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A Novel Application of an Effervescent Agent in Naproxen Liqui-Pellets for Enhanced Drug Release

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ABSTRACT

Liqui-Pellet formulations have been introduced as a technology to improve the dissolution rate of poorly water-soluble drugs. This study aimed to incorporate sodium bicarbonate ($NaHCO_3$) into the Liqui-Pellet formulation to explore the potential impact on the drug release rate. Naproxen Liqui-Pellet formulations containing 5%, 12%, 22%, 32%, and 42% w/w of $NaHCO_3$ were successfully produced and their physicochemical properties were investigated and compared with a physical mixture pellet formulation. Incorporation of such a large amount of functional excipient is impossible or near impossible in the classical liquisolid formulation due to weight and size limitations, particularly for high-dose drugs. The results showed that $NaHCO_3$ is an effective functional excipient to enhance the drug dissolution rate. The Liqui-Pellet formulation with 42% w/w $NaHCO_3$ released 76.4% of drug after 2 hours at pH 1.2, which was 14 times faster than the physical mixture pellet (5.5% drug release in 2 h). In general, a faster dissolution rate was observed with increasing $NaHCO_3$ concentration; however, there was a limit to this effect. Above a certain limit, the influence of $NaHCO_3$ on the dissolution rate lessened. The flowability test showed that all formulations have good to excellent flowability. Overall, this study demonstrates the flexibility of Liqui-Pellets in terms of formulation design, which in turn further supports the potential of Liqui-Pellets as the next generation oral dosage form.

KEYWORDS: Liqui-Pellet, Liqui-Mass system, liquisolid, effervescent agent, dissolution enhancement

INTRODUCTION

Liqui-Pellets (LPs) are a recently developed oral dosage form that uses a wet mass system called the Liqui-Mass system. The primary purpose of this technology is to improve drug efficacy and reduce the risk of side effects, with manufacturing cost and feasibility in mind. The Liqui-Mass system brings versatility to formulation design and is essential to overcome the technological issues of the classical liquisolid technology (*1*–*3*). A diagram of the Liqui-Mass system and processes are shown in Figure 1. In brief, the Liqui-Mass system can produce LPs, liqui-tablets, free granules, and moldable wet mass dosage forms. It should be noted that this technology is still at an early stage and its potential has yet to be fully realized.

One of the key purposes of LPs is to tackle drugs with low bioavailability through improving drug dissolution rates with consideration to commercial manufacturing (*1*, *2*). Poor bioavailability due to poor dissolution is a major challenge in the pharmaceutical industry, with approximately 60% of drugs in the market considered poorly soluble in gastro-intestinal fluids, and around 40% of drugs in the development pipeline are poorly water-soluble according to the biopharmaceutical classification system (BCS) (*4*, *5*). It has also been reported that up to 90% of drugs in the development pipeline could be poorly water-soluble (*6*). In this study, naproxen was selected as the model drug due to its poor water solubility, particularly in acidic conditions. It is reported that naproxen solubility at 35 °C in a dissolution medium with pH of 1.2 is 1.16 × 10−4 mol/L or 27 mg/L. However, in a dissolution medium with pH of 7.4, naproxen solubility is 1.455 × 10−2 mol/L or approximately 3347 mg/L, which is considered extremely soluble (*7*).

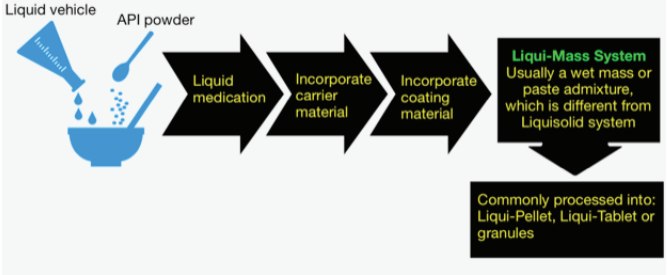

Figure 1. Diagram summarizing the novel Liqui-Mass system used to make Liqui-Pellets.

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In general, LP technology (also known as Liqui-Mass technology) stems from combining the concept similar to a powdered solution or liquisolid technology with pelletization technology (*1*, *2*). Despite both sharing similarities, there is a crucial difference that distinguishes them. LP uses the more versatile Liqui-Mass system whereas liquisolid pellet uses a liquisolid system (*1*, *2*, *8*). To understand what is considered a liquisolid formulation, it is imperative to know what exactly is the liquisolid system. Spireas, who is the inventor of liquisolid technology, along with the scientific community's extensive publications on liquisolid technology since 1998, define the liquisolid system as dry-looking and free-flowing powder containing liquid medication that should be compressible by adding carrier and coating materials (*9*). It is worth pointing out that the liquisolid system is limited to free-flowing powder admixture, whereas the Liqui-Mass system is usually a wet mass or paste admixture, even before a granulating liquid is added, which will eventually evaporate. In LPs, the admixture becomes free-flowing once it undergoes a pelletization process. This fundamental difference gives greater potential and versatility to LP compared to the liquisolid formulation, as more liquid vehicle and additional excipients can be incorporated into the formulation while still achieving commercially acceptable flowability and dosage form size (*1*, *2*, *10*). In addition, LPs are not restricted by the equation developed by Spireas for liquisolid formulation (*9*). The equation dictates the amount of carrier and coating material that are required depend on the amount of liquid medication to ensure acceptable flow property; however, this limits the classical liquisolid technology from producing high dose dosage forms with acceptable size for commercial use.

LPs have demonstrated excellent flow property while having as high as 38% of total pellet mass made up of liquid vehicle (*2*). Previous studies on LPs have proven it to be robust, capable of a having a smooth surface (i.e., potential for application of coating technology), and having narrow particle size distribution. Furthermore, the method of manufacturing is simple, economical, capable of green technology, capable of versatile modification (i.e., apply coating technology, incorporation of functional excipients, and inherent versatility of being a multi-unit dosage form), and the potential for easy upscale of production and excipients used are common, generally safe, and easily obtainable. Hence, it LPs may be attractive for commercial drug development (*1*, *2*, *10*).

In terms of drug safety, the technology uses small uniform size pellets, which make drug dispersion and distribution in the gastrointestinal tract more predictable than larger standard monolithic dosage forms (*11*). The improved drug distribution can prevent side effects caused by having high drug concentration at the local site (*12*). Additionally, the small size LPs have less variation in gastric emptying, which minimizes inter- and intra-variability of plasma drug profiles, thus improving drug safety and pharmacokinetic predictability (*13*, *14*).

So far, in studies by the authors, microcrystalline cellulose (MCC) is the only carrier material used for making LPs. This is because extrusion-spheronization is the key choice of the method used in producing LPs. In the extrusion-spheronization technique, MCC is the gold standard carrier because it can form a wet mass with unique properties, such as good rheological properties, plasticity, and cohesiveness (*15*, *16*). The unique properties are due to MCC having high internal porosity and large surface area, which allows a large amount of water to be absorbed and retained (*17–20*). Such properties are required for the successful production of pellets. Also, the MCC-based pellet has good sphericity, smooth surface, high density, and low friability (*15*).It is also well known that the MCC-based pellet is not suited for fast release formulation due to its resistance to disintegration (*21–27*). LP carrier composition is not restricted to only MCC.

In this study, sodium bicarbonate ($NaHCO_3$) will be applied to naproxen LP formulations as a functional material to enhance the drug release rate. $NaHCO_3$ is considered an effervescent agent when in contact with acid (*28*). Its function is to enhance LP dissolution through promoting disintegration when in contact with the acidic gastric fluid (*28*). The increase in drug dissolution via promoting disintegration and increasing the surface area for dissolution is explained using the Noyes-Whitney equation (*29*). According to the equation, enhanced disintegration increases the surface area for drug release, which is proportional to the dissolution rate (*29*). Thus, greater surface area for disintegration results in an increased drug release rate (*30*). In addition to enhancing the dissolution rate, $NaHCO_3$ can reduce gastric irritation of weakly acidic drugs due to its alkali property and is generally regarded as a non-toxic and non-irritant material (*28*).

MATERIALS AND METHODS

Materials

Naproxen (TCS Co, Japan), MCC (Avicel PH-101; FMC Corp., UK), colloidal silicon dioxide (Aerosil 300; Evonik Industries AG, Hanau, Germany), sodium starch glycolate type A (Primojel; DFE Pharma, Goch, Germany), $NaHCO_3$ (Acros, NJ, USA), synthetic magnesium alumino-metasilicate

(Neusilin US2; Fuji Chemicals, Japan) and polysorbate 80 (Tween 80; Acros, The Netherlands) were used. All other reagents and solvents were of analytical grade.

Preparation of Naproxen Effervescent Liqui-Pellets

Naproxen LP formulations containing 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively) were prepared as follows. A specified amount of naproxen and polysorbate 80 were placed in a mortar then mixed using a pestle until a consistent and uniform paste formed. The use of polysorbate 80 as a liquid vehicle was determined to be the most appropriate liquid vehicle according to the authors' previous studies (*1*). A specified amount of MCC (carrier) was then incorporated into the liquid medication and mixed. Effervescent agent ($NaHCO_3$) followed by a superdisintegrant (sodium starch glycolate type A) was then incorporated and mixed for 2 min at 125 rpm (Caleva Multitab, Caleva Process Solutions Ltd, UK). The superdisintegrant was added intra-granularly, as previous studies showed this was better in promoting disintegration than extragranular incorporation (*2*). A quantified amount of deionized water (granulating liquid) was then added gradually into the wet mass admixture to obtain a suitable rheological property for extrusion (Caleva Multitab). The wet mass along with granulating liquid was blended for 5 min. Coating material (colloidal silicon dioxide) was then added to the admixture and further blended for 5 min before the extrusion process. After extrusion of the formulation, the extrudate was spheronized using a spheronizer at 4000 rpm. Spheronization speed was adjusted by decreasing to 2000 rpm if agglomeration seemed likely. The spheroids were then placed in an oven set at 40 °C overnight to remove excess water content. Table 1 shows the physical mixture pellet and LP formulations with different concentrations of $NaHCO_3$. Apart from different concentrations of $NaHCO_3$ and water content, all other components were kept constant for all formulations, and the carrier to coating ratio was kept constant at 20:1.

Flowability Test on Formulated Effervescent Liqui-Pellets

The flow behavior of LPs was investigated in terms of angle of repose, flow rate (g/s) and Carr's Index (CI%) for all formulations. For more details on the procedure to perform these three experiments, refer to our previous work (*2*). All measurements were done in triplicate and the results are listed in Table 2.

Particle Size Analysis (Sieve Method)

Analysis of the pellet size for all successfully made formulations was carried out using specified sieves (Test sieve, Retsch, Germany) and mechanical shaker (AS 200, Retsch). A specified sample of a formulation with a mass of 5 g was placed in a sieve with sizes of 2000, 1000, 850, 500, and 250 µm. The sieve then placed on a mechanical shaker and set under two different vibration amplitudes.

Table 1. Key Formulation Characteristics of the Investigated Capsules

	$NaHCO_3$ (%w/w)	Water content during extrusion-spheronization (mL)*	Carrier (mg)	Coating material (mg)	Total weight (mg)
Physical mixture pellet	-	12	58.15	2.90	90.58
F-1	5	5.59	62.54	3.15	141.20
F-2	12	5.18	62.54	3.15	152.20
F-3	22	4.59	62.54	3.15	172.90
F-4	32	5.60	62.54	3.15	197.20
F-5	42	4.78	62.54	3.15	231.10

**Values are the amount of water used per 20 g of admixture of API and excipients.*
Note – all Liqui-Pellet formulations (F-1–F-5) contain 25 mg of naproxen; primojel 4.4% w/w; liquid vehicle 27.96% w/w, and carrier to coating material ratio is 20:1. The concentration of primojel and liquid vehicle were calculated using the total mass of admixture of API and excipients excluding $NaHCO_3$.

Table 2. Flow Rate, Angle of Repose, and Carr's Compressible Index (CI%) for All Formulations

	Flow rate (g/sec)	Angle of repose	CI%	Inference according to angle of repose	Inference according to CI%
Physical mixture pellet	10.72 ± 0.33	19.96 ± 1.43	11.11 ± 0.62	Excellent flowability	Good flowability
F-1	6.77 ± 0.49	28.95 ± 1.62	10.82 ± 1.33	Excellent flowability	Excellent-good flowability
F-2	7.55 ± 0.21	26.98 ± 0.37	9.85 ± 0.00	Excellent flowability	Excellent flowability
F-3	8.35 ± 0.25	25.37 ± 0.68	11.32 ± 0.65	Excellent flowability	Good flowability
F-4	8.10 ± 0.17	26.71 ± 0.20	10.23 ± 0.00	Excellent flowability	Excellent-good flowability
F-5	8.08 ± 0.19	27.84 ± 0.05	10.01 ± 0.00	Excellent flowability	Excellent-good flowability

Data are mean ± standard deviation (SD) (n = 3).
Naproxen Liqui-Pellet formulations contained 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively).

The first amplitude was set at 60 for only 1 min to quickly separate the particles. Such high amplitude generates high force that could damage the pellets if exposed for a prolonged length of time, so the process proceeded with a lower amplitude of 40 for a further 9 min. The collected fractions were weighed, and the size distribution was recorded for each formulation.

Friability Test on Formulated Effervescent Liqui-Pellets

To investigate the robustness of the manufactured formulations, a friability test was carried out. Briefly, weighing a few grams of specified pellets (around 3 g) was placed in a friabilator (D-63150, Erweka, Germany) along with the equivalent mass of glass beads. The friabilator container was sealed to stop pellets from leaving the drum and was set to rotate for 100 times (4 min set at 25 rpm). The weight of the sample before (initial weight) and after (final weight) the test was used determined and the percentage weight loss due to friability testing.

Dissolution Test

Dissolution profiles were obtained from all feasible formulations. The in vitro drug dissolution test was carried out with a USP apparatus 2 (paddle) (708-DS Dissolution Apparatus and Cary 60 UV-Vis, Agilent Technologies, USA) using identical parameters as in previous studies on LPs with naproxen as a drug model (*1*, *2*). Each hard gelatin capsule was filled with the specified pellet equivalent to 25 mg of naproxen. The filled capsules (n = 3) underwent a dissolution test. The chosen dissolution media were HCl buffer solution at pH 1.2 and phosphate buffer solution at pH 7.4, which simulates gastrointestinal fluid without the enzymes. The volume of dissolution medium was 900 mL, maintained at 37.0 ± 0.5 °C and 50 rpm. At set time intervals, the dissolution medium was automatically pumped into the ultraviolet spectrophotometer, and the absorbance of the solution was determined at 271 nm.

Yuksel et al used one-way analysis of variance (ANOVA)-based dependent and independent models to investigate which method is more reliable and discriminative for comparison of dissolution profiles (*31*). They showed that ANOVA-based tests and model-dependent techniques are more discriminative than independent models, such as similarity and difference factor analysis, despite independent models being recommended by the US FDA and implemented in various guidance documents published by the FDA (*32*–*35*). Therefore, the ANOVA test was used in the current study.

RESULTS AND DISCUSSION

Preparation of Naproxen Effervescent Liqui-Pellets

All formulations were successfully made into pellet form. Formulations F-4 (32% $NaHCO_3$) and F-5 (42% $NaHCO_3$) required a relatively higher amount of deionized water (i.e., granulating liquid) than the other formulations. This is because these two formulations have the two highest amounts of $NaHCO_3$ content, consequently a larger amount of total powder admixture; thus, more deionized water is required to obtain a reasonable rheological property of wet mass for successful extrusion. The plastic property is essential to allow for shaping and retaining the desired shape of extrudate. This ideal rheological property is primarily due to moisture in the powder admixture, which has been subjected to much research (*36*–*41*).

The fact that LPs can contain 42% of $NaHCO_3$ in the dosage form total weight is interesting. Such a large amount of functional excipients while maintaining good dosage form size and weight for swallowing would be difficult or impossible with classical liquisolid technology. This is because the liquisolid formulation requires a large amount of carrier and coating material when the liquid load factor (L_f) (i.e., the weight ratio of the liquid medication and the carrier material used in the formulation) is high as 1. Yet, LP formulation F-5 contains 42% of $NaHCO_3$ and the dosage weight is only 231 mg, which shows the promising commercial potential of LP.

Flowability

The flow data reported in Table 2 indicate that all formulations have excellent, excellent-good, or good flow properties. Similar results were also observed in previous flowability studies on LPs (*1*, *2*, *10*), verifying that flowability is not a major issue for LPs as it is for liquisolid formulation. Hence, Spirea's mathematical equation, which determines the amount of API and excipients to be used in maintaining a reasonable flow property, does not apply to LPs (*9*, *38*). Without such a restriction, the formulation design with LPs can be more flexible.

Particle Size Distribution

All LP formulations had a narrow particle size distribution, which falls under 500 µm (Table 3). This suggests that increasing the NaHCO3 content in the formulation does not appear to have an effect on its size. LP size is inherently small, allowing fast gastric emptying similar to liquid, which would expose the weakly acidic naproxen to the more alkaline fluid in the small intestine quicker (*12*). Note that weakly acidic drugs tend to be more soluble in alkaline conditions; hence, the dissolution rate can be enhanced (*43*).

The narrow particle size distribution of LP formulations is ideal for manufacturing, particularly on an industrial

scale. This is due to a low risk of failing the uniformity of the content quality control tests. The probability of nonuniform filling of capsules due to LP size variation is low.

Table 3. Particle Size Distribution for All Formulations

Particle size (µm)	Frequency for Liqui-Pellet formulations (%)					
	Physical mixture pellets	F-1	F-2	F-3	F-4	F-5
250	0	0.21	0.28	0	0	0
500	0.24	96.95	99.47	99.27	99.91	99.95
850	45.21	2.88	0.34	0.68	0.09	0.1
1000	53.95	0	0	0.05	0	0
2000	0.07	0	0	0	0	0

Naproxen Liqui-Pellet formulations contained 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively).

Friability

The friability test results (Table 4) show that all formulations display a good level of robustness. All formulations have less than 1% weight loss after being treated in the friabilator. This is considered an acceptable weight loss for tablets under USP standards. However, at the current time of carrying out the investigation, there is no USP standard for friability test on pellets, thus the tablet standard was adapted.

Table 4. Weight Loss of 3 g of Each Formulation Under Rotational Speed of 25 rpm for 4 min

Formulation	% Weight loss
Physical mixture pellet	0.14
F-1	0.21
F-2	0.05
F-3	0.24
F-4	0.13
F-5	0.14

Naproxen Liqui-Pellet formulations contained 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively).

The LPs in this study use MCC as the carrier material, which has strong bonding within its structure when water is added. This, along with the plastic property that polysorbate 80 contributes, makes LPs resistant to friability. The resistance to friability is ideal to ensure that the integrity of the product is maintained during manufacturing and transportation. It also reduces dusting, which can improve safety for the operator, particularly if potent drugs are being manufactured.

Dissolution Studies

Results from the dissolution studies under an acidic environment (Fig. 2) show a marked increase in drug release rate for F-4 (32% $NaHCO_3$) and F-5 (42% $NaHCO_3$) in comparison to the physical mixture pellet. The cumulative dissolution rates after 2 hours were 72.9% for F-4 and 76.4% for F-5, which is about 13–14 times faster than the physical mixture pellet (5.5%). This shows that NaHCO3 is an effective functional excipient in naproxen LPs for enhanced drug release.

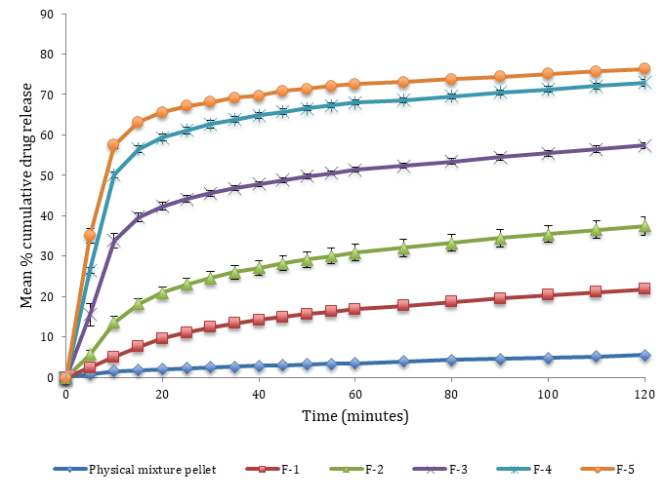

Figure 2. Dissolution profiles of all formulations at pH 1.2. Each capsule contained 25 mg of naproxen. Naproxen Liqui-Pellet formulations contained 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively).

The dissolution profiles at pH 1.2 (Fig. 2) show an overall trend that an increase in $NaHCO_3$ concentration increases the drug release rate quite markedly. The ANOVA test showed that the effect of the concentration of $NaHCO_3$ on drug release was significant ($p < 0.05$). F-5 had a slightly higher dissolution rate than F-4, but the difference was not significant (Tukey's $p > 0.05$). This suggests that there is a limit of $NaHCO_3$ concentration that can cause a noticeable improvement in drug release rate; above this limit, $NaHCO_3$ has less influence on the LP drug dissolution rate. Thus, the 10% increase in $NaHCO_3$ does not seem worthwhile, and 32% $NaHCO_3$ appears sufficient for drug release enhancement.

It is interesting to note that the percentage drug release can be predicted when the concentration of $NaHCO_3$ is plotted against the percentage drug release at 60 min. The results show a high correlation (r^2 0.9951) between these two parameters, as shown in Figure 3. This indicates that the drug release can be predicted well when the concentration of bicarbonate is between 0 and 32%. Because there was no difference in drug release between the 32% (F-4) and 42% (F-5) concentrations, F-5 was excluded when correlation was established.

When comparing the drug dissolution profile of naproxen effervescent LPs in this study to previous studies on naproxen LPs, it can be seen how the incorporation of $NaHCO_3$ can noticeably improve the drug release rate, particularly for F-4 and F-5, where its drug release rate is more superior than earlier naproxen LP formulations (*1*, *2*, *10*). Although F-4 and F-5 have the fastest drug release rate at acidic pH, it is noteworthy to point out that both formulations have yet to be further optimized by taking parameters such as water content and co-solvent content into account. Previous studies by the authors have already shown how these parameters can significantly affect the drug release rate. Hence, despite already obtaining considerable enhancement of drug release rate, the potential of effervescent LP formulations is yet to be realized.

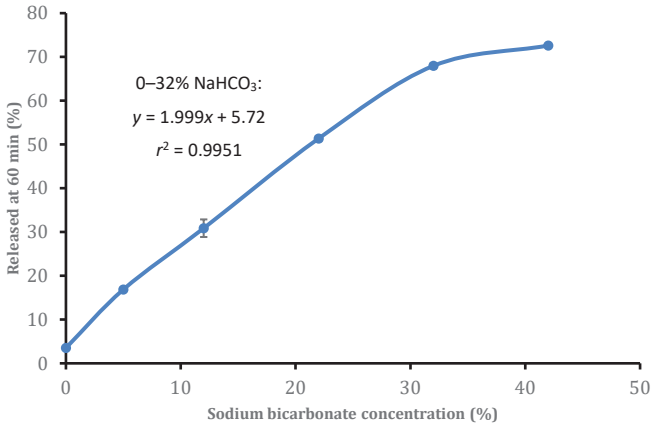

Figure 3. Correlation between $NaHCO_3$ concentration and the percentage drug release obtained in pH 1.2 at 60 min (correlation applies between 0 to 32%).

$NaHCO_3$ has two key mechanisms that promote drug release in naproxen LPs. It is well known that $NaHCO_3$ produces CO_2 gas when in contact with the acidic environment, such as the gastric fluid in the stomach (*28*, *44*). The first drug release enhancement mechanism is due to promotion of disintegration of LPs, owing to the formation of CO_2 gas. The formulation in this study uses MCC as a carrier, and MCC is known to form virtually nondisintegrating pellets via the extrusion-spheronization technique due to the strong bond within its structure (*21–27*). CO_2 gas serves as a mechanical force within the LP to aid disintegration, which consequently results in creating a larger surface area for dissolution. The second key mechanism is that $NaHCO_3$ is an alkalizing agent (*28*). Because naproxen is a weakly acidic drug, $NaHCO_3$ can make the pH at the microenvironment more alkaline, thus improving naproxen solubility, which in turn improves the drug release rate. For APIs that are basic or neutral, this improved solubility may not be present; however, rapid disintegration is still present in the acidic stomach condition. In principle, the use of $NaHCO_3$ excipient seems to be most effective for weakly acidic APIs and may not necessarily be suitable for weakly basic drugs due to possible reduction of solubility. However, the improved disintegration should also be considered.

The dissolution test was also performed for all formulations at pH 7.4 (Fig. 4). The results show drug release rapidly nearing 100% within 20 min for all formulations, which is expected as naproxen is soluble at pH 7.4.

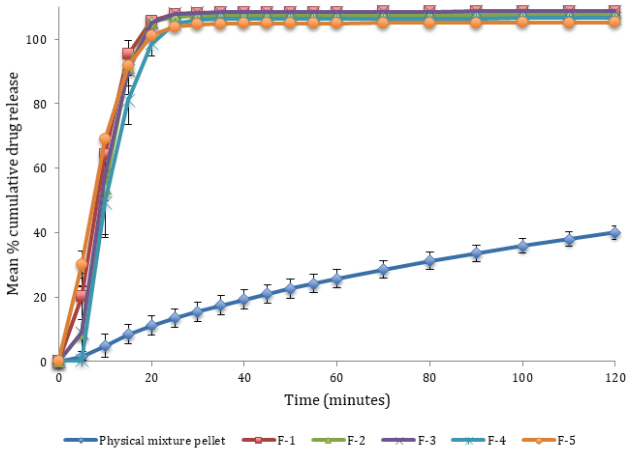

Figure 4. Dissolution profile of all formulations at pH 7.4. Each capsule contained 25 mg of naproxen. Naproxen Liqui-Pellet formulations contained 5%, 12%, 22%, 32%, and 42% w/w $NaHCO_3$ (labeled as F-1, F-2, F-3, F-4, and F-5, respectively).

Overall, this study proves that LPs are indeed a versatile formulation with the ability for flexible modification such as the addition of an effervescent functional excipient. The addition of functional excipients has proven to be effective in the enhancement of dissolution as shown in the results. LPs can incorporate functional excipients because they are capable of achieving a high liquid load factor or high amount of non-volatile liquid vehicle while maintaining excellent/good flow properties. This means there is no need to increase the amount of carrier and coating material to achieve acceptable flow properties, which would otherwise render the high-dose dosage form too bulky for swallowing. With less carrier and coating material needed, there is an option for the addition of functional excipients without making the final dosage form too bulky. Such flexibility to incorporate additional functional excipients in large amounts is difficult or near-impossible to achieve using the classical liquisolid or powdered solution technology.

CONCLUSION

This study proved that it is feasible to embed an

effervescent agent into LP formulation, whilst obtaining excellent or good flow property and yet keeping the overall dosage form small and light enough for swallowing. The incorporation of 42% $NaHCO_3$ in the formulation made the total weight of each capsule unit containing LPs to be only 231 mg. This would have been very difficult or near impossible to achieve with liquisolid technology, particularly in a high-dose drug, where a high liquid load factor would result in a heavy and bulky formulation due to increase carrier and coating material being required, let alone the addition of functional excipients. The dissolution test results show a considerable increase in the drug release rate with $NaHCO_3$, where such formulations are around 14 times faster than a physical mixture pellet after 2 hours. As $NaHCO_3$ concentration increases, so does the drug release rate; however, there is a limit to how much $NaHCO_3$ can be added before its influence on the drug release rate lessens. Therefore, it is imperative to know this limit to balance the weight of capsule and drug release performance into an ideal dosage form. The data from this investigation verifies that the effervescent LP can achieve good robustness and excellent or good flow properties with narrow particle size distribution. Overall, the results support the potential for taking the concept of a liquid API in a solid matrix dosage form in a commercial direction. Future study will include investigating the feasibility of effervescent LPs in high-dose formulation.

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CONFLICTS OF INTEREST

This technology is protected by International patent WO2020/021254 A1 (filed July 24, 2019, published January 30, 2020).

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