

Recent solubility and dissolution enhancement techniques for repaglinide a BCS class II drug: a review

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Abstract

Repaglinide is an oral blood-glucose-lowering drug used to manage type-2 diabetes mellitus by lowering post-prandial glucose by stimulating insulin secretion from pancreatic beta cells.

According to the biopharmaceutical classification system, repaglinide falls under the class II category. For such drugs, limited solubility and poor dissolution rate are the major hurdles to overcome by formulation scientists, as they hinder drug absorption and lead to inadequate therapeutic effects.

Therefore, this review aims to discuss in depth the various approaches investigated in the past five years to improve the solubility and dissolution of orally administered repaglinide: namely, solid dispersion, co-amorphous technology, cyclodextrin complexation, phospholipid complexes and polymeric micelles, nanocrystals, nanosuspensions and nanofibers.

Keywords

solubility enhancement, repaglinide, solid dispersion, nanocrystals, nanofibers, nanosuspension

Introduction

Diabetes mellitus (DM) is a chronic and complex metabolic disorder that has reached epidemic levels globally, representing an important concern: in particular for poorly developed nations, as DM adds to already existing burdens within health care (Olokoba et al. 2012; Standl et al. 2019). Furthermore, the disease has considerable impacts on individuals' functional abilities and quality of life, resulting in substantial morbidity and early mortality (Khan et al. 2020). DM is principally classified into type-1 and type-2, in which the first type is insulin-dependent while the second type is non-insulin-dependent (Alldredge et al. 2013).

Repaglinide (RPG) is a carbamoylmethyl benzoic acid derivative that has one weakly basic ($pK_a = 6.01$) and one weakly acidic ($pK_a = 4.16$) functional groups (Mandić and Gabelica 2006).

RPG is used therapeutically to lower blood glucose in type-2 diabetes after eating by working through stimulating insulin secretion from the pancreas (Hatorp 2002). While the use of some oral antidiabetic agents is associated with adverse events such as hypoglycemia, secondary treatment failure linked to pancreatic beta-cell exhaustion and cardiovascular complications, RPG is devoid of such adverse effects (Natrass and Lauritzen 2000). Moreover, RPG is very useful in individuals with both diabetes and impaired

renal function since the major proportion of RPG is excreted through the bile duct (Guardado-Mendoza et al. 2013).

Despite the advantages mentioned earlier, RPG displays an extremely short half-life, of approximately one hour, in addition to low oral bioavailability of only 45–65% (Hatorp 2002). The bioavailability of drugs given orally depends on the ability of drugs to dissolve in gastrointestinal fluids (GI) and their ability to permeate through the membranes to reach the systemic circulation. Falling into the second class within the biopharmaceutics classification system (BCS), RPG suffers from low aqueous solubility: 34.6 µg/mL at a temperature of 37 °C, while being highly lipophilic ($\log p = 3.97$) (Mandić and Gabelica 2006; Bhanja et al. 2011), meaning that it is characterized by poor solubility, but have an excellent ability to cross membranes, hence, to improve the bioavailability of RPG, it is necessary to increase RPG solubility and/or the drug dissolution rate. Therefore, in the past five years, a range of strategies for enhancing solubility and dissolution properties of orally administered RPG have been assessed, including solid dispersion, co-amorphous technology, cyclodextrin complexation, phospholipid complexes and polymeric micelles, nanocrystals, nanosuspension and nanofibers.

Techniques applied so far for repaglinide solubility enhancement

Solid dispersion

Certainly, solid dispersion stands among the most broadly applied strategies for solubility and dissolution rate enhancement of hydrophobic drugs (Mogal et al. 2012). As stated by Chiou and Riegelman, the term 'solid dispersion system' refers to a dispersion of single or multiple active pharmaceutical ingredients in inert matrices or carriers generated through fusion (through melting), solvent, or a strategy that combines these two approaches (Chiou and Riegelman 1971).

In line with the Noyes-Whitney equation, enhancement of dissolution rates can be expected in these systems since solid dispersion techniques improve drug dispersibility, thus increasing the surface area available for the drug to dissolve. Furthermore, this approach can result in a high-energy state of the drug that largely improves the drug dissolution, such as amorphous, colloidal crystal, or molecular states (Zhang et al. 2018).

Compared to other chemical methods that enhance solubility and dissolution without changing the active target, such as salt formation and prodrug approaches, solid dispersion offers the advantages of being a more applicable approach and easier to produce (Vasconcelos et al. 2007). Solid dispersions can be categorized as follows: the first generation solid dispersion, consisting of low molecular weight crystalline carriers (Kim et al. 2011), whereas in second-generation solid dispersion, the carrier used are amorphous and are considered more effective compared

to the first generation due to their thermodynamic stability (Vasconcelos et al. 2007; Bindhani and Mohapatra 2018).

Furthermore, the design of third-generation systems aims to maximise solubility while preventing altered morphologies that could occur during administration and aging by incorporating carriers that have a surface activity or emulsifying properties (Vasconcelos et al. 2007). Finally, fourth-generation solid dispersion is also referred to as controlled release solid dispersion since the carriers used in this type can be either water-soluble or water-insoluble carriers (Yang et al. 2016; Bindhani and Mohapatra 2018).

Case studies

Yang et al. prepared solid dispersion of RPG through solvent evaporation method using polyethylene glycol 4000 (PEG 4000) as a hydrophilic carrier in three-drug to PEG 4000 ratios (1:1, 1:3 and 1:5). The results of X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) showed that no crystallinity due to RPG existed in the prepared solid dispersions, and RPG was entirely converted into an amorphous state. Fourier transform infrared spectroscopy (FT-IR) demonstrated the presence of intermolecular hydrogen bonding between PEG 4000 and RPG in the solid dispersion. Moreover, further increase in RPG aqueous solubility was observed with increases in PEG 4000 concentration in solid dispersion formulas, and maximum solubility was attained at 1:5 drug: PEG 4000 ratio with an enhancement in the solubility of pure RPG in distilled water was observed from 22.5 ± 5.0 to 235.5 ± 5.0 µg/mL at 37 °C. Based on the in vitro release study carried out in phosphate buffer (pH 7.4), a burst release of between 80% and 86% from the solid dispersion preparations was observed in the first fifteen minutes (Yang et al. 2016).

Nabrawi et al. prepared solid dispersions of RPG containing Polyvinylpyrrolidone K30 (PVP K30), PEG 4000, Hydroxypropyl methylcellulose E5 (HPMC E5), Hydroxypropyl methylcellulose E50 (HPMC E50) at 1:1, 1:2 and 1:4 drug:polymer ratios via solvent evaporation method. These dispersions demonstrated better solubility as well as faster dissolution rates over the tested ratios than the plain drug at pH = 6.8, pH = 1.2 and pH = 5.5. Nabrawi et al. found that the drug to polymer ratio directly affects RPG solubility and dissolution from the solid dispersions; if RPG were used at a higher percentage compared to the carrier, a small amount of RPG crystal would be formed inside the solid dispersion rather than remaining molecularly dispersed thereby decreasing the solubility and release rate of RPG. However, if the carrier percentage was high, it will result in the complete absence of any crystalline structure of RPG and thereby significantly increases RPG's solubility and release rate. Solid dispersion containing PEG 4000 at 1:2 drug to polymer ratio exhibited the most promising results, as it achieved the highest dissolution rate, with burst release of about 75.28 % after 5 minutes in (pH = 6.8) 20% propylene glycol and 20% ethanol at 37 °C \pm 1. The improvement in dissolution rate was attributed to the amorphous nature of solid dispersion, which

was confirmed by DSC, XRPD and scanning electron microscopy (SEM) results (El-Nabarawi et al. 2016).

RPG Solid dispersions in the two previously reported case studies were prepared by solvent evaporation using rotary evaporator. Although there was an improvement in RPG's solubility and dissolution rate, such findings were not supported by *in vivo* study. Moreover, many disadvantages are associated with employing solvent evaporation method using rotary evaporator to prepare solid dispersions, such as residual solvent toxicity which may negatively affect the chemical stability of RPG. In addition to the risk of phase separation and recrystallization of the drug can easily occur during the relatively long drying process (Vo et al. 2013). Accordingly, further studies are needed to evaluate the possibility of scaling up this technique using a scalable industrial process such as spray drying or fluid bed drying, and further stability studies should be carried to establish the optimum type, concentration and molecular weight of the polymers used for stabilization of RPG solid dispersions.

Spray drying

Spray drying refers to a one-step technique through which suspensions, emulsions, or solutions are transformed to dry powder by passing an atomized spray of such liquids through a high-temperature gaseous medium (Broadhead et al. 1992). Spray drying is an efficient technique to produce solid dispersion as it allows extremely rapid solvent evaporation, which leads to a fast transformation of the drug-carrier solution to solid drug-carrier particles. The accelerated evaporation of the solvent causes the viscosity to rise rapidly, with the drug becoming kinetically trapped within the matrix of the carrier (Sosnik and Seremeta 2015).

Spray drying involves a pump system that transfers carrier and drug solution to a nozzle that atomises the solution into fine droplets. The rapid evaporation of the solvent impacts the resulting particles in terms of density, size and morphology, and these characteristics are also influenced by the formulation composition and the process parameters (Vo et al. 2013). Optimization of the parameters involved in spray drying is therefore highly significant, including inlet and outlet temperature, atomization rate, the rate of feed transfer and on /off spraying periods (Shendge and Sayyad 2013).

A number of benefits are attributed to spray drying: it is a fast and one-step production method; it increases drug solubility and dissolution rates; it is applicable for treating material regardless of whether it is sensitive to heat; and it is low cost and offers substantial reductions in the time required to process larger biomolecules in comparison with lyophilization (Van Eerdenbrugh and Taylor 2011; Paudel et al. 2013).

Case study

Varshosaz et al. enhanced RPG solubility by employing spray drying techniques for solid dispersions preparation using various carrier materials: Eudragit E100, hydroxyl propyl cellulose Mw 80000 (HPC Mw 80000) and poly vi-

nyl pyrrolidone K30 (PVP K30). In order to prepare the physical mixture, RPG was blended separately with each polymer at 1:1, 1:3 and 1:5 drug to polymer ratios, then RPG was dissolved separately with each polymer (Eudragit E100, PVP and HPC) in ethanol, using the three ratios described above for each. Afterward, spray-drying of the resulted solutions was performed with the laboratory scale Büchi B290 spray drier (Büchi, Labortechnik AG, Flawil, Switzerland). Spray-dried dispersions containing Eudragit E100 at 1:3 drug:polymer ratio gave the greatest solubility enhancement, at 100-fold with a value of $2370.4 \pm 80.8 \mu\text{g/mL}$ in phosphate buffer (pH = 5). Nevertheless, the release profile in phosphate buffer (pH = 5) at sink condition for all spray-dried dispersion and physical mixture at a 1:3 drug:polymer ratio showed comparable 100% RPG release, by the 5-minute time point: thus, to compare the release profiles, a corresponding *in vitro* study of drug release was conducted in phosphate buffer (pH = 5) at non-sink condition. Under such conditions, spray-dried dispersions containing Eudragit E100 at 1:3 ratio showed the highest dissolution rate, of $100\% \pm 6.32\%$ after 5 minutes; therefore, Eudragit E100 at 1:3 ratio was selected as the optimum carrier for the preparation of RPG spray-dried solid dispersions and was subjected to further testing. DSC analysis showed a remarkable increase in RPG melting point, probably due to strong hydrogen bonds between RPG and Eudragit E100, whereas no clear interaction was identified between the RPG and Eudragit E100 based on FT-IR spectra. Additionally, the enhancement of RPG dissolution was attributed to the conversion of RPG from crystalline to amorphous form, as confirmed by XRPD spectra. Furthermore, physical stability for the optimized spray-dried dispersion was confirmed since there was no considerable change in dissolution profiles at the time of preparation and six months after storage at ambient temperature. Based on the results of *in vivo* study conducted in diabetic rats, the optimized spray-dried RPG dispersion containing Eudragit E100 significantly decreased ($p < 0.05$) the glucose level in blood at 30 and 60 minutes and during the 8 hours of getting blood samples in comparison with RPG powder (Varshosaz et al. 2017). Based on the finding of this study, generating RPG solid dispersions containing Eudragit E100 by spray drying approach proved to be a successful approach that produced a stable solid dispersion with improved solubility, dissolution and antidiabetic effect compared to pure RPG. Moreover, using spray drying technology can pave the way for efficient and robust large-scale production (Patel et al. 2015).

Cyclodextrin inclusion complex

Cyclodextrins (CDs) form a group of non-hygroscopic crystalline substances composed of cyclic oligosaccharides formed by 6 (α CD), 7 (β CD) or 8 (γ CD) (α -1,4)-linked D-glucopyranose units (Davis and Brewster 2004). Since each glucopyranose unit has a chair structure, the CD molecule has a cone-shaped structure with the hydroxy groups extending from the outside, making cyclodextrin

a very hydrophilic molecule externally but hydrophobic internally (Khadka et al. 2014).

Cyclodextrin has a number of benefits, including greater solubility, bioavailability, stability, and prevention of incompatibility (Nekkanti et al. 2009). Alpha cyclodextrins have a tendency to form an inclusion complex with aliphatic hydrocarbons, whereas beta cyclodextrins tend to form inclusion complexes with aromatic molecules; beta cyclodextrins are in more frequent use because they are more water-soluble compared to the other types of cyclodextrin and due to their accessibility and affordability. On the other hand, gamma cyclodextrins form inclusion complexes with bulkier groups (Davis and Brewster 2004).

Preparation of cyclodextrin can be done through various techniques, including kneading, grinding, co-precipitation, solvent evaporation, spray drying, freeze drying, neutralization precipitation, super-critical anti-solvent method and microwave irradiation (Wen et al. 2004).

Case study

Vakani et al. explored the potential of 2-hydroxypropyl-beta-cyclodextrin (HP β CD) to enhance oral-route RPG delivery with and without auxiliary substances such as L-arginine (ARG) and polyvinyl pyrrolidone-K30 (PVP). Formulations of RPG-HP β CD as an equimolar binary system and RPG-HP β CD-ARG and RPG-HP β CD-PVP as equimolar ternary systems were performed using constituents that had been sieved. A 1:1 M stoichiometric ratio was employed with the binary system. The ternary system with ARG was prepared in equimolar ratio with the binary system (1:1:1 M), while the ternary system containing PVP was prepared by adding PVP in an optimized concentration of 0.7 % w/w to the equimolar binary system. For the preparation of cyclodextrin complexes, three different methods were utilized, namely: physical mixing by geometric mixing of each component; kneading by incorporating binder solution within a physical mixture and co-evaporation performed using rotary evaporator. The solubilizing efficiency data, calculated as the ratio of RPG solubility in 15 mM aqueous solution of cyclodextrin to RPG solubility in water, demonstrated that when only HP β CD was used, this improved the RPG's solubility 5.38-fold. However, when ARG and PVP were present in the formulation, solubility was raised by 95.74 and 35.35-fold, respectively. Overall, the ternary complex with ARG prepared by co-evaporation method showed a maximum increase in the drug's water solubility (17.90 ± 0.493 mg/mL) and the fastest dissolution rate, with $99.64 \pm 2.33\%$ drug release in phosphate buffer (pH 6.8) at five minutes, indicating that the drug had been amorphized and entrapped completely in HP β CD, as identified from the DSC and XRPD results. Moreover, Vakani et al. attributed the improvement in solubility and dissolution to altered particle shape, reduced particle size and close contact between HP β CD and ARG in the complexes as indicated by SEM images (Vakani et al. 2015).

It is clear from the study conducted by Vakani et al. that the RPG-HP β CD-ARG system prepared by co-evapora-

tion method remarkably enhanced RPG aqueous solubility, achieved the fastest dissolution rate with $99.64 \pm 2.33\%$ drug release at pH 6.8. Nevertheless, such results were not supported by in vivo study, and the stability of the complex was not investigated. Additionally, performing co-evaporation by using rotary evaporator is not a suitable method for adaptation to a commercial process.

Coamorphization

Amorphization is among the most efficient approaches to improve solubility and bioavailability of pharmaceutical substances with poor aqueous solubility (Murdande et al. 2010). On the other hand, due to their lower thermodynamic stability and their potential to recrystallize while they are being processed or stored or in dissolution, the approach's pharmaceutical applications in the formulation and drug development are limited (Kaushal et al. 2004). Among the most promising and extensively used amorphization techniques for enhancing aqueous solubility are solid molecular dispersions and coamorphous dispersions (Ojarinta et al. 2017). In polymeric solid dispersions, drugs are integrated into glass polymeric matrix as molecular dispersion, and their stability comes from the molecules being physically separate inside the polymeric chains (Karagianni et al. 2018). Nevertheless, polymeric solid dispersions present many disadvantages: for example, the hygroscopic nature of most polymers leads to plasticized systems, consequently increasing the active pharmaceutical ingredients' ability to move at the molecular level and the tendency of the drug to recrystallize. Another disadvantage is the large volume of drug dosage form because of poor drug solubility in polymers (Chavan et al. 2016).

On the other hand, coamorphous systems that can be prepared by mixing of co-formers with low molecular weight offer various advantages over polymeric solid dispersions, such as the lesser quantity of co-former required for system stability and elimination of hygroscopic problems related to polymeric solid dispersion systems (Dengale et al. 2016).

Coamorphous systems are classified as either drug-excipient or drug-drug coamorphous systems. The ability of such systems to remain physically stable is due to hydrogen bonding and other interactions between molecules, such as bi-bi and ionic interactions (Zhu et al. 2018). Amino acids and sugars such as mannitol, lactose and trehalose are used for the possibility they offer of stabilizing coamorphous systems (Descamps et al. 2007; Laitinen et al. 2014). Various methods are employed for coamorphous systems preparation, including quenching, ball melting and solvent evaporation (Dengale et al. 2016).

Case study

A coamorphous drug delivery system containing RPG-tadalafil was prepared by Su et al. via solvent evaporation method, where RPG-tadalafil was used in a ratio of 1:1. DSC and XRPD verified that the mixture had been

amorphous by identifying a single value for glass transition temperature at 73.1 °C instead of endothermic melting peaks corresponding to the two drugs; and the disappearance of crystallinity. Although equilibrium solubility was not increased in either of the drugs following coamorphization, in distilled water, each drug within the coamorphous system showed a substantial intrinsic dissolution rate increase of 1.5–3-fold compared to their crystalline forms and physical mixtures. Tadalafil in the crystalline form displayed a linear release profile and had an intrinsic dissolution rate (IDR) of $3.35 \times 10^{-4} \text{ mg cm}^{-2} \text{ min}^{-1}$, while the dissolution profile of tadalafil in coamorphous was biphasic and had 2 IDRs, with $10.20 \times 10^{-4} \text{ mg cm}^{-2} \text{ min}^{-1}$ being the IDR for the first twenty minutes, followed by $3.66 \times 10^{-4} \text{ mg cm}^{-2} \text{ min}^{-1}$ for the subsequent 70-minute period. In addition, crystalline RPG exhibited a single linear release profile with $4.97 \times 10^{-3} \text{ mg cm}^{-2} \text{ min}^{-1}$ IDR. In contrast the IDR of RPG within the coamorphous system was 1.48-fold higher than that of crystalline RPG, with a $7.36 \times 10^{-3} \text{ mg cm}^{-2} \text{ min}^{-1}$ IDR. Finally, the coamorphous system was more physically stable than amorphous RPG alone when exposed to mechanical stress simulating normal compression forces of oral tablets (75 MPa – 375 MPa), long-term storage condition (at 25 °C/60% relative humidity up to 60 days) and accelerated storage conditions (at 40 °C/75% relative humidity for 60 days) (Su et al. 2020). In addition to improving solubility and dissolution behaviour of RPG, RPG-tadalafil coamorphous system offered an additional advantage over polymeric solid dispersions in terms of physical stability; however, these improvements are not confirmed by an in-vivo study, additionally, using rotary evaporation in formulating RPG-tadalafil coamorphous system is not readily scalable method since solvent volumes become too large, leading to very long evaporation times.

Phospholipids complexes and polymeric micelles

Among the various methods that could improve the solubility and permeability of drugs with low water solubility is the complexation of such drugs with phospholipids (Loftsson 2017). Chemically, phospholipids are composed of a glycerol backbone esterified with fatty acids in positions one and two, and phosphate in position three (Varelis et al. 2018). Due to their amphiphilic nature, phospholipids are capable of self-assembly upon contact with aqueous media to form particles at the nanoscale, between 20 and 60 nm, with a round form and hydrophobic centre, in which substantial quantities of a low water-solubility drug can be solubilized (Pathan and Bhandari 2011).

A unique feature of phospholipids as drug carriers is their ability to penetrate across the cell membrane of living cells with no impact on the cell's lipid bilayer since they are naturally present as a significant constituent within the mammalian cellular membrane (Guo et al. 2014). Additionally, phospholipids can lower the interfacial tension at the interface where gastrointestinal fluids

meet the developed system, thus, allowing the transport of active drug molecules across different cell membranes (Semalty et al. 2009).

Micelles are colloidal-sized clusters that have a hydrophobic centre but a hydrophilic surface. Micelles are formed when there is an accumulation of surfactant or amphiphilic molecules within a solution over a certain level, termed the critical micelle concentration (Mall et al. 1996). Depending upon drug hydrophobicity, type of surfactant and solution conditions, surfactant micelles can increase the water solubility of a low water soluble drug through the incorporation of such drug into the hydrophobic centre of micelles, interacting with the head groups on the surface of the micelle, and orientation or incorporation of the drug at an intermediate location in the palisade layer (Mall et al. 1996).

Comparable to micelles based on conventional surfactants, polymeric micelles display separate block domains of hydrophobicity and hydrophilicity and are composed of amphiphilic block copolymers that can solubilize poorly water-soluble drugs (Torchilin 2001). However, due to the capacity to interact hydrophobically at many locations inside the polymer molecule, the polymeric micelle has high kinetic stability (Yokoyama et al. 1993). In addition, such systems cannot be simply dissociated in vivo since amphiphilic co-polymers display critical micellar concentration (CMC) of as little as 10^{-6} - 10^{-7} M (La et al. 1996; Kabanov et al. 2002).

Interestingly, non-ionic poloxamers, a block copolymer that forms polymeric micelles, can interact with phospholipids in an aqueous solution, and this promotes structural stabilization due to reduced free energy and surface tensions (Mata et al. 2005).

Case study

Kassem et al. explored micelle enrichment with RPG-phospholipid complexes as a potential drug delivery system that could facilitate oral absorption of RPG. The authors successfully prepared four RPG phospholipid complexes (RPG-PLC) using solvent evaporation method at the following RPG and phospholipid (PL) molar ratios: 1:0.5, 1:1, 1:2 and 1:3 w/w. RPG-PLC complex formation was verified by FT-IR, DSC and XRPD techniques. Subsequently, poloxamer 188 (P188) was used as a surfactant to prepare RPG-PLC enriched micelles (RPG-PLC-Ms). Solvent evaporation was used to prepare eight RPG-PLC-Ms, at two RPG-PLC complex/surfactant weight ratios (1:1 and 1:2). The potential for RPG-PLC to be used in the fabrication of micelles was evident from the high encapsulation efficiency of all RPG-PLC-Ms, ranging from 93.81 to 99.38% at various drug loading values; 5.23–27.17%. The authors indicated that the micelles might offer the advantages of being easily absorbed and more stable based on offering smaller particles of (500.61–665.32 nm) of monodisperse distribution with higher zeta potential (less than –29.8 mV). Dissolution of RPG from RPG-PLC-Ms systems was explored using the dialysis bag diffusion me-

thod. Interestingly, following enrichment with RPG-PLC, the micelles displayed a pH-dependent release profile, with slower release at pH = 1.2, whereas, at pH = 6.8, the drug was released more rapidly, attaining as much as 99.05% compared to free RPG, which exhibited a percentage release of only 17.02% after 24 hours. Additionally, it was observed that the percentage release of RPG increased as the concentration of phospholipids increased at the same surfactant/complex ratio due to the amphiphilic nature of phospholipids that led to increased solubilization efficiency of the complex.

Oral antidiabetic effect of two optimized RG-PLC-M formulations with the smallest particle size, poly dispersibility index and highest zeta potential values, namely; RG-PLC-M2 (composed of 37.6 mg RPG, 62.4 mg PL, 100 mg P188, 1:1 RPG/PL and 1:1 RPG-PLC/P188) and RG-PLC-M6 (composed of 25.1 mg RPG, 41.6 mg PL, 133.3 mg P188, 1:1 RPG/PL and 1:2 RPG-PLC/P188), were evaluated in an alloxan-induced diabetic rat model, in contrast to RG marketed tablets both formulations depicted normal blood glucose, serum malondialdehyde and insulin levels as well as an improved lipid profile after seven days of daily oral treatment (Kassem et al. 2017). Unfortunately, despite excellent RPG release at pH 6.8, enhanced absorption and improved oral antidiabetic effect offered by RPG phospholipid complexes enriched micelles, the solvent evaporation method used to prepare RPG-PLC-Ms is not suitable for adaptation to a commercial process since it requires large surface areas and heat transfer (Duong et al. 2014).

Nanocrystals

Nanocrystals can be used as carrier-free nanoparticles formed solely from the pharmaceutical agent with a diameter in the nano-sized range (Müller et al. 2006). Due to the high surface to mass ratio, nanocrystals possess interesting features, including enhancement in dissolution velocity, increased interactions with surfaces, and improved saturation solubility since dissolution pressure is increased (Buckton and Beezer 1992; Mosharraf and Nyström 1995). Nanocrystals are considered superior carriers over other types of traditional nanocarriers because of their nearly 100% drug loading, physical stability and relative ease of production (Lu et al. 2016).

Nanocrystals can be prepared by top-down techniques through reducing the size of a large drug crystal and by bottom-up approaches by aggregating molecules to form nanocrystals (Gao et al. 2015; Roberts et al. 2017).

Case studies

Rahul Gadadare et al. employed both bottom-up (anti-solvent precipitation-ultrasonication) and top-down (wet media milling) approaches to prepare RPG nanocrystals. Findings demonstrated that the anti-solvent precipitation ultrasonication produced smaller crystals on average than the top-down approach. However, it was found that nanocrystal dispersions fabricated through this approach had

lower stability compared to those produced through the top-down approach at the same stabilizer concentration. Therefore, in order to inhibit the growth in particles during storage, which occurs based on Ostwald ripening, further studies were carried out using RPG nanocrystals produced through wet milling which contained Soluplus (SLPS) (TD-A) as a stabilizer and wet-milling RPG nanocrystals formulated with SLPS and Kolliphor E-TPGS as oral absorption enhancer (TD-B). Based on DSC thermograms and XRPD diffractograms, the wet media milling process did not have an impact on the crystalline state of the drug, as the crystalline form of RPG was conserved in all types of nanocrystals. Saturation solubility for pure RPG microcrystals in distilled water (12.02 µg/mL) improved by approximately 19.86-fold in comparison to TD-A and 25.67-fold in comparison to TD-B nanocrystals. Only 32.88 ± 4.36% release of RPG from pure RPG microcrystals occurred across 120 minutes in distilled water, while cumulative dissolution at fifteen minutes for TD-A nanocrystals was 80.38±6.21 (%±SD) and for TD-B was 90.80 ± 4.53 (% ± SD). In vitro dissolution study was conducted in fasted state simulated gastric fluid at pH 1.6 (FaSSGF) as well as in fed state simulated gastric fluid (FeSSGF) of pH 5.0, in either case, pure RPG microcrystals dissolution did not exceed 50% across 120 minutes. Additionally, for the pure drug microcrystals, the cumulative percentage of dissolution measured was 13.05% less in FeSSGF than in FaSSGF. Conversely, both TD-A and TD-B nanocrystals showed more than 60% dissolution after 5 minutes with negligible variation in FeSSGF and FaSSGF. Based on the in vivo pharmacokinetic study carried out in fed and fasted state using Wistar rats, approximately 10 (TD-A) and 15 (TD-B)-fold improvements in the oral bioavailability of nanocrystals was observed regardless of the fasted/fed state in comparison to pure RPG. Additionally, oral hypoglycaemic activity was assessed in streptozotocin-induced diabetic rats, where (TD-A) and (TD-B) formulations demonstrated significant ($p < 0.001$) hypoglycaemic activity with an onset of action of less than 30 minutes and up to 8 hours duration of action compared to pure RPG which had a slower onset of action (after 60 minutes) and shorter duration of action lasting up to 4 hours only. Finally, both nanocrystal formulations showed insignificant ($p > 0.05$) growth of crystal size and ZP throughout the stability period of 90 days at 25 °C/60% RH and 40 °C/75% RH (Gadadare et al. 2015). Besides improving RPG solubility, release, bioavailability and hypoglycaemic activity of RPG, engineering RPG nanocrystals using wet media milling offered other interesting advantages such as reducing the influence of food on RPG oral absorption, overcoming the potential stability problems of nanocrystals through steric stabilization with SLPS, additionally, particles produced by the above method has a potential to be introduced into the market since wet milling is an industrially feasible scalable method (Malamatari et al. 2018).

A nanocrystal formulation of RPG was effectively prepared by Gajanan Shinde et al. by high-pressure homogenization using a Taguchi design to optimize the various formulation variables. The optimized parameters were as

follows: the polymer type was PEG 4000, at 2.25% concentration, with ten cycles and 1500 BAR homogenization pressure. The formation of nanocrystal drug particles was confirmed by SEM images of the lyophilized optimized batch. DSC thermogram indicated minimal crystalline shape alteration physically, and this was attributed to PEG 4000 presence. The optimized batch was found to have the required sized particles, of 187 ± 5.09 nm, as well as -29.4 ± 1.00 mv zeta potential, a 0.248 ± 0.04 polydispersity index and enhanced in vitro drug release, with 80.58% of RPG released in 0.1 N HCl media within 180 minutes. Following this, a stability study was run at three conditions ($5^\circ\text{C} \pm 3^\circ\text{C}$, $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \pm 5\%$ relative humidity, $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\%$ relative humidity) according to the ICH stability guideline, over three months, and did not result in significant changes to zeta potential and size of particles (Shinde et al. 2015). High-pressure homogenization (HPH) is a widely used approach for the preparation of nanocrystals in the pharmaceutical industry since it is easy to scale up and produce high-quality products (Möschwitzer 2013); in this study, such technique improved the in vitro release of RPG at pH 1.2, however, further release experiments should be conducted at additional pH for example at (pH = 6.8) to simulate the pH evolution of the GIT, besides that, enhanced dissolution of nanocrystals should be confirmed in vivo.

Nanosuspension

Nanosuspensions are liquid dispersions consisting of particles of pharmaceutical agents in the submicron range stabilized by appropriate surfactants or polymers. Nanosuspensions can be applied to deliver insoluble, high melting point agents in either oil or water, as such agents are made more soluble in nanosuspensions due to decreased particle sizes that consequently increase the surface area (Müller et al. 2011).

The advantages offered by nanosuspensions over other nanoparticles include higher drug loading, lower concentration of surfactants and avoiding the need for co-solvents which may cause toxicity, in addition to the feasibility of scale-up (Rabinow 2004).

The major processes employed to engineer stable nanosuspension include top-down, bottom-up and combined approaches. Top-down approach technology includes media milling and high-pressure homogenization, while bottom-up techniques involve precipitation, such as in anti-solvent precipitation, precipitation under sonication as well as flash nanoprecipitation. Combination approaches use firstly bottom-up techniques and then top-down techniques (Lakshmi and Kumar 2010; Zhang et al. 2017).

Case studies

Chandrudu prepared seven formulations of RPG nanosuspension with varied concentrations of surfactants (Lutrol F68 and Tween 80) using the solvent evaporation method. In vitro testing in phosphate buffer (pH 1.2) was used to

evaluate different formulas, among which were formula F4, composed of 8 mg RPG, 6 mL methanol, 0.25% w/v Lutrol F 68, 2 mL Tween 80 and 20 mL aqueous solvent, showed the highest % drug release of 98.08% after 2 hours. In contrast, formula F3, composed of 8 mg RPG, 6 mL methanol, 0.75% w/v Lutrol F 68, 1 mL Tween 80 and 20 mL aqueous solvent, exhibited the lowest % drug release of 78.941% after 2 hours. Accordingly, a stability study at 4°C , room temperature (29°C), ($45^\circ\text{C} \pm 2^\circ\text{C}$) and 75% relative humidity (RH) was performed for F4, and the results of the stability study conducted indicated that there was a reduction in drug content of RPG when stored at $45^\circ\text{C} \pm 2^\circ\text{C} / 75\%$ RH (Chandrudu 2019). Although RPG nanosuspension prepared by Chandrudu improved RPG release at pH 1.2, several issues need attention, including; the instability of the nanoparticles at $45^\circ\text{C} \pm 2^\circ\text{C} / 75\%$ RH, conducting another release experiment at pH 6.8, linking release experiment data to bioavailability study additionally the simple solvent evaporation method used is associated with possible environmental hazards and residual toxicity of methanol (Yadollahi et al. 2015).

Nanofibers

Nanofibers are ultra-fine threads or filaments with diameters from a few nanometres to 1000 nm and a length that is not necessarily small but instead determined according to the manufacturer's purpose (Alubaidy et al. 2013). Nanofibers can be categorized according to their size, which is determined by utilizing certain devices to measure diameter, length, or both, and based on morphology and construction, to form three types of structures: core-shell, hollow and porous nanofibers (Tolochko 2009; Khajavi and Abbasipour 2012).

Nanofibers are one of the promising nanoformulations to improve dissolution rates and solubility of poorly water soluble drugs, owing to the distinctive characteristics which these nanofibers have, including their high surface area to volume ratio, high porosity, small pore size in addition to their ability in converting crystalline drugs into an amorphous form (Vrbata et al. 2014; Akhgari et al. 2017).

A limited number of techniques are applicable for producing nanofibers. Generally, production can be carried out through electrospinning (Goonoo et al. 2014), self-assembly (Hartgerink et al. 2001), phase separation (Gupte and Ma 2012) and template synthesis (Wang et al. 2010).

Case study

To improve apparent solubility and dissolution rate in drugs with low aqueous solubility, Thakkar et al. prepared nanofibrous oro-dispersible films using electrospinning technique, with RPG as the poorly water-soluble model drug and a polymeric composite made from polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) polymers as the filament-forming matrix. The use of a PVA-PVP blend instead of PVA alone was based on Huang et al.'s findings, indicating that the blend was mechanically stronger than PVA alone (Huang et al. 2017). To obtain nanofibers with

no beading, the optimized composition for PVA and PVP was 7.5 and 10% w/v, respectively. Moreover, 25 kV is adjusted to obtain homogeneous morphology at flows of 0.5 mL/h and tip to collector distance of 20 cm. Additionally, RPG was added to a polymeric solution of PVA and PVP and stirred for 30 minutes, and the resultant nanofibrous film was vacuum dried for two days. To investigate the potential benefits of nanofibers, a comparison was made to a conventional film preparation approach: thus, the same concentrations and processes were applied to prepare casted films. RPG's physical and chemical compatibility with both polymers and the polymeric blend were concluded based on DSC thermogram and FTIR spectra, respectively. SEM images for nanofibers showed smooth and beadless surface morphology with an average 600–800 nm diameter. When comparing with casted film, electrospun nanofibers had a total elongation of around $216.6 \pm 18.9\%$, while casted film's total elongation was around $31.1 \pm 8.5\%$. Moreover, the nanofibers were more elastic than casted film, since Young's modulus in respect to nanofibers and casted films was 0.7 ± 0.1 MPa and 148 ± 22.5 MPa, respectively. On the one hand, DSC analysis found the polymer to be in crystalline form, as evident by the retention of melting endotherms across casted film and nanofiber samples. By contrast, RPG was in an amorphous form which was attributed to the presence of hydrophilic polymers. In phosphate buffer (pH 6.7), nanofibers exhibited the highest increase in drug release of approximately 90% within 10 minutes, followed by casted films with 73% drug release within the same time frame. In comparison, for the pure RPG, just 10% was released within that time period. The possible reason for better release of both formulations is attributed to the use of hydrophilic polymers, which imparted high wettability since complete wetting of nanofibers using phosphate buffer (pH 6.7) as wetting media was observed in 30 seconds. In contrast, the casted film was wetted in 2 minutes time period. Additionally, the higher release from nanofibers is due to the enhanced surface area of aligned fibers in the nanometer range and the highly porous nature of nanofibers compared to casted film. The improved release of RPG led to faster absorption and consequently improved the bioavailability of RPG, as evident by in vivo study conducted on Sprague Dawley rats, in which nanofibers and casted films significantly decreased glucose levels compared to the pure drug in 30–120 minutes following single-dose administration (Thakkar et al.

2019). The electrospinning approach used by Thakkar et al. is considered a favourable technique for large-scale production of nanofibers as it is a practical approach; also the setup is not time-consuming nor expensive (Goonoo et al. 2014). Moreover, the nanofibers produced exhibited an enhanced drug release, improved bioavailability and significantly decreased glucose level compared to pure RPG; however, there was insufficient information regarding the stability of RPG nanofibers.

Conclusion

For orally administered drugs to exert a pharmacological response, they must achieve the desired concentration in systemic circulation by initially dissolving in gastrointestinal fluid before permeating the gastrointestinal membrane and entering the systemic circulation. Therefore, for orally administered drugs, solubility is considered a critical factor in formulation development.

This article has provided a comprehensive overview of the literature on various solubility and dissolution enhancement techniques that have been applied to the poorly water-soluble drug RPG, including solid dispersion, co-amorphous technology, cyclodextrin complexation, phospholipid complexes and polymeric micelles, nanocrystals, nanosuspension and nanofibers. All these methods successfully improved RPG solubility and dissolution to some extent or another, however only the following case studies confirmed these findings in vivo: generating RPG solid dispersions containing Eudragit E100 by spray drying approach, engineering RPG nanocrystals using wet media milling, producing nanofibers by electrospinning method and formulating RPG phospholipid complexes enriched micelles. Moreover, the systems produced by the approaches mentioned above can be introduced into the market since such methods are feasible and scalable.

However, preparing RPG drug delivery systems using RPG solid dispersions containing PEG 4000, RPG-HP β CD-ARG system, RPG-tadalafil coamorphous system, RPG nanosuspension and RPG phospholipid complexes enriched micelles is associated with poor industrial applicability due to the difficulty in scaling up since all these approaches prepared RPG formulations via solvent evaporation method using rotary evaporator.

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