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The Combination of Liqui-Mass System and Pelletization to Improve Pharmaceutical Properties of Hydrochlorothiazide

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ABSTRACT

Liqui-Pellet technology has recently been developed and has shown to be promising in achieving a rapid drug release rate with water insoluble drugs. At present, only naproxen and ketoprofen have been applied to an oral solid dosage form for immediate release. The present investigation aims to explore the drug release performance of the poorly water-soluble hydrochlorothiazide (HCTZ) using the Liqui-Pellet technology. Various non-volatile co-solvents such as Tween 80, PG, Kolliphor EL, and PEG 200 were used to make HCTZ Liqui-Pellet formulations to investigate the influence of Liqui-Pellet technology on the drug release profile. Saturation solubility studies showed HCTZ was most soluble in PEG 200 (156 mg/mL), which is also reflected in the drug release data where HCTZ Liqui-Pellet containing PEG 200 had the most enhanced drug dissolution profile. A binary mixture of carriers consisting of Avicel PH-101 and Neusilin US2 was investigated, as this mixture has been shown to improve drug release rate in a previous study. Surprisingly, the binary mixture of carriers did not improve the drug release rate in this study. The best formulation reached 100% drug release at approximately 40 min. Other physicochemical analysis tests showed the Liqui-Pellets' flow property, robustness, and size distribution are generally acceptable and pose no major issue in terms of manufacturing. In conclusion, the Liqui-Mass system combined with extrusion-spheronization is a viable approach to enhance HCTZ dissolution.

KEYWORDS: Liqui-Pellet, Liqui-Mass system, dissolution enhancement, pelletization, co-solvent, dissolution

INTRODUCTION

Liqui-Pellet is produced by using Liqui-Pellet technology, which is also termed as Liqui-Mass technology. It is a newly developed technology that was patented and first appeared in the scientific literature in 2019 (*1*). It is considered to have the potential to contribute to the next generation of oral dosage forms. Recent studies have displayed Liqui-Pellet technology as a promising approach to enhance drug release rate performance, while having beneficial considerations for industrial manufacturing (*2, 3*). Liqui-Pellet comes from complementary concepts from liquisolid technology with pelletization technology. It should be made clear that the Liqui-Pellet technology is fundamentally different from liquisolid technology in that it uses Liqui-Mass system instead of liquisolid system (*4*). A liquisolid system is defined as a dry non-adherent and free-flowing powdered admixture, containing liquid medication and carrier along with coating materials. A Liqui-Mass system, on the other hand, contains considerably more liquid co-solvent, which usually makes the admixture wet and cohesive. It becomes flowable when the wet mass is converted into pellets (*4*). This key difference is the reason why Liqui-Pellet can achieve a fast drug release performance that is superior to liquisolid compact along with features that make it easy to manufacture, particularly the flow property (*2 ,3, 5*).

To appreciate the implication of Liqui-Pellet, it is prudent to understand that inadequate bioavailability of a drug is a major concern in the pharmaceutical industry. It has long been revealed that a large percentage of drugs on the market and in the development pipeline have poor bioavailability and poor dissolution rates, due to poor water solubility (*6*). An estimated 60% of synthesized drugs have poor solubility in gastrointestinal fluids, and around 90% of drugs in development are poorly water-soluble (*7*). Hence, energy and money have been invested into trying to overcome this global challenge.

In this study, hydrochlorothiazide (HCTZ), which has

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poor solubility in water, is used as the drug candidate for the Liqui-Pellet enhanced release dosage form. HCTZ is a thiazide diuretic and is used in the treatment of oedema, chronic heart failure, and high blood pressure (*8*). According to sources from the Clarke Analysis of Drugs and Poison, HCTZ is practically insoluble in water (*9*). HCTZ solubility is around 0.556 mg/mL at pH 6, which is considered to be very slightly soluble, making HCTZ a suitable drug model for this investigation (*10*).

Previous studies on Liqui-Pellet technology have shown that naproxen Liqui-Pellets have the potential for remarkable enhanced drug release, which is superior to liquisolid formulation (*2*, *3*, *5*). Naproxen is a weakly acidic water-insoluble drug; however, by applying Liqui-Pellet technology, it is able to achieve 100% drug release within 20 min at pH 1.2 despite being practically insoluble in such acidic conditions (*2*). Since this technique has the potential to be applied to a wide range of drugs with poor water solubility, it is considered a promising drug delivery platform. The technique itself can omit processes that require a high level of heat, making it suitable for heat-sensitive drugs along with being designed with sustainable technology in mind, which further adds to its potential value as a new drug delivery platform.

Liqui-Pellet has demonstrated that it is capable of overcoming the major disadvantages of liquisolid formulation such as poor flowability and the end product being too bulky for actual use in patients, particularly in high dose drugs (*2*, *3*, *6*, *11–15*). Furthermore, it carries key inherent advantages such as the ability to achieve a high liquid load factor and to exist as a multi-unit dosage form. It is also simple to apply, cost-efficient, and the typical excipients used are considered safe and widely available in the market (*11*). The pelletization aspect of the technology allows good flowability, potential to combine incompatible drugs or drugs with different release profiles in the same dose unit, flexibility for modification via coating technology, and reduced risk of side effects due to dose dumping in film-coated formulation (*16*, *17*).

It has been stated that the Liqui-Pellet technology has the potential to be manufactured at an industrial level given the excellent flow property, high liquid load factor, end product size, and drug releasing performance, which the liquisolid technology is lacking. Although there are other technologies attempting to overcome the same issue of poor dissolution rate of water-insoluble drugs, those other technologies may require advanced techniques or sophisticated machinery to prepare, may not be as cost-efficient, or may not perform as well (*11*). Such methods include altering crystalline drug into its amorphous state, micronization, solid dispersion, nanosuspension, salt formation, self-emulsifying drug delivery system, co-grinding, and inclusion of drug solution in a soft gelatin capsule (*18*, *19*).

With the array of advantages of this newly developed technology, there is much to investigate including studying its performance on a wide range of APIs. This led to the current study where it was investigated whether Liqui-Pellet technology can improve the dissolution of poorly water-soluble HCTZ.

MATERIALS AND METHODS

Materials and Chemicals

HCTZ was acquired from Spectrum Chemical MFG Corp (USA). Excipients used in making the formulation included microcrystalline cellulose (Avicel PH-101 and Avicel PH-102, FMC corp., UK); colloidal silicon dioxide (Aerosil 300, Evonik Industries AG, Hanau, Germany); sodium starch glycolate Type A (Primojel, DFE Pharma, Goch, Germany); synthetic magnesium alumino-metasilicate (Neusilin US2, Fuji Chemicals, Japan); polysorbate 80 (Tween 80, Acros, Netherlands); propylene glycol (PG) (SAFC, Spain); polyethylene glycol 200 (PEG 200, Fisher Scientific, Leicester, UK), and macrogol glycerol ricinoleate 35 (Kolliphor EL, BASF SE, Ludwigshafen, Germany). All other reagents and solvents were of analytical grades.

Solubility of Hydrochlorothiazide (HCTZ) in Non-volatile Co-Solvents

Saturation solubility studies of HCTZ were carried out in four different non-volatile co-solvents: Tween 80; PG; Kolliphor EL, and PEG 200. Pure API drug crystals were added in excess in 10 mL of specified non-volatile co-solvent to create the saturated solutions. The vial was then subjected to mechanical agitation (shaking speed of 40 rpm) and constant temperature (37 °C) using a bath shaker (OLS Aqua Pro, Grant Instruments Ltd, UK) for 96 h. A pre-heated filter with a pore size of 0.22 µm (Merck Millipore Ltd., Ireland) was used in the filtration of the supernatant. The sample was then subjected to dilution with methanol and concentration was determined via UV/vis spectrophotometer (Biowave II, Biochrom Ltd., UK) at a wavelength 272 nm. Each test was carried out in triplicates.

Preparation of HCTZ 12.5-mg Liqui-Pellet and Physical Mixture Pellet

All of the formulations using the Liqui-Pellet approach were made in a similar method except for the variation in parameters such as carrier composition, choice of non-volatile co-solvent, and the amount of granulating liquid

(Table 1). The liquid medication was made by blending a known amount of active pharmaceutical ingredient (API) with a known amount of non-volatile co-solvent, using the mortar and pestle mixing technique. The liquid medication was then blended into a known amount of carrier, which is either completely Avicel PH-101, completely Avicel PH-102 or a mixture of Avicel PH-102 and Neusilin US2 at ratio of 1:1. All formulations contained 5.5% w/w sodium starch glycolate superdisintegrant (Primojel) and carrier to coating ratio of 20:1. The coating material incorporated was colloidal silicon dioxide (Aerosil 300). With the exception of the physical mixture pellet, all Liqui-Pellet formulations had 34% w/w of a specified non-volatile co-solvent and a liquid load factor (L_f) of 0.79.

The liquid medication, carrier material, and Primojel were blended for 2 min at 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). The Primojel was incorporated into the admixture intragranularly, as previous studies showed this was better at promoting disintegration than extragranular incorporation (*13*). A stated quantity of liquid used for granulation (deionized water) was added gradually to achieve good rheological property for extrusion. The length of time of mixing the admixture with deionized water was 5 min. Aerosil 300 was then added into the admixture and further blended for 5 min before being extruded. Once a sample was extruded, it underwent spheronization at an almost constant setting of 4000 rpm, which could be reduced to 2000 rpm depending on the likelihood of agglomeration. The duration of spheronization depended on the extrudate's plastic property and was shortened if the formulation was prone to agglomeration or lengthened to ensure good spherical pellets. The wet pellets were then subjected to drying in an oven under 40 °C overnight to evaporate excess water.

Flowability Studies

Physical mixture pellet and all of the Liqui-Pellet formulations flow properties were assessed using three approaches, which includes flow rate in grams per second, angle of repose (Flowability tester, Copley Scientific, UK and Digimatic height gage, Mitutoyo, Japan) and Carr's compressibility index using the tapped density tester (SVM D-63150, Erweka, Germany). Flow rates were measured by recording sample mass in grams and the time in seconds of pellets flowing through a 10-mm diameter orifice funnel. The angle of repose test was carried out by placing specified formulation in a funnel and letting a heap of sample form on a circular test platform. Utilizing the Digimatic height gauge and micrometer, the height and diameter of the heap of the sample was measured. These measurements were used to calculate the angle of repose. Carr's compressibility index (CI%) was determined from the poured and tapped densities using CI equation. Tapped density was calculated using the data generated from tapped density tester, which was set to tap 100 times. All measurements were done in triplicates and standard deviation of the mean was calculated.

Friability Studies

The robustness of all formulations was examined using the friability test. The weight of 3 g of the specified sample and 3 g of glass beads were placed in a friabiliator drum (D-63150, Erweka, Germany). The friabilator drum was

Table 1. Composition of All Formulations

Formulation	Amount of granulating liquid (mL) per 20 g admixture of API and excipient	Non-volatile co-solvent	Carrier composition	Carrier (mg)	Coating material (mg)	Total weight of 12.5 mg HCTZ Liqui-Pellet (mg)
Physical mixture pellet	22.50	-	100% Avicel PH-102	104.37	5.22	133.34
F-1	2.46	Tween 80	100% Avicel PH-102	104.37	5.22	202.84
F-2	2.46	Tween 80	100% Avicel PH-101	104.37	5.22	202.84
F-3	2.46	PG	100% Avicel PH-102	104.37	5.22	202.84
F-4	2.46	Kolliphor EL	100% Avicel PH-102	104.37	5.22	202.84
F-5	2.46	PEG 200	100% Avicel PH-102	104.37	5.22	202.84
F-6	7.39	PEG 200	100% Avicel PH-102	104.37	5.22	202.84
F-7	7.39	Kolliphor EL	50% Avicel PH-101 and 50% Neusilin US2	104.37	5.22	202.84
F-8	12.32	PEG 200	50% Avicel PH-101 and 50% Neusilin US2	104.37	5.22	202.84

Note - All Liqui-Pellet formulations contain 12.5 mg of HCTZ, non-volatile co-solvent concentration of 34% w/w, Lf of 0.79, Primojel ~5.5% w/w, and carrier to coating material is at a ratio of 20:1.
API: active pharmaceutical ingredient; HCTZ: hydrochlorothiazide.

enclosed to stop the sample of pellets from leaving the container. The friabilator drum was then set to rotate 100 times in 4 min. The percentage weight loss of the sample was then calculated using the weight of the sample before and after the friability test.

Particle Size Analysis

The particle size distribution was examined on all formulations using the sieve method. Specified formulation of Liqui-Pellet weighing 5 g was placed in a sieve (Test sieve, Retsch, Germany) of sizes 2000, 1000, 850, 500, and 250 µm. The sieves were stacked with the largest sieve size on top and the smallest sieve size at the bottom and placed on a mechanical shaker (AS 200, Retsch, Germany). The mechanical shaker was set to vibrate with an amplitude of 60 for 1 min, then an amplitude of 40 for 4 min. The size distribution of Liqui-Pellet was determined based on the pellet fraction between 250 and 2000 µm and presented as the percentage of total pellet weight.

In-Vitro Drug Dissolution Test

The drug release rate of all formulations was examined using USP dissolution apparatus II (708-DS Dissolution Apparatus and Cary 60 UV-Vis, Agilent Technologies, USA). The dosage form subjected to the dissolution test was a hard-shell capsule filled with specified Liqui-Pellet formulation or physical mixture pellet. Each capsule contained an equivalent to 12.5 mg of HCTZ. Dissolution test vessels contained 900 mL of dissolution medium, which was kept at 37.3 ± 0.5 °C and paddle agitation was 50 rpm. The dissolution medium used was HCl buffer solution with a pH of 1.2 without enzymes, which were used to mimic pH in gastric fluid. The parameters were based on United States Food and Drug Administration (FDA) draft guidance for HCTZ/metoprolol oral tablets (*20*). The cumulative drug release was examined using the UV/Vis spectrophotometer method, which read absorbance at a wavelength of 272 nm every 5 min for 1 hour then 10 min for another hour. Preliminary work using Beers Lambert calibration curve (Fig. 1) was applied to dissolution test data to determine the concentration of HCTZ.

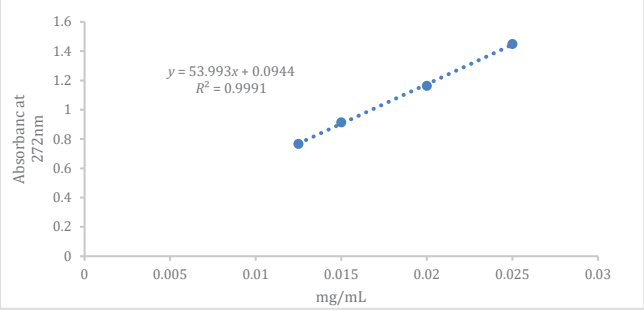

Figure 1. Beers Lambert calibration curve of hydrochlorothiazide at pH 1.2.

Model-independent analysis was used to compare the dissolution profiles of the various formulations. This included difference factor (f_1) and similarity factor (f_2), as described by Moore and Flanner (*21*). Such mathematical analysis has been recommended by the FDA and can be seen in various guidance documents (*22, 23*). In general, when the f_1 value is between 0 and 15 and the f_2 value is between 50 and 100, this indicates equivalence of the two dissolution profiles (*24*). Details of the equations can be found in various literature (*25–28*).

RESULTS AND DISCUSSION

Solubility of HCTZ in Non-Volatile Co-Solvents

The data obtained from the saturation solubility test (Table 2) indicate that HCTZ is most soluble in PEG 200 (156 mg/mL) compared to the other non-volatile co-solvents. This indicates that HCTZ is freely soluble in PEG 200, making it the most suitable liquid non-volatile co-solvent candidate for HCTZ Liqui-Pellets. This is because it is generally considered that the non-volatile co-solvent in which an API is most soluble in would exhibit the fastest drug release rate. This is due to reduced API in the ordered crystalline form and more in the solubilized or molecularly dispersed state, resulting in increased surface area for drug release (*29*).

Table 2. Solubility of Hydrochlorothiazide in Various Liquid Vehicles at 37 °C (n = 3)

Non-volatile solvent	Concentration, mg/mL (mean ± SD)	Inference
Tween 80	27.46 ± 1.31	Sparingly soluble
PG	11.35 ± 4.94	Sparingly soluble
Kolliphor EL	95.93 ± 5.81	Soluble
PEG 200	155.92 ± 6.33	Freely soluble

SD, standard deviation

The next non-volatile co-solvent in which HCTZ is most soluble in followed by PEG 200 is Kolliphor EL, then Tween 80, and finally PG. Despite the solubility test results, formulations F-1 (Tween 80) and F-4 (Kolliphor EL) have a very similar drug dissolution profile even though data indicate HCTZ is more soluble in Kolliphor EL than Tween 80. Therefore, it should be noted that API solubility is not the only factor that can influence the drug dissolution rate. Other physicochemical characteristics of the liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure, and molecular mass may affect the drug release (*6*). Nevertheless, in general, drug solubility in a liquid vehicle does greatly influence drug release profile.

Flowability Studies

The data from flowability studies are shown in Table 3. According to the data obtained from the angle of repose test, all formulations have excellent flowability. As for CI,

Table 3. Formulation Flow Properties and Friability Data

Formulation	Flow Rate, g/sec	Angle of repose	Carr's CI%	Inference According to Angle of Repose	Inference According to Carr's CI%	% Weight Loss
Physical mixture pellet	7.73 ± 0.21	24.38 ± 0.73	11.62 ± 0.00	Excellent	Good	0.91
F-1	6.93 ± 0.10	27.57 ± 1.00	8.83 ± 0.00	Excellent	Excellent	0.10
F-2	6.28 ± 0.61	28.19 ± 0.84	11.71 ± 1.56	Excellent	Good	0.02
F-3	6.33 ± 0.19	26.38 ± 0.77	15.16 ± 0.00	Excellent	Good-fair	0.60
F-4	6.31 ± 0.33	28.86 ± 0.60	11.12 ± 0.00	Excellent	Good	0.20
F-5	6.00 ± 0.18	27.96 ± 0.46	9.80 ± 1.70	Excellent	Excellent	0.81
F-6	7.93 ± 0.15	25.26 ± 0.14	8.84 ± 0.00	Excellent	Excellent	0.05
F-7	7.27 ± 0.09	24.42 ± 0.49	11.40 ± 0.00	Excellent	Good	0.00
F-8	7.63 ± 0.20	23.41 ± 0.43	11.77 ± 0.00	Excellent	Good	0.14

Data are mean ± standard deviation (SD) (n = 3).
CI%: compressible index.

the inference of flowability is slightly more dispersed; there are excellent, good, and good-fair flow properties. In general, the flow properties of all of the formulations do not raise any concerns in terms of the potential to be manufactured at an industrial scale. This is supported in the previous studies on Liqui-Pellet where flowability was also not a major issue (*2*, *3*, *12–14*, *30*). It also marks a big leap forward in the powder-solution approach to solid oral dosage forms, because the high amount of non-volatile co-solvent historically gave rise to a manufacturing issue. This is due to the liquid in the powder contributing to a surface-surface interaction, which causes the admixture to be too cohesive, rendering it unsuitable for large-scale manufacturing. This is also the reason why there is currently no product in the market that uses classical liquisolid technology.

With the combination of the nanosized silicon dioxide coating material (Aerosil 300) and the spherical characteristic of the pellet, flow properties are not an issue for Liqui-Pellets as it is for liquisolid formulation. The coating material reduces the wetness of the pellet, thereby reducing interfacial tension among the Liqui-Pellets and its surroundings. This consequently improves the flow property. Hence, this suggests that coating material plays an important role in Liqui-Pellet smooth flow properties.

Also, the fact that the pellets that are produced are spherical in shape, the round edges reduce the surface area of particles interacting with one another. This reduces surface-to-surface interactions such as van der Waals forces between particles and effectively reduces cohesive force, resulting in a smooth flow property.

Friability Studies

All formulations pass the friability test as the percentage weight loss is below 1% (Table 3). This indicates that all formulations have acceptable robustness. In general, Liqui-Pellet has shown a good level of robustness since it was first introduced in the scientific literature in 2019 (*12*). In addition, it has been stated in Muley et al. review paper that pellet dosage forms are less friable (*31*).

Particle Size Studies

All formulations generally have a reasonably narrow pellet size distribution, with a particle size below 2000 µm. Formulations F-1, F-4, F-5, F-7, and F-8 are mostly within 500 µm, and formulations F-2, F-3, and F-6 are mostly within 850 µm (Fig. 2). Narrow size distribution is ideal for manufacturing as it will reduce weight and content variation when filled into a capsule.

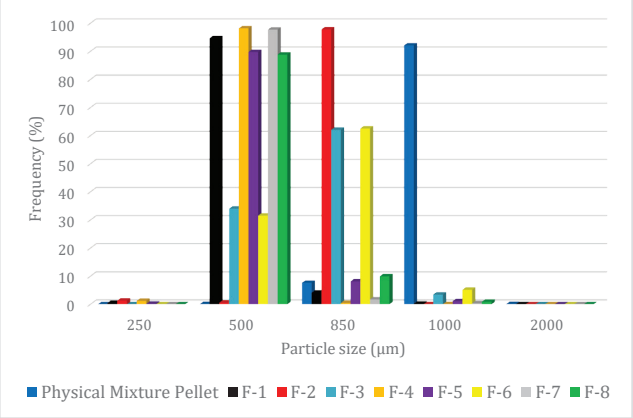

Figure 2. Particle size distribution of hydrochlorothiazide formulations.

It is worth pointing out that the size distribution of pellets is rather difficult to control. It has been stated in the literature that numerous factors can influence pellet size when prepared using the extrusion-spheronization technique. Such factors include API and excipients size

(*32–37*); extruder types; extrusion speed; properties of extrusion screen; spheronization speed (*38*); duration of spheronization time (*39-42*); and spheronization load (*40, 41, 43*). Overall, all of the pellet sizes are within the range that is expected, and most formulations achieved narrow size distribution.

In-Vitro Dissolution Test

According to the dissolution profiles shown in Figure 3, formulation F-5 (containing PEG 200 non-volatile co-solvent) showed the fastest drug release rate, where 100% drug release is achieved in approximately 40 min. This drug release profile is considered rapid because more than 85% of the drug is released within 30 min (*44*). In fact, this Liqui-Pellet formulation has faster drug release than technology such as solid dispersion. HCTZ solid dispersion from a study by Khan et al (*45*) achieved approximately 90% drug release after 45 min (USP apparatus I at 100 rpm in 900 mL 0.1 HCl), which is slower than Liqui-Pellet, suggesting Liqui-Pellet could be a competitive technology.

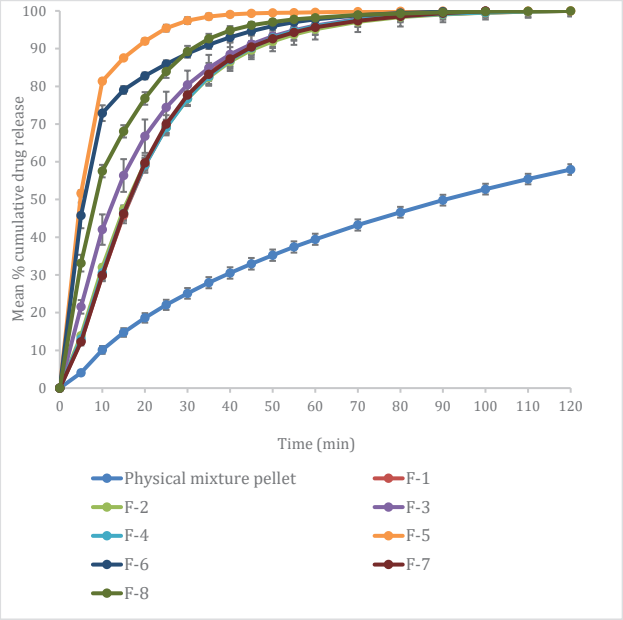

Figure 3. Dissolution profiles of physical mixture pellet and Liqui-Pellet hydrochlorothiazide formulations at pH 1.2.

The two next fastest drug release Liqui-Pellet formulations were F-6 (7.39 mL granulating liquid) and F-8 (12.39 mL granulating liquid). F-6 composition is the same as F-5 (best formulation) (Table 1), except the water content used during the mixing and extrusion-spheronization process was different. The water content used is higher in F-6 (7.39 mL) than F-5 (2.46 mL). According to the dissolution profile in Figure 3, the increased water content in F-6 resulted in a slightly slower drug release rate than F-5. Such influence on drug release rate by water content is supported in a previous study on Liqui-Pellet technology, which investigated the effect of water content on Liqui-Pellet physicochemical properties (*14*). It was observed that a reduction of water content effectively reduces cohesive strength within the Liqui-Pellet structure, improving its propensity for disintegration, thus enhancing dissolution (*14*). Despite F-6 showing a slightly slower drug release rate than F-5, F-6 is more mechanically robust than F-5, which is shown in the friability studies (Table 3). This suggests that formulation scientists will need to adjust water content when manufacturing Liqui-Pellets to compromise between drug release performance and mechanical robustness of the dosage form.

According to Sarkar and Liew (*46*), the improved disintegration property with reduced water content can be explained in terms of microcrystalline cellulose (MCC) aggregates. MCC constitutes aggregates of small subunits that are held together by hydrogen bonding. To cause the de-aggregation of the MCC subunit, the mentioned hydrogen bond must first be broken. This would suggest that when less amount of polar deionized water is used in the blending stage, there would be less de-aggregation. As a result, the MCC should have a larger particle size. Throughout the granulation and extrusion process with this larger particle of MCC, along with less moistening liquid content, there will be less surface tension and van der Waals forces. The resultant extrudate and pellet will have reduced internal cohesive strength, leading to improved disintegration for a faster drug release rate.

Formulation F-8, which has a different carrier composition and more water content than F-5, showed a slower drug dissolution profile than F-5 (f_1= 38.95, f_2= 37.25). This is interesting because F-8 contains Neusilin US2 and Avicel PH-102 as part of the carrier material. It has been observed in previous work on Liqui-Pellet technology that Neusilin US2 significantly improves the drug dissolution rate of effervescent Liqui-Pellet (*2,3*). However, Neusilin US2 does not seem to have the same effect as the HCTZ Liqui-Pellet in this study.

In general, the three best performing formulations (F-5, F-6, and F-8) all contain PEG 200 as the non-volatile co-solvent. Formulations containing PEG 200 have the fastest drug release rate among all of the other formulations with a different liquid vehicle. This is supported by the saturation solubility studies, where HCTZ is most soluble in PEG 200 among the different non-volatile co-solvents. The solubility test data indicate that HCTZ is considered freely soluble in PEG 200 (156 mg/mL), which is a suitable liquid vehicle for HCTZ.

It can be clearly seen that formulations F-1, F-2, F-4, and F-7 have almost identical drug dissolution profiles. Avicel

PH-102 is used for F-1 and Avicel PH-101 is used for F-2; both have an almost identical drug dissolution profile (f_1 = 1.89, f_2 = 90.53), indicating that the two different Avicel do not have any major effect on the drug release rate.

Formulations F-1 (containing Tween 80) and F-4 (containing Kolliphor EL) have almost identical drug release profiles despite containing different non-volatile co-solvents. This is unusual because HCTZ showed markedly different solubility in Tween 80 (~27.46 mg/mL) and Kolliphor EL (~95.93 mg/mL). Usually, it would have been expected that the liquid vehicle that can dissolve more API gives a faster drug release rate. Such results serve as another reminder that the drug dissolution results may not always correlate to the saturation solubility test data. Other physicochemical characteristics of the liquid vehicle such as lipophilicity, viscosity, polarity, chemical structure, and molecular mass may too affect drug release rate (*6*).

Formulations F-4 and F-7 are very similar in terms of composition. Both formulations have almost identical drug dissolution profiles (f_1 = 1.02, f_2 = 96.42). The key difference in these formulations is that F-7 contains a binary carrier (Neusilin US2 and Avicel PH-102) and around three times more water content used during the production compared to F-4. Previous studies on Liqui-Pellet have shown that Neusilin US2 can markedly improve drug release rate; however, this is not the case for F-7. Perhaps the larger amount of water content levels out the fast drug releasing influence of Neusilin US2, resulting in F-7 having a similar drug release rate as F-4. The reason why water content is increased in F-7 relative to F-4 is that the Neusilin US2 in F-7 seems to require greater water content for the Liqui-Pellet to be successfully produced.

Overall, it is possible to achieve enhanced drug release of HCTZ using Liqui-Pellet formulations. However, there is room for optimization to bring out the potential of how fast HCTZ can be released in the Liqui-Pellet dosage form. Further investigation is currently undergoing to realize the potential of enhanced release HCTZ Liqui-Pellet.

CONCLUSION

Liqui-Pellet is proven a viable approach for dissolution enhancement of HCTZ. It is found that among the non-volatile co-solvents used in this study, PEG 200 is the most suitable. HCTZ Liqui-Pellet is able to achieve 100% drug release in approximately 40 min and is considered as a rapid releasing dosage form. However, there is potential for further improvement as the formulation is yet to be optimized. Water content has been shown to affect the drug dissolution rate as expected; therefore, it is a crucial parameter to consider in Liqui-Pellet technology during production. Formulation containing the binary mixture of carriers (Avicel PH-101 and Neusilin US2) surprisingly did not show improvement in drug release rate; however, this could be due to high water content overlapping the influence of Neusilin US2. Avicel PH-101 and PH-102 did not show a significant difference in drug dissolution performance. The use of HCTZ Liqui-Pellet shows no issue in flowability, robustness, and particle size distribution, which reflects the potential industrial manufacturing feasibility. Overall, Liqui-Pellet seems like a commercially viable option for the rapid drug-releasing dosage form of poorly water-soluble drugs.

CONFLICTS OF INTEREST

This technology is protected by international patent WO2020/021254 (filed July 24, 2019, published January 30, 2020).

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