui-pellets can be compressed into a tablet or encapsulated. Patients can open the capsule to get small swallowable pellets. A cup of water may be used to disperse the tablet. It soon redisperses back to a pellet shape, making it easier to ingest.
3. Patients who are unable to swallow medications are frequently given crushed pills in solution through a catheter that runs from the nasal cavity to the stomach. To manage the rate of medication release, many pharmaceuticals are coated in a film (sustained release). The film coating is damaged when crushed, rendering the sustained release feature useless. Liqui-pellets can be re-dispersed into microscopic pellets and supplied by nasogastric tube maintenance film [15].

Differences Between Normal Pellets and Liqui-Pellets:

Table 1: Differences between pellets and liqui-pellets

Normal pellets	Liqui-pellets
1.Pellets are agglomerates of fine powders or granules of bulk drugs and excipients.	1.Liqui-pellets are acceptably flowing and compressible powdered forms of liquid medications.
2.Pellets for pharmaceutical purpose are usually produced in the size range of 0.5mm-2mm.	2.Liqui-pellets size ranges between 850µm-1mm.
3.Drug loading incorporated in pellets is solid state.	3.Drug loading incorporated in liquid-pellets is liquid state.
4.Finally obtained pellets encapsulated in hard gelatin capsules or compressed tablets.	4.Liqui-pellets encapsulated in soft gelatin capsules or compressed tablets.
5.The pelletized product shows maximum drug absorption.	5. Liqui-pellets shows to improve solubility, dissolution rate, drug release rate in GIT.

Materials used in Liqui-Pellets

1) **Active pharmaceutical ingredient (API):** Liqui-pellets technique is applicable for poorly water-soluble drugs. BCS class 2 drugs like Ritonavir, Naproxen and so on whose bioavailability is to a lesser degree can undergo this advanced technology of liquid-pellets.
2) **Carriers:** Mostly used carrier in liquid-pellets is Avicel pH101 i.e., MCC. Because of its rheological characteristics, cohesiveness, and plasticity, Avicel pH101 is a gold standard carrier in the extrusion-spheronization method, resulting in strong spherical pellets [16]. The main disadvantage of Avicel pH 101 in pelletization is that it forms strong linkages, resulting in non-disintegration of the pellets.
3) **Coating Material:** Mostly used Aerosil 300 is a colloidal silicone dioxide. Aerosil 300 is utilised as an adsorbent, tablet disintegrant, thermal stabilizer, and viscosity raising agent in addition to its coating function [17]. Aerosil 300 is a hygroscopic substance that can absorb a lot of water without liquifying [17]. This allows for the detection of excess water during the granulation process in the manufacturing of liquid pellets.
4) **Super disintegrants:** The most often used super disintegrant is Sodium Starch Glycolate (SSG), also known as Primojel. Cross povidone is also employed to help the liquid-pellet composition disintegrate faster.
5) **Liquid vehicle (non-volatile solvents):** The most often used liquid vehicles are polysorbate 80 (tween 80), PEG 200, propylene glycol (PG), and kolliphor EL [10].

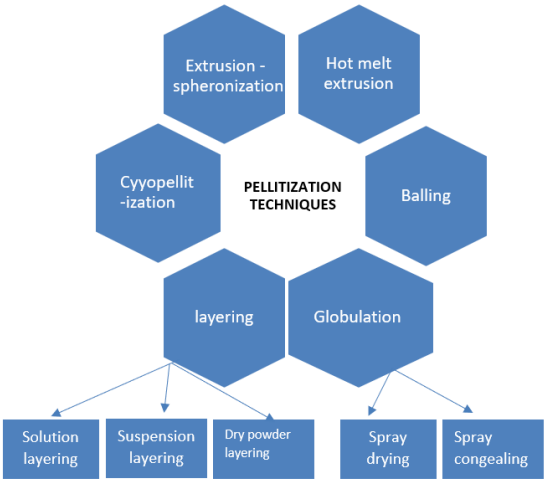

Figure 1: Different types of Pelletization techniques

Method

To make Liqui-pellet mixtures, extrusion-spheronization is employed. It is a multi-step procedure for producing uniformly sized Liqui-pellets from wet extrudates. This procedure demands the following steps:

- Ingredients are dry mixed to produce homogeneous powder dispersions.
- Next, wet massing in which formation of abundantly plastic mass by wet blending.
- An extrusion step, in which wet matter is extruded into extrudate.

Spheronization of extrudates, followed by drying of pellets[18].

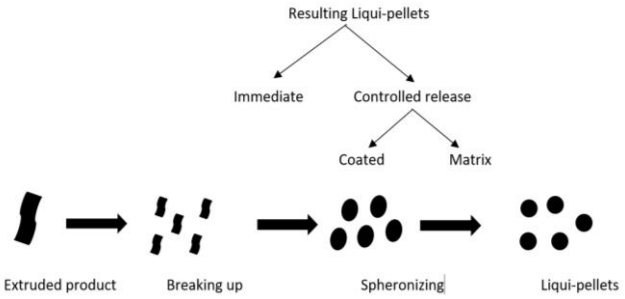

Figure 2: Formation of Liqui-pellets from extruded product

Solubility Studies

To conduct saturation solubility investigations, non-volatile solvents such as polyethylene glycol 200 (PEG200) and propylene glycol (PG), tween80, and kolliphore EL were utilised (they were chosen based on published publications and their influence of solubilization on the medications). To determine the which liquid vehicle for increasing drug release liquid-pellets preparations is the major objective using different suggested liquid vehicles. To make a saturated solution, extra pure API is added to a small vial holding 10ml of an acceptable liquid vehicle. Place the samples in an OLS Aqua Pro bath shaker (Grant Instruments Ltd., Ireland) for 48 hours at 37°C with a 40rpm vibrating speed. Filtration with a pre-heated filter (pore size 0.22 m, Millex GP, Merck Millipore Ltd., Ireland) and diluting with an appropriate buffer solution. The samples will next be analysed using UV/vis spectroscopy (Bio wave Ltd., UK) at a wavelength of appropriate nm in order to ascertain the concentration of each sample [4].

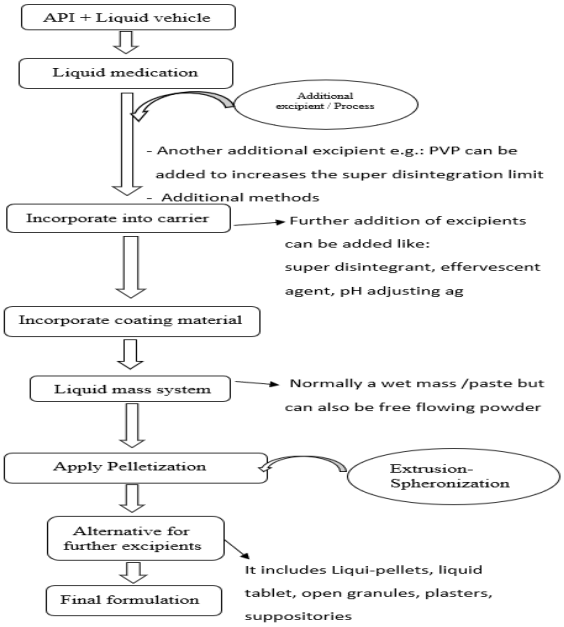

Figure 3: Preparation of Liqui-pellets

Preparation

Using a mortar and pestle, the Liqui-pellets were created by combining pure API with a chosen liquid vehicle (PEG 200, PG, Tween 80, kolliphore EL). Weigh the coating substance (avicel pH 101) and the carrier (avicel pH 101) carefully (aerosol 300). All formulations have liquid load factor is 1. The liquid load factor is the ratio of liquid medication to carrier powder weight.

$$LF = W/Q$$

When the above liquid medication was added to the carrier, it was absorbed by the carrier and mixed in the mortar when it was transformed into a mixer (Multitab, Caleva Process Solution Ltd. UK). Rotate at a continuous speed of 125 rpm for 10 minutes. The sample was diluted with distilled water, which was gradually added to achieve the desired plasticity for extrusion (Caleva Multitab, Caleva Process Solutions Ltd. UK). The amount of water in an extrudate was once regarded to be a critical way of producing high-quality spherical pellets after spheronization (Caleva Multitab, Caleva Process Solutions Ltd. UK).

The coating material (aerosol 300) was added to the following admixture and mixed for 10 minutes before the extrusion-spheronization process. Spheronization was set to a steady rotation of 4000 rpm, with a reduction to 3500 rpm for agglomeration and an increase to 4500 rpm for increased pellet sphericity. The time of spheronization diversified pre formulation based on extrudate property of plasticity. To remove any remaining water, the pellets were placed in an oven and held at a constant temperature of 30°C overnight to remove any remaining water. The point to be taken into consideration is that physical mixture. Pellet was obtained in the same way as that of Liqui-pellets excluding liquid vehicle is omitted [6].

Figure 4: a) Denotes an extrudate of a high-water-content formulation with a high plasticity.

b) Illustrates an extrudate of a formulation with a lower water content and less plasticity.

c) Shows extrudate of physical mixture formulation [4].

Figure 5: a) After spheronizing a formulation with a high-water content and longer threads, the result is an agglomerated product. b) After spheronizing a formulation with decreased water content and shorter threads, superior quality pellets are produced. c) Shows reasonable quality pellets of physical mixture formulation [4].

Figure 6: Extrusion-Spheronization equipment

Characterization of Liqui-Pellets

1.Determination of Particle Size:

Pellet size is determined by sieve method. Pellets (5g) were sieved for 1 minute on a mechanical shaker with an amplitude of 40 using 2000, 1000, 850, 500, and 250 m sieves (AS 200, Retsch, Germany). The pellets yield was determined. Based on a pellet fraction of 250 to 2000 m and expressed as a percentage of total pellet weight [6].

2.Flowability Test:

Three distinct methodologies were used to determine flowability. They are:

- Gram/second flow rate (flowability tester, Copley Scientific UK)
- Angle of repose (flowability tester, Copley Scientific, UK and Digimatic height gauge, Mitutoyo, Japan)
- The SUM tapped density tester (D-63150, Erweka, Germany) was used to calculate Carr's compressibility index [19].

A few grammes of the suitable formulation were placed in a funnel with a 10 mm orifice diameter to determine the flow rate. The Liqui-pellets mixture was poured onto a circular test platform with a diameter of 100 mm. After that, the height of the pellet pile on the platform was determined and angle of repose was calculated by using equation-1.

Angle of repose = $\tan^{-1}$ (height of pile of sample/radius of pile of sample)

$$\Theta = \tan^{-1}\left(\frac{h}{r}\right) \quad \text{..... (1)}$$

Carr's index is calculated by the bulk (ρb) & tapped (ρt) densities (100 taps) were measured by equation 2

$$CI\% = \frac{\rho t - \rho b}{\rho t} \times 100 \quad \text{..... (2)}$$

Hausner's ratio is calculated by using equation 3

$$HR = \frac{\rho\ tapped}{\rho\ bulk} \quad (19) \quad \text{..... (3)}$$

The aspect ratio (AR) value (n=500) i.e., the ratio between the longest caliper distance and the caliper distance perpendicular. It was determined by using optical microscope (SMZ-168, Motic, China) combined with a photographic camera (Moticam 10 M, Motic, China) followed by image analysis (size meter1.1, LCP, UFSC, Brazil) [20].

3.Friability Test:

An approach similar to that used in Hu research was used to alter the friability test [21]. In these two better optimised formulations were tested. Erweka friabilator included liquid-pellets (3g) and glass beads (3g) (D-63150, Erweka, Germany) and then seal the apparatus to prevent the leakage of liquid-pellets from the container. The friabilator revolved at a normal speed of 25 rpm for 4 minutes. Before and after the friability test, keep track of the weight of the pellets. These weights are used to calculate the % of weight loss <1% i.e., weight loss is acceptable.

Therefore, it can be concluded that all tested formulations are robust, which is ideal for materialistic manufacturing in terms of Quality Control. It can also be advanced that the robustness is due to carrier (MCC) forming adequate bonds within its structure then water is incorporated, hence producing robust pellets. The plasticizing activity of tween 80 when added to Liqui-pellets can increase the plasticity of the pellets. Which successfully enhance the pellet resistant to friability [6].

4.Hardness Test:

A tablet hardness tester was used to test each formulation of Liqui-pellets tablet (TBH 25, Erweka, Germany). The amount of force needed to break the tablet was recorded. The hardness of three tablets made from each recipe was examined, and the mean was computed [22].

5.Surface Morphology:

It was determined using scanning electron microscopy (SEM). Total samples were placed in double layered carbon tape and sputter coated with gold target and argon gas at 5 kV for 5 minutes, after which they were placed in a SEM device. SEM operating at 3kV. At magnifications of X80 and X800, the surface morphology was investigated. Mostly all Liqui-pellets has smooth round pebble like appearance. Physical mixture pellets do not have this appearance (PMP). The surface structure of all forming Liqui-pellets is rather smooth, which is a key component in coating effectiveness. In Liqui-pellets formulation coating is the major consideration when prepare sustained and controlled release Liqui-pellets formulations via polymeric coating. Liqui-pellets feature a smooth surface and a spherical shape, making it easier to apply a taste masking polymer, which has a number of advantages in paediatric formulations [14].

6.Solid State Analysis:

a) DSC Studies:

By using DSC (DSC 4000, Perkin Elmer, USA) to determine the fastest dissolution rate of Liqui-pellets formulations as well as its excipients and pure API after secondarily evaluate the solid state of API in the preparations using data from thermograms. Samples are weighed ranges between 3-6 gm using aluminium foil for sealing the samples and incorporated in DSC apparatus under nitrogen environment, at a scanning rate of 10°C min (from 25 to 200°C).

b) XRPD Studies:

After evaluating the solid state of the material utilised, x-ray powder diffraction investigations were conducted on API, excipients, and using an x-ray diffractometer, we found the best formulas (D 5000, Siemens, Germany). Samples were examined throughout a two-dimensional range of 2 at a voltage of 40kV and a current of 30 mA, with an examining angle of 5-40 at a rate of 0-2/s. Using the integrated peak approach, calculate the % relative crystallinity [4].

7.In-Vitro Drug Release Test:

Using a USP- II dissolving apparatus, Matthew Lam et al. performed dissolution tests on all profitability generated formulations. 25mg of API loaded capsules are subjected to dissolution and maintained at physiological conditions. To recreate GI fluid with enzyme depletion, the pH is either pH 1.2 (or) pH 7.4, and the dissolving media is chosen according to the pharmacopoeia. At 271nm, absorption was recorded with various intervals in between. He

discovered that lowering the R-value increases the disintegration rate. The scientist concluded that the rapid dissolution rate is due to increased concentration of aerosil 300(hydrophilic) which emphasizes water penetrates into the pellet there by leading to enhanced drug release rate at pH7.4.

8.Stability Studies:

Accelerated stability test were concluded on specific formulations like which formulation like which formulation shows fastest dissolution rate. For three months, the storage temperature was set to 40°C with a relative humidity of 75 %. Drug dissolution profiles were recorded for each of the three months, and the dissolution profiles of Liqui-pellets formulations were compared [19].

Table 2: Some Research works carried out by using Liqui-Pellets Technique

Sl. No.	Title	Authors	Drugs
1.	Liqui-solid pellets: a pharmaceutical strategy to improve the dissolution rate of ritonavir [20].	Brenda De Espindola, Andre O'Reilly Beringhs, Diva Sonaglio, Heller Karine stulzer and so on.	Ritonavir
2.	The crucial effect of water and co-solvent on Liqui-pellets pharmaceutical performance [14].	Matthew Lam, Daniel Commandeur, Mohammed Maniruzzaman and so on.	Naproxen
3.	Liqui-mass technology as a novel tool to produce sustained release Liqui-tablet made from Liqui-pellets [22].	Matthew Lam, Nour Nashed, Ali Nokhodchi	Propranolol HCl
4.	Optimising the release rate of naproxen Liqui-pellets: a new technology for emerging novel oral dosage form [6].	Matthew Lam, Taravat Ghafourian, Ali Nokhodchi	Naproxen
5.	Rapid releasing naproxen Liqui-pellets using effervescent agent and neusilin US 2 [19].	Matthew Lam, Kofi Asare-Addo, Ali Nokhodchi	Naproxen
6.	Liqui-solid pellets and liquid-pellets are not different.	Bianca Ramos Pezzini, Andre O'Reilly Beringhs, Humberto Gomes Ferraz, Marcos	–
7.	The utility of Pap cell block preparations with liquid-prep™ cell pellets to clarify the cytological diagnosis of atypical squamous cells of undetermined significance and atypical glandular cells.	Antonio Segatto Silva and so on. Fernandez and Maria Concepcion Robledo. Matthew Lam, Taravat Ghafourian, Ali Nikhodchi.	–
8.	Liquid-pellets: the emerging next-generation oral dosage form which stems from Liqui-solid concept in combination with Pelletization technology [4]	Nicholas B. George, Jashua Haddad Baldassari, Digno A. Perez Taveras, Maria Jose	Naproxen
9.	Factors affecting performance and manufacturability of naproxen liquid-pellet [10].	Matthew Lam, Ali Nikhodchi.	Naproxen

CONCLUSION

This review summarises the perspective of innovative technique in the field of pharmaceutical industry. In the gastrointestinal tract, the Liqui-pellets improve solubility, bioavailability, and drug release rate. Liqui-pellets was prepared by extrusion-spheronization method. Liqui-pellets has own advantages and limitations. It can be concluded that due to good compatibility, good flowability, ability high liquid load factor, ability to produce a high dose dosage form of a tolerant size. As a result, Liqui-pellets automation is a cutting-edge pharmaceutical technology, and Liqui-pellets are predicted in the future, to play a vital role in the design and manufacture of a variety of new drug delivery systems.

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