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Original article

Directly compressed rosuvastatin calcium tablets that offer hydrotropic and micellar solubilization for improved dissolution rate and extent of drug release

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ABSTRACT

The objective was to use caffeine and Soluplus® to improve the dissolution rate and to maintain a concentration of BCS Class II rosuvastatin calcium that exceeds its solubility. Caffeine and Soluplus® together substantially improved the dissolution rate and the extent of rosuvastatin release. Formulations for direct compression tablets included Formulation F1, a control with drug but with neither caffeine nor Soluplus® present; F2 with drug-caffeine complex; F3 with drug and Soluplus® and F4 with drug-caffeine complex and Soluplus®. Each formulation blend provided satisfactory flow properties. Tablets were comparable in mass, hardness and friability. A marked decrease in disintegration time occurred when the hydrotropic or micellar agent was included in the formulation. Assay (98–100%) and content uniformity (99–100%) results met requirements. Release studies in pH 1.2, 6.6, and 6.8 buffers revealed the superiority of F4. At 45 min sampling time, F3 and F4 tablets each provided a cumulative drug release greater than 70% in each medium. F2 tablets exhibited compliance to official standards in pH 6.6 and 6.8 buffers but not in pH 1.2 buffer, whereas tablets based on F1 failed in each medium. Two-factor ANOVA of the release data revealed a statistical difference across the four formulations in each release medium. Pairwise comparison of release profiles demonstrated that, of the four formulations, F4 provided the most effectively enhanced dissolution rate, improvement to the extent of drug release and support of a concentration higher than the solubility of rosuvastatin calcium.

1. Introduction

Approximately 40% of the drugs in the market and 90% of the drugs in the development stage are considered poorly soluble in water (Fridgeirsdottir et al., 2016). New drug development generally fails due to the poor solubility of the drug candidate that oftentimes leads to low bioavailability (Kalepu and Nekkanti, 2015) and ultimately therapeutic failure (Liu, 2018). Drug permeability is acknowledged as the second important property that affects oral bioavailability (Stegemann et al., 2007). The emerging trends in Combinatorial Chemistry and drug design have led to the development of drug candidates with greater lipophilicity, higher molecular weight and the resultant poor solubility in water leading to problems with poor oral absorption (Shekhawat and Pokharker, 2017; Carr and Hann, 2002; Lipinski, 2000).

According to "The Biopharmaceutics Classification System (BCS) Guidance from the Food and Drug Administration" (U.S. Food & Drug Administration, 2016), a drug is considered highly soluble when the highest dose administered is soluble in 250 ml or less of aqueous media over the pH range 1.0–7.5. A drug is considered highly permeable when the extent of intestinal absorption is

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determined to be 90% or higher, based on mass-balance or in comparison to an intravenous reference dose. The Biopharmaceutics Classification System (Amidon et al., 1995) has provided a scientific framework for correlating *in vitro* drug dissolution with *in vivo* bioavailability (Shargel et al., 2012). Drugs have been divided into four classes based on their solubility and permeability characteristics. Those drugs that demonstrate low solubility and high permeability appear in Class II. For these drugs, poor solubility is a major obstacle in their formulation and product development (Yasir et al., 2010). Poor solubility limits drug dissolution and absorption rates. However, high permeability offers advantages that might compensate to some extent for the disadvantages stemming from low solubility. For this reason, researchers have focused their attention on this class of drugs in an attempt to improve their oral bioavailability by enhancing the concentration and dissolution rate of these drugs using different approaches (Shekhawat and Pokharker, 2017; Kumar and Anil, 2013; Kumar and Singh, 2013; Onoue et al., 2012; Urbanetz, 2006).

Rosuvastatin calcium (Fig. 1a), a BCS Class II drug, is used to reduce LDL cholesterol, apolipoprotein B and triglycerides, and to increase HDL cholesterol in the management of hyperlipidaemia as well as in patients with homozygous familial hypercholesterolaemia. It may be used to reduce the progression of atherosclerosis and for the primary prevention of cardiovascular disease (Sweetman, 2009; Nissen et al., 2006; Lennernas and Fager, 1997). Due to its low solubility in water, reported as 0.33 mg/ml (Alshora et al., 2016; Kulkarni et al., 2015), rosuvastatin exhibits poor solubility in gastrointestinal fluids and, with extensive first-pass metabolism, its oral bioavailability is limited to about 20% (Rohini et al., 2014; Scott et al., 2004).

In several published studies, formulation scientists have developed products that are able to improve the dissolution rate and oral bioavailability of rosuvastatin, but with some disadvantages. As with many poorly soluble drugs, complexation with cyclodextrin has been pursued to provide a drug containing-complex within an aqueous medium that can hold the rosuvastatin in the core,

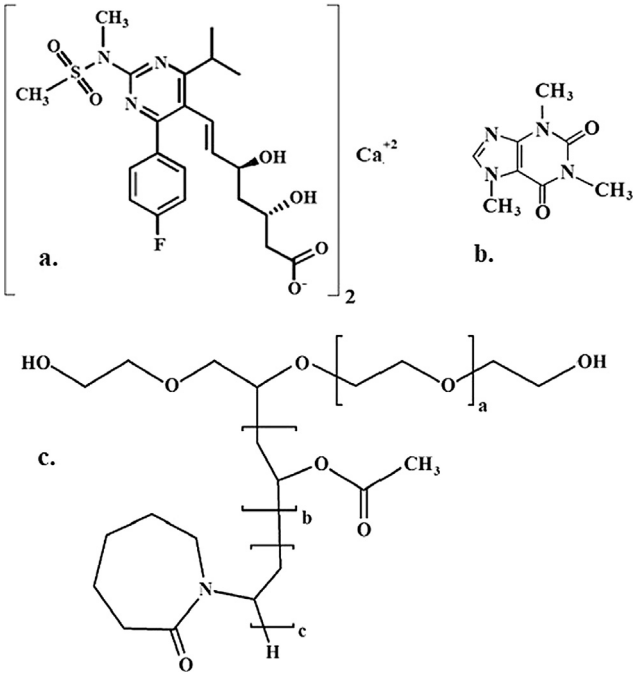

Fig. 1. Chemical structure of (a) rosuvastatin calcium, (b) caffeine, and (c) Soluplus®.

readily available for release into the physiological fluid as free drug is absorbed (Kuhad, 2017; Venkatesh et al., 2014). Polymerization of cyclodextrins with other polymers or monomers can enhance their ability to improve the dissolution rate and oral bioavailability (Sarfraz et al., 2017). β-cyclodextrin-g-AMPS hydrogel particles were prepared by a polymeric graft onto β-cyclodextrin through aqueous free radical polymerization with ammonium persulfate as the initiator and N,N′-methylene bisacrylamide as the crosslinking agent (Sarfraz et al., 2017). pH-independent swelling of these rosuvastatin calcium-containing hydrogels is offered by the presence of 2-acrylamido-2-methylpropane sulfonic acid (AMPS) grafted onto the cyclodextrin. In pH 6.8 buffer, 92% of drug was released within 1 h from the hydrogel particles, whereas only 44% of drug was released in 3 h by the marketed rosuvastatin calcium tablet, Rovista™ (Getz Pharma, Karachi, Pakistan). In addition, solubility improved by 10.66-fold at pH 6.8, which maintained a higher drug concentration in the small intestine and improved rosuvastatin oral bioavailability in albino rabbits by 1.45-fold.

An elaborate nanosponge delivery system for rosuvastatin was developed to improve its oral bioavailability (Gabr et al., 2018). The nanosponges were developed by crosslinking β-CD molecules with pyromellitic dianhydride at different molar ratios. Rosuvastatin was added to the nanosponge-containing aqueous medium and lyophilization was used to prepare the dried particles. Oral administration of the particles to Sprague Dawley rats revealed a profound improvement in oral bioavailability when compared to a suspension and marketed tablets (Gabr et al., 2018). At issue is that cyclodextrins are expensive (Khinchi et al., 2011; Laza-Knoerr et al., 2010; Szejtli, 1997; Szejtli, 2004) and the permeability and toxicity of some cyclodextrins are a major deterrent for their use in pharmaceutical applications (Loftsson and Duchene, 2007). Chemical modifications of cyclodextrins can be complicated, expensive and involve toxic reagents (Szejtli, 1997; Szejtli, 2004), although cyclodextrins themselves have proved to be nontoxic (Szejtli, 2004).

Immediate release tablets of rosuvastatin calcium were prepared by a wet granulation method using various superdisintegrants (Velivela et al., 2016). The compressed tablets demonstrated acceptable mechanical strength with a hardness of 4–6 kg that yet disintegrated rapidly (0.72–1.8 min). A formulation containing 1.5% of the superdisintegrant Polyplasdone XL 10 or XL 100 provided 100% drug release in 45 min in pH 6.8 phosphate buffer. Orally disintegrating tablets of rosuvastatin calcium were fabricated by kneading the drug with β-cyclodextrin and superdisintegrants including sodium starch glycolate, crospovidone and croscarmellose. Cyclodextrin complexation with the addition of superdisintegrants provided rapid dissolution, enhanced drug concentrations and achieved a cumulative drug release of 99.4% in 45 min in simulated gastric fluid (Kapse Vidya et al., 2016). However, these are expensive excipients (Dass and Mazumdar, 2013; Goel et al., 2010).

Amphiphilic lipid vesicular systems called pharmacosomes with drug loading of 90–94% w/v were investigated for their ability to enhance dissolution and systemic availability of rosuvastatin calcium (Kumar et al., 2016). The concentration of drug achieved via pharmacosomes was found to be higher, compared to that of pure drug. Maximum drug released was 67% and maximum drug permeation through egg membrane was 49.5% (Kumar et al., 2016). When rosuvastatin was delivered using chitosan nanoparticles prepared by ionic-gelation, rapid dissolution and concentrations in excess of the solubility of rosuvastatin were observed. A 1:1 drug to polymer ratio provided high entrapment efficiency and drug loading (Ponnuraj et al., 2015). Nanocrystal technology for dissolution rate enhancement of rosuvastain calcium formulations was also pursued (Palani et al., 2015). Rosuvastatin calcium nanocrystals were formulated using sodium lauryl sulfate, hydrox-

ypropyl methylcellulose, poloxamer 188, Tween 80 or poly (vinylpyrrolidone). The *in vitro* release studies revealed a 36% increase in the dissolution profile while the *in vivo* studies showed about 1.87 fold increases in the bioavailability of rosuvastatin calcium (Palani et al., 2015). Liquisolid technology was investigated for the enhancement of the dissolution rate and concentration of rosuvastatin calcium (Lennernas and Fager, 1997). Tablets were prepared that contained 15–25% w/v drug in a liquisolid form. Avicel pH 102 and Aerosil 200 were used as the carrier and coating material, respectively. Results of the *in vitro* release study revealed enhanced drug release from liquisolid compacts in comparison to the directly compressed marketed tablet of rosuvastatin. The liquisolid compacts contain a solution of the drug in PEG 200 where PEG not only facilitates the wetting of drug particle by decreasing the interfacial tension between the particle surface and the dissolution medium (Kamble et al., 2014) but also increases the concentration of the drug in aqueous medium by acting as a cosolvent. A nanoemulsifying delivery system (Kamel and Mahmoud, 2013; Balakumar et al., 2013) and a microemulsifying drug delivery system (Kapure et al., 2013) successfully achieved solubilization of rosuvastatin. However, most novel techniques require expensive excipients and they can be complex in nature and time-consuming.

It has been reported that hydrotropy and micelle formation have individually been able to solubilize rosuvastatin (Nainwal et al., 2011). The hydrotropes were sodium acetate, sodium benzoate, and sodium salicylate. At a high concentration, hydrotropes accomplish solubilization by forming a weak association with the poorly soluble solute as a complex in solution (Behera et al., 2010). Sodium benzoate was the prototype hydrotropic salt (Nidhi et al., 2011; Neuberg, 1916) and the three hydrotropes in that study followed its pattern of an anionic functional group and an aromatic ring or other hydrophobic functional group to achieve success as a hydrotrope. In that same study, cetrimide, sodium lauryl sulfate and Tween 80 provided a cationic, an anionic and a neutral micelle-forming surfactant, respectively. It was discovered that the hydrotropes at 2.0 M allowed more rosuvastatin to dissolve in the medium than did 1.0% w/v of the micelle-forming surfactants.

Because caffeine (Fig. 1b) can act as a hydrotrope (Hodgon and Kaler, 2007; Evstigneev et al., 2006; Roy and Moulik, 2003), it has been used to enhance the dissolution rate and concentration in solution of poorly soluble drugs. This is attributed to the fact that caffeine forms soluble complexes, with 1:1 and 1:2 drug:caffeine ratios reported (Linglei et al., 2014; Tsutsumi, 2012; Fouad et al., 2010; Shakeel and Faisal, 2010; Lim and Go, 2000). In addition, caffeine offers the potential to improve oral bioavailability (He at al., 2017; Renner et al., 2007) and duration of pharmacological effect (Renner et al., 2007).

Soluplus® is a polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Fig. 1c) designed for the manufacture of solid solutions (Sambath et al., 2013; Shamma and Basha, 2013). It has been used successfully with polyvinylpyrrolidone (PVP), β-cyclodextrin and other excipients to further enhance solubility of poorly soluble drugs such as carvedilol (Shamma and Basha, 2013), gliclazide (Sambath et al., 2013), efavirenz (Shankar and Chowdary, 2013), and meloxicam (Noor et al., 2017). The enhanced concentration of carvedilol in solution was attributed to the ability of Soluplus® to form micelles (Shamma and Basha, 2013). Indeed, Soluplus® is reported to form micelles in aqueous media at a very low concentration of 7.6 μg/ml (Yu et al., 2013). Soluplus® was more effective than β-cyclodextrin at improving the dissolution rate and concentration of efavirenz in solution (Shankar and Chowdary, 2013).

The role of complexing agents in combination with micelle-forming excipients for solubilization of rosuvastatin calcium has not yet been reported. However, synergistic effects in terms of solubilization have been observed when hydrotropes were added to surfactant or polymer solutions (Hodgon and Kaler, 2007) where micelle formation was expected. The objective of the present work was to study the role of caffeine as a hydrotrope alone or in combination with the micelle-forming Soluplus® for the enhancement of the concentration achieved by rosuvastatin in physiological fluids. What is expected is that caffeine will enhance the dissolution rate and concentration of rosuvastatin in solution when the drug is released in the gastrointestinal tract; rosuvastatin in excess of what can complex with caffeine will be found primarily in the core of the Soluplus® micelles. Drug in the core of the Soluplus® micelles will act as a depot reserve of readily available rosuvastatin as free drug is being absorbed.

2. Methods

2.1. Materials

Rosuvastatin calcium BP was kindly provided by Searle Pharmaceuticals (Pvt.) Ltd. (Karachi, Pakistan) and the graft copolymer Soluplus® by BASF SE (Ludwigshafen, Germany). Avicel pH 102, sodium starch glycolate, lactose, talc, methanol, sodium citrate dihydrate, citric acid anhydrous, potassium phosphate monobasic, sodium hydroxide, potassium chloride, hydrochloric acid, lead acetate, chloroform, and sulfuric acid were purchased from Merck KGaA (Darmstadt, Germany). Tea was purchased from a local market in Karachi, Pakistan.

2.2. Caffeine extraction

Caffeine was extracted from tea leaves using a modified literature method ((Shakeel and Faisal, 2010; Murray and Hanssen, 1995). Briefly, 25 g of tea leaves were boiled for 10–15 min in 200 ml of distilled water and filtered through a muslin cloth. The process was repeated twice using the filtered tea instead of distilled water. A 50 ml sample of 5% w/v lead acetate solution was added to the collected tea extract. The acetate raises the pH and the lead precipitates tannins that can accompany the caffeine (Hammp, 1996). The mixture was boiled for an additional 10 min, filtered, and poured into a separatory funnel. A few drops of sulfuric acid and 20 ml of chloroform were added to the separatory funnel and the contents shaken thoroughly. The chloroform layer was collected and evaporated at room temperature. The crude caffeine thus obtained was purified by sublimation at 170 °C (O'Neil, 1985; Shakeel and Faisal, 2010). The melting point of the purified caffeine, 237 °C, determined using a capillary melting point apparatus, agrees with the reported 236 °C melting point (Haynes, 2013; Rosin, 1946).

2.3. Preparation of rosuvastatin-caffeine complex

A molecular complex of caffeine and rosuvastatin was prepared by a solvent evaporation method to allow use of the complex as a replacement powder for rosuvastatin calcium in the manufacture of tablets (Fouad et al, 2010; Shakeel and Faisal, 2010). An accurately weighed 1 g (5.15 mmoles) of caffeine was dissolved in 100 ml of distilled water, and 1 g (1.00 mmoles) of rosuvastatin calcium was dissolved in 100 ml of methanol. The caffeine solution was added to the rosuvastatin solution with stirring to maintain the highest level of methanol in the solvent system as the mixing occurred. The mixture was then heated on a water bath at 50 °C until the solvents were evaporated. The residue provided the molecular complex of caffeine and rosuvastatin.

2.4. Rosuvastatin tablet formulation

A 10 mg quantity of rosuvastatin calcium was placed in a porcelain mortar, and a pestle was used to triturate it well with the required quantity of lactose (see Table 1). The resulting mixture was then passed through a United States Standard Sieve No. 30. Avicel PH 102, sodium starch glycolate, and the rosuvastatin-lactose mixture matching formulation F1 were tumbled in a polyethylene bag for 10 min. Talc previously passed through Sieve No. 80 was added to the polyethylene bag and the powder mixture was further blended for 5 min. The same procedure was adopted for the remaining formulations with modification of factor levels based on formulation composition. In F2, the rosuvastatin-caffeine complex was used instead of the rosuvastatin calcium; in F3, Soluplus® was used with rosuvastatin calcium whereas in F4 the rosuvastatin-caffeine complex and Soluplus® were used in combination (Table 1). Tablets were produced by direct compression using a Korsch EKO single station press (Erweka, Frankfurt, Germany) with a 9 mm circular, standard concave punch and die set.

2.5. Evaluation of precompression powder blends

2.5.1. Characterization of powder blends

The Angle of Repose, Carr's Compressibility Index, and the Hausner ratio were determined by data generated using the fixed funnel method. Briefly, a funnel was fixed perpendicular to the bench top so that the tip of the funnel was 1 cm above a sheet of graph paper. The formulation blends were each poured through the funnel and the height and the radius of the powder circle were measured for the Angle of Repose, θ, calculated using tan θ = h/r. Approximately 2 g of a powder blend was poured into a 10 ml graduated cylinder. The initial volume was noted as the bulk volume, V_b, with subsequent tapping until no further change in the powder volume occurred. The final volume was recorded as the tapped volume, V_t. Calculations are as follows.

$$\text{Carr's Compressibility Index} = 100 * (V_b - V_t)/V_t \quad (1)$$

$$\text{Hausner Ratio} = V_b/V_t \quad (2)$$

2.5.2. Evaluation of physicochemical properties of compressed tablets

Ten tablets were randomly selected for evaluation of specific properties and to observe any tableting problems that occured during compression. Variation in mass, thickness, diameter and parameters ascertaining the mechanical strength of the tablets (hardness and friability) were determined to ensure compliance of trial formulations with standard specifications (United States Pharmacopoeia, 2007). Hardness was measured using a Fujiwara, Seisakusho hardness tester (Ogawa Seiki Co., Ltd., Tokyo, Japan) and friability using an Erweka GmbH (Heusenstamm, Germany) TA 200. The disintegration test was carried out in 800 ml distilled water at 37 ± 2 °C using a basket rack assembly (British Pharmacopoeia, 2009).

Drug assay and content uniformity were evaluated as described before (Gupta et al., 2009). Briefly, 100 mg of rosuvastatin calcium was dissolved with shaking in 20 ml methanol in a 100 ml volumetric flask. The volume was diluted with methanol to achieve a rosuvastatin calcium concentration of 14 μg/ml that was then analyzed at 244 nm using a Shimadzu model 1800 UV-Vis spectrophotometer. For sample preparation, 5 tablets were powdered in a mortar and pestle. Powder equivalent to 50 mg rosuvastatin calcium was transferred to a 50 ml volumetric flask and the API was dissolved in some methanol. The resulting solution was filtered through a Whatman No. 1 filter and transferred to a 50 ml volumetric flask. The solution was then made up to volume with methanol. This was serially diluted to arrive at a solution equivalent to 14 μg/ml that was analyzed at 244 nm. Eq. (3) was used for assay calculation.

$$\text{Assay}(\%) = (\text{Absorbance of sample}/\text{Absorbance of standard}) * 100\% \quad (3)$$

For content uniformity, 10 tablets of rosuvastatin calcium were chosen randomly. Each of the tablets was weighed and tested individually by the procedure described above. Content uniformity was calculated using Eq. (4).

$$\text{Content uniformity}(\%) = (\text{Absorbance of sample}/\text{Absorbance of standard}) * 100\% \quad (4)$$

2.5.3. Drug release studies

The in-vitro release study was carried out using an Erweka DT600 USP apparatus II with 900 ml of three different degassed media, including 0.1 N HCl buffer (pH 1.2), 0.05 M sodium citrate buffer (pH 6.6), and 0.05 M phosphate buffer (pH 6.8). The HCl and phosphate buffers mimic the stomach and small intestine conditions, respectively, whereas the citrate buffer is recommended for dissolution studies of rosuvastatin calcium by the United States Food and Drug Administration (FDA, 2015). The temperature of the dissolution medium was maintained at 37.0 ± 0.5 °C. One tablet from a particular batch was placed in each of six vessels and the paddle operated at 50 rpm. Aliquots of 10 ml were drawn at 5, 10, 15, 30, 45, and 60 min and fresh medium was added to maintain a constant volume of dissolution medium. The concentrations were accommodated mathematically to deal with the dilution occurring with each dissolution medium addition. Samples were filtered through 0.45 μm Whatman filter paper and analyzed by spectrophotometry at 244 nm (sodium citrate and HCl buffer samples) or 241 nm (phosphate buffer samples) against their respective medium to determine drug release using the following formula:

$$\%\ \text{Drug released} = (\text{Absorbance of sample}/\text{Absorbance of standard}) * 100\% \quad (5)$$

where the standard was at the concentration representing 100% drug released.

Table 1
Composition of tablet formulations F1-F4 in mg per tablet.

Ingredient	F1	F2	F3	F4
Rosuvastatin Calcium	10	–	10	–
Rosuvastatin-Caffeine Complex*	–	20	–	20
Soluplus®	–	–	3	3
Lactose	134	124	131	121
Avicel PH102	50	50	50	50
Sodium Starch Glycolate	4	4	4	4
Talc	2	2	2	2

* 20 mg of the complex provides 10 mg of rosuvastatin calcium and 10 mg of caffeine.

3. Results and discussion

3.1. Caffeine as a complexing agent

Caffeine can improve the concentration of certain poorly soluble chemicals by formation of a complex that can exist in solution (Hodgon and Kaler, 2007; Evstigneev et al., 2006; Roy and Moulik,

2003). A neutral xanthine derivative that cannot become ionized at physiological pH (Dean, 1985), caffeine can still form soluble complexes with poorly soluble rosuvastatin by multiple types of intermolecular forces. Permanent dipoles in caffeine and rosuvastatin can lead to Keesom and Debye forces of attraction and the uncharged carboxylic acid and the alcohol groups on rosuvastatin can be donors for hydrogen bonds with the dipoles of caffeine. When the aromatic rings of the two chemicals approach each other intimately due to their planarity, short-range electrostatic effects can influence the strength of attraction between the two molecules. In particular, the imidazole ring of caffeine is aromatic (Gibson and Fowler, 2014) and this can lead to a charge-transfer complex due to the formation of π-bonds between an aromatic ring of caffeine and an aromatic ring in the drug molecule.

An increase in the concentration of caffeine enhances the concentration of rosuvastatin in solution, but a plateau is observed beginning near 8.2 mM caffeine (Fig. 2). Such a plateau is expected when the complex reaches its solubility (Chen et al., 1994). Although 1:1 and 2:1 caffeine:rosuvastatin complexes could be formed, data analysis of the curved portion of the data in Fig. 2 indicates that the 2:1 complex dominates to the extent that the 1:1 association constant cannot be calculated even if the 1:1 complex did exist. This is not surprising since stacking of caffeine with itself is considered its primary hydrotropic effect, and incorporation of the poorly soluble drug into that complex is considered the secondary effect (Cui, 2010; Higuchi and Kristiansen, 1970) such that the 1:1 complex might indeed not exist to a measurable extent. Caffeine in aqueous media is known to form dimers and tetramers in equilibrium with discrete caffeine molecules (Higuchi and Kristiansen, 1970; Guttman and Higuchi, 1957). The dimer is reported to appear at caffeine concentrations as low as 0.050 M, but the tetramer does not reveal itself until the caffeine concentration exceeds about 0.20 M (Guttman and Higuchi, 1957). It has been suggested that the dimerization of a hydrotrope occurs prior to the association with the individual poorly soluble drug (Higuchi and Kristiansen, 1970). Eq. (6) describes the curved portion of Fig. 2 data:

$$\text{Rosuvastatin concentration(mM)} = 4.68 + 0.0257(\text{caffeine mM concentration})^2 \quad (6)$$

This quadratic relationship between rosuvastatin and caffeine in the complex describes the stoichiometric relationship and supports formation of a 2:1 complex. Efforts to increase the chemical concentration by further increases in the caffeine concentration result in the complex coming out of solution (Hadkar, 2007; Zughul and Badwan, 1997; Chen et al., 1994), although higher order soluble complexes might appear if higher caffeine concentrations were used (Hadkar, 2007).

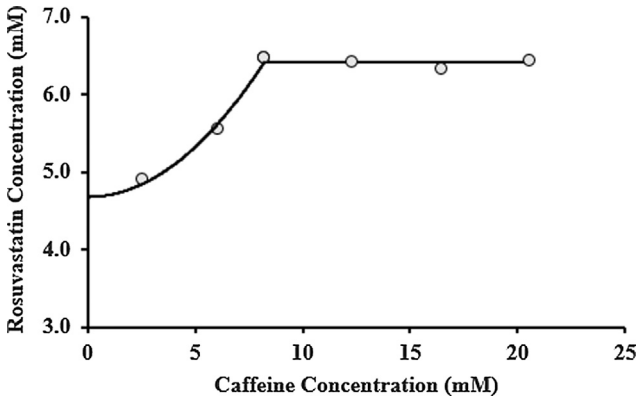

Fig. 2. Solubility of rosuvastatin in aqueous caffeine solutions.

With the almost 5:1 molar ratio of caffeine to rosuvastatin in the mixture to prepare the complex with rosuvastatin, the 2:1 complex is expected to exceed its solubility in water. Since the 1:1 methanol/water solvent system does not form an azeotrope (Griswold and Dinwiddie, 1942), the higher vapor pressure of methanol allows it to evaporate earlier, leaving water as the end solvent. The 2:1 caffeine:rosuvastatin complex will eventually exceed its solubility as the methanol concentration lowers (Fig. 2) and nuclei will form that lead to the precipitation of the 2:1 complex.

Analysis of the rosuvastatin-caffeine complex was possible using FTIR. The spectrum for rosuvastatin calcium (Fig. 3) reveals certain characteristic peaks at 1550, 1507, 1390, 1330, 1229, 1066, 840 and 771 cm^{-1} that are confirmed in the literature (Mostafa et al., 2014). These peaks are representative of the C═N stretch (1550), the C—C stretch in an aromatic ring and the N—H bending (1507), the C—N stretch and the symmetric bending of the CH_3 group (1390), the asymmetric vibration of S═O (1330), the ⩾C═O stretch in a carboxylic acid group (1229), the S═O stretch (1066), the C—F stretch (8 4 0) and the C—H out of plane bending for aromatic rings (7 7 1), respectively (Mostafa et al., 2014; Salih et al., 2013; Siriwardane and Woodruff, 1995). Fig. 4 presents the FTIR spectrum of caffeine with its identifying peaks at 1699, 1638, 1540, 1360, 1229 and 745 cm^{-1} that are confirmed in the literature (Rajam et al., 2013; Paradkar and Irudayaraj, 2002). In addition to the sources for the peaks identified above, the caffeine peaks at 1699 and 1638 cm^{-1} correspond to the C═O stretch in cyclic hydrocarbons and the C═N stretch in cyclic hydrocarbons, respectively (Silverstein et al., 1981). The spectrum for the rosuvastatin-caffeine complex (Fig. 5) supports the existence of intermolecular interactions between rosuvastatin and caffeine since peaks associated with rosuvastatin or caffeine alone have shifted. The low magnitude of the peak shift in most cases indicates that the interactions are not strong, a desirable property since the complex should be disrupted to readily release rosuvastatin *in vivo*. These shifts can be increases or decreases in the wavenumber, depending on the influence of the type of interaction (Ryu, et al., 2010; Kolhe and Kannan, 2003). Alterations to the spectra include the shift of the 1699 peak to 1707 and the 1638 peak to 1654 cm^{-1} for caffeine, with the 1507 peak of rosuvastatin increased to 1511, the 1390 peak reduced to 1372, the 1229 peak increased to 1233, the 840 peak increased to 845 and the 771 peak reduced to 743 cm^{-1}. Shifts in these peaks indicate interactions of caffeine with rosuvastatin at its aromatic ring with the fluoride substituent and at the heterocyclic ring with its adjacent methyl groups.

3.2. Precompression studies on powders and powder blends

3.2.1. Flow properties of the drug-caffeine complex and formulation blends

Comparable micromeritic parameters were observed for the drug-caffeine complex and for the formulation blends. This indicates that the drug-caffeine complex alone or in combination with the formulation excipients possessed an excellent or good flow property (Table 2) and thus created no problem in the consolidation and compression of formulation blends.

3.3. Postcompression physicochemical evaluation

The compressed tablets were white with a smooth surface. No tableting problems were detected during postcompression studies. Comparable mass across the tablets was found with each trial formulation, thus they complied with United States Pharmacopeia standards for weight variation, namely ±7.5 mg for tablets

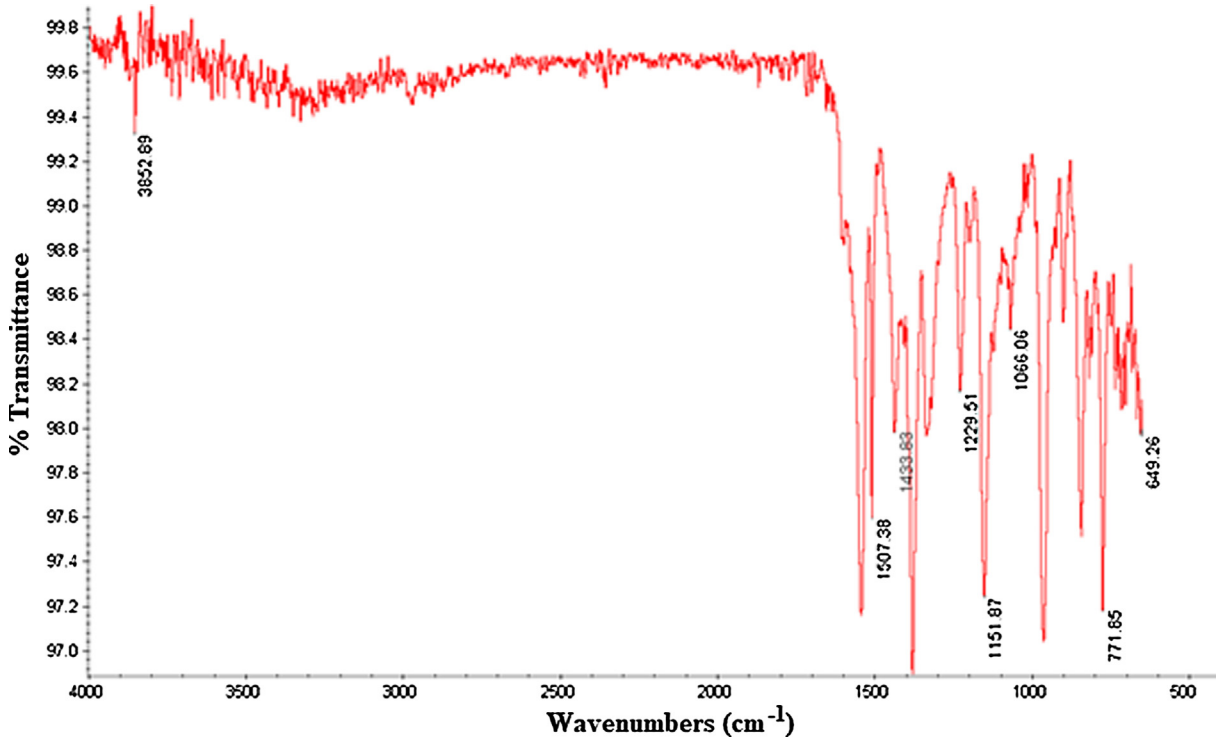

Fig. 3. FTIR spectrum for rosuvastatin calcium.

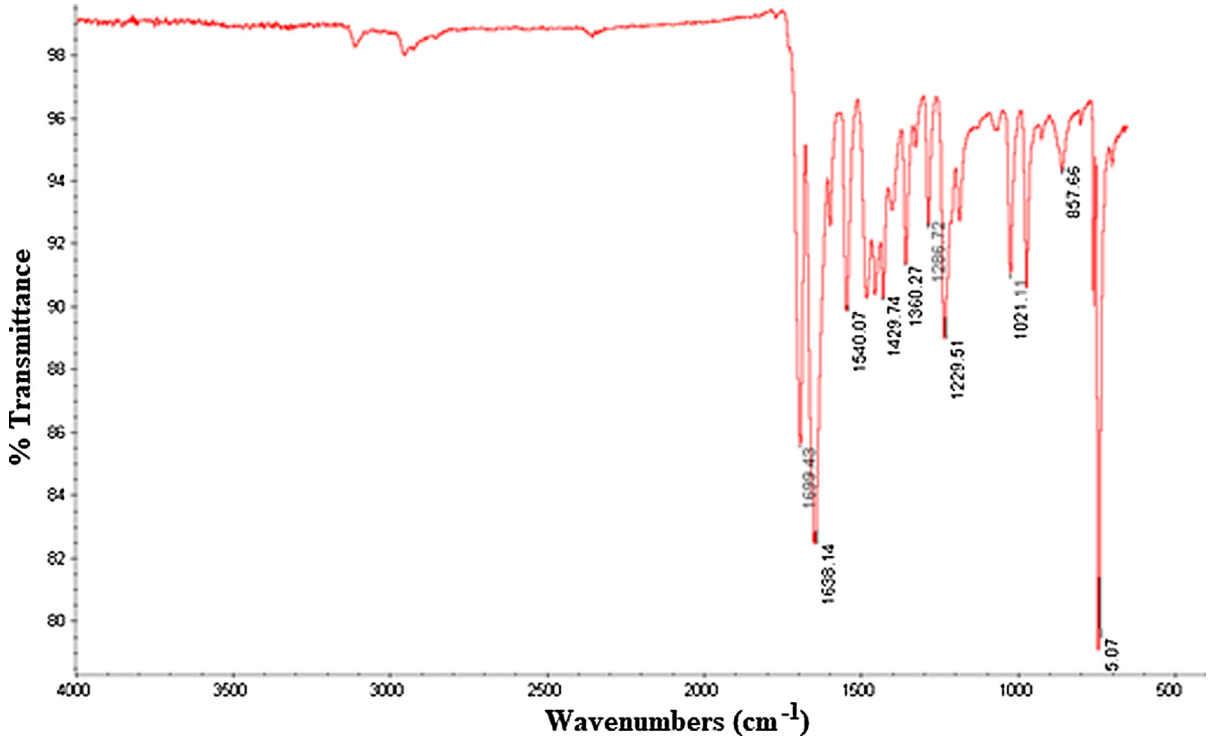

Fig. 4. FTIR spectrum for caffeine.

compressed to a target mass of 200 mg. This indicates that a reasonably uniform die fill occurred during compression that led to a minimal weight variation. These results were expected since the formulation blends demonstrated good or excellent flow in the precompression studies. As with mass variation, consistent values are observed for the thickness and diameter of the compressed tablets (Table 3).

Most of the tablets were compressed to a hardness of 5 kg (Table 3) which is regarded as a satisfactory hardness for compressed tablets. Oral disintegrating tablets of rosuvastatin formulated in a previous study were compressed to a lower hardness (4.00–4.65 kg) [Rohini et al., 2014; Rohini 2013]. This might be deliberate due to the nature and rapid disintegration purpose of the tablets. Formulations F2 and F4 provided higher friability

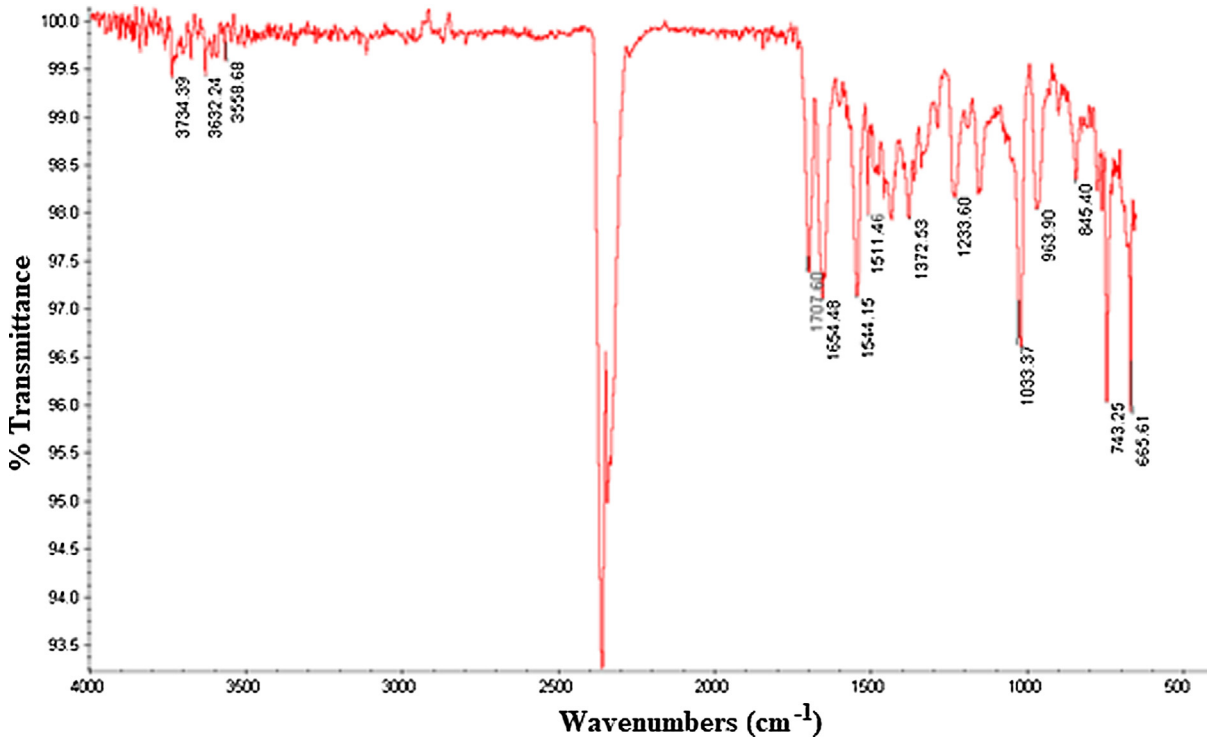

Fig. 5. FTIR spectrum for the rosuvastatin-caffeine complex.

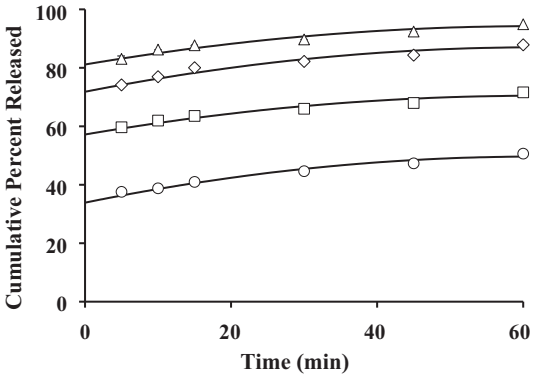

Fig. 6. Drug release profiles in pH 1.2, 0.1 N HCl, (circle (F1), square (F2), diamond (F3) and triangle (F4) consistently in release profiles).

values compared to F1 and F3. The higher friability might be due to lower tablet hardness that indicates weaker bonds within the tablet.

Nevertheless, each of the trial formulations of rosuvastatin calcium possessed friability values that lie within the official limits. Velivela et al. (2016) reported lower tablet friability values (0.17–0.23%) that might be due to the use of a wet granulation method. Rohini (2013) reported orally disintegrating tablets of rosuvastatin with friability in the 0.227–0.449% range, well within the official limits.

Tablets from each of the four formulations demonstrated BP compliance with the Assay and Content Uniformity tests (Table 3). It appears that the preblending and post blending of the API with excipients provided random mixing within the formulation blends. Tablets from each of the trial formulations disintegrated within 2.5 min and thus complied with BP standards set for disintegration tests and were similar to what has been reported for other rosuvastatin dosage forms (Rohini et al., 2014; Venkatesh et al., 2014). The tablet disintegration times in ascending order were F4 < F3 < F2 < F1 (Table 3), suggesting the same order should exist for faster drug release from the greater surface area afforded by disintegrated tablets that resulted in a burst release of drug at early times.

In the drug release profiles, the variability in the rosuvastatin concentration in samples drawn at a particular time for a particular type of tablet was low such that, when the standard deviation is presented using y-error bars, the error bar is hidden under the marker for each data point. In the pH 6.6 sodium citrate buffer, tablets based on formulation F4 that contained drug-caffeine complex and Soluplus® provided the highest cumulative drug release of 98.3%, followed by F3-based tablets with drug and Soluplus®, F2 with the drug-caffeine complex, and F1 with drug only (Fig. 8). A similar ranking in cumulative release was found in pH 6.8 phosphate buffer where the performance of tablets based on formulation F4 again

Table 2
Flow properties of drug-caffeine complex and trial formulations of rosuvastatin.

Formulation code	Angle of repose (deg)	Carr's compressibility index (%)	Hausner ratio	Flow property
Drug-Caffeine Complex	29.4	7.46	1.08	Excellent
F1	34.0	14.0	1.15	Good
F2	33.0	12.0	1.12	Good
F3	29.3	9.85	1.00	Excellent
F4	26.9	9.00	1.04	Excellent

Table 3
Physicochemical parameters of rosuvastatin tablets produced with different formulations.

Parameter	F1	F2	F3	F4
Average Mass (mg)	200 ± 2.76*	200 ± 2.20	200 ± 3.07	200 ± 3.87
Thickness (mm)	3.55 ± 0.29	3.90 ± 0.26	3.51 ± 0.45	3.61 ± 0.32
Diameter (mm)	8.43 ± 0.25	8.34 ± 0.23	8.35 ± 0.26	8.33 ± 0.24
Hardness (kg)	5.03 ± 0.76	5.60 ± 0.70	5.82 ± 0.88	4.92 ± 0.83
Friability (%)	0.46 ± 0.03	0.76 ± 0.02	0.51 ± 0.05	0.91 ± 0.01
Disintegration Time (min)	2.26 ± 0.10	1.48 ± 0.08	1.19 ± 0.05	1.04 ± 0.04
Assay (%)	98.1 ± 0.69	100 ± 0.89	99.9 ± 0.45	99.3 ± 0.40
Content Uniformity (%)	99.0 ± 0.66	99.0 ± 1.18	99.1 ± 1.82	100 ± 1.13

* Mean ± s.d.

superceded that of all other formulations (Fig. 7). With pH 1.2 HCl buffer, formulation F4 maintained its superior influence with the highest cumulative drug release (see Fig. 6), although release profiles for each tablet from formulations F2 and F3 were reduced in hydrochloric acid buffer when compared to results in sodium citrate or phosphate buffer due to the pH-dependent poor solubility of rosuvastatin itself, leading to a lower free rosuvastatin concentration in acidic media (Satyanarayana and Someshwar, 2006). When comparing the release profile for tablets produced using formulation F1 to the corresponding release profiles for tablets produced using formulation F2 the improvement in the rate and extent of drug release accomplished in each of the three media due to prior complexation of rosuvastatin with caffeine becomes evident. Likewise, inclusion of Soluplus® in the formulation F3 enhanced release from tablets and supported a higher concentration of rosuvastatin in each medium. Formulation F4 that contained both the rosuvastatin-caffeine complex and Soluplus® provided tablets with

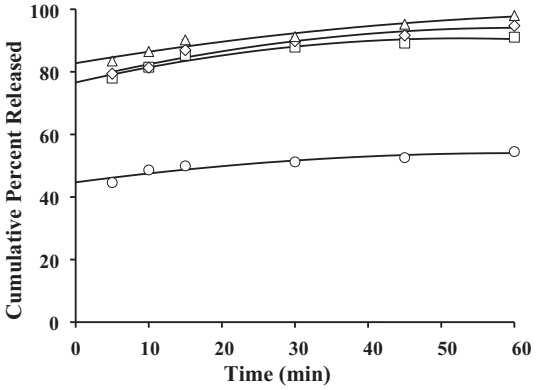

Fig. 7. Drug release profiles in pH 6.8, 0.05 M phosphate buffer (symbols as described for Fig. 3).

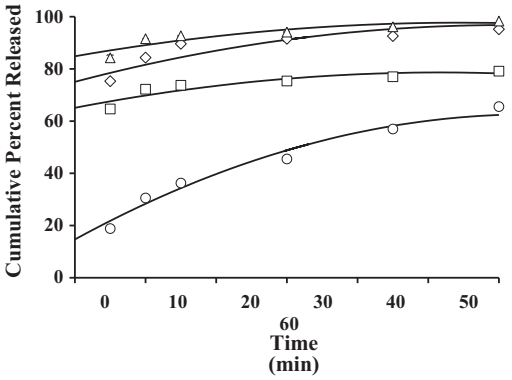

Fig. 8. Drug release profiles in pH 6.6 N, 0.05 M citrate buffer (symbols as described for Fig. 6).

the ability to outperform tablets from any of the other formulations in any of the three media.

Release profiles were examined using Two-factor ANOVA that revealed at least one statistically different release profile for each of the three release media. Dissolution data at multiple time points in different media were analyzed by One Way ANOVA followed by a posthoc Tukey's test at the 0.05 level of significance. At most of the sampling times, a significant difference ($p < 0.05$) was detected in release profiles of trial formulations that were further confirmed by Tukey's test. Acknowledging a burst release of drug in the profile in Fig. 6 for drug release from a tablet based on F1, represented by b in the following equation, an appropriate fit of the Higuchi model (Paramita and Kasapis, 2019; Siepmann and Peppas, 2001; Ritger and Peppas, 1987):

$$M_t/M_\infty = k_H(t)^{1/2} + b \quad (7)$$

to the release data was possible that reveals drug release by diffusion of fluid into the solid dosage form, dissolution of the drug, and then diffusion of dissolved drug through an essentially intact matrix to accomplish release. The fitted model equation gives the following equation:

$$M_t/M_\infty = 2.38(t)^{1/2} + 31.7 \quad (8)$$

that provides a good description of the data ($R^2 = 0.9933$) and reveals a burst release of 31.7% of the rosuvastatin load in the tablet. Other profiles can also be described by this square root of time relationship, suggesting that diffusion is the release mechanism for rosuvastatin from tablets from each of the formulations. It is apparent that drug release profiles for tablets based on formulation F4 appear to be similar across the three media. Use of the dissimilarity factor, f_1, and the similarity factor, f_2, as often calculated to determine the similarity of release profiles, is accomplished using the following equations (Anderson et al., 1998):

$$f_1 = 100 * (\Sigma|R_t - T_t|)/(\Sigma R_t) \quad (9)$$

$$f_2 = 50 * \log\{100/[1 + (1/n) * \Sigma(R_t - T_t)^2]\} \quad (10)$$

where R_t refers to the fraction released in a reference profile at a particular time, t, and T refers to a second profile considered a test profile with T_t at each time point for comparison. The profile for tablets based on formulation F4 at pH 6.8 was considered the Reference release profile. Comparison to the profile for tablets at pH 6.6 revealed an $f_1 = 2.27$ and an $f_2 = 99.9$; whereas comparison to the profile for tablets at pH 1.2 revealed an $f_1 = 1.96$ and an $f_2 = 99.9$. Since an f_1 in the range 0–15 and an f_2 of 50–100 indicate similar profiles (Freitag, 2001; Sathe et al., 1996), in each case, the test profile is similar to the reference profile. The release profile for tablets produced using formulation F4 are similar in the three release media.

Although rosuvastatin calcium has a low solubility in water, as a BCS Class II drug it is acknowledged to experience a high permeability. Rosuvastatin complexed with caffeine can leave that

complex to replace dissolved drug that undergoes absorption from the gastrointestinal tract by readily re-establishing the equilibrium between free and complexed rosuvastatin. The saturated solution of free rosuvastatin in a physiological medium will be maintained by the equilibrium between free drug, complexed drug, and drug located in the micelles, as opposed to a permeability rate reduced by slow dissolution of the poorly soluble form of the solid drug. Therefore, dissolution of the poorly soluble drug is not required for re-establishment of the equilibrium with free drug that is then available for absorption.

4. Conclusions

The easily formed drug-caffeine complex using inexpensive caffeine complemented by Soluplus® that can form micelles at a very low concentration effectively provided 94.9–98.0% release within 60 min in fluids that mimic physiological fluids. A cost-effective tablet form of rosuvastatin was thus fabricated by a direct compression method that might be beneficial for patients and the pharmaceutical industry alike. The role that Soluplus® plays in the presence of caffeine has been explored to further highlight the importance of this amphiphilic agent that might provide new insights for future formulation work. Thus, in the present work, an improved dissolution rate and concentration of rosuvastatin in solution with the added benefit of a high percentage released within one hour were successfully accomplished by a simple and cost-effective complexation approach.

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Declaration of interest

None.

References

Alshora, D.H., Haq, N., Alanazi, F.K., Ibrahim, M.A., Shakeel, F., 2016. Solubility of rosuvastatin calcium in different neat solvents at different temperatures. J. Chem. Thermodyn. 94, 230–233.

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.

Anderson, N.H., Bauer, M., Boussac, N., Khan-Malek, R., Munden, P., Sardaro, M., 1998. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. J. Pharm. Biomed. Anal. 17, 811–822.

Balakumar, K., Raghavan, C.V., Selvan, N.T., Prasad, R.H., Abdu, S., 2013. Self nanoemulsifying drug delivery system (SNEDDS) of rosuvastatin calcium: Design, formulation, bioavailability and pharmacokinetic evaluation. Colloids Surf. B: Biointerfaces 112, 337–343.

Behera, A.L., Sahoo, S.K., Patil, S.V., 2010. Enhancement of solubility: A pharmaceutical overview. Der Pharmacia Lettre. 2, 310–318.

British Pharmacopoeia (BP), 2009. British Pharmacopoeia Commission. The Stationary Office, London.

Carr, R., Hann, M., 2002. The right road to drug discovery? Mod. Drug Disc. 5, 45–48.

Chen, A.X., Zito, S.W., Nash, R.A., 1994. Solubility enhancement of nucleosides and structurally related compounds by complex formation. Pharm. Res. 11, 398–401.

Cui, Y., 2010. Parallel stacking of caffeine with riboflavin in aqueous solutions: The potential mechanism for hydrotropic solubilization of riboflavin. Int. J. Pharm. 397, 36–43.

Dass, S., Mazumder, S.A., 2013. An updated precise review on superdisintegrants. Indo Am. J. Pharm. Res. 3, 5342–5355.

Dean, J.A. (Ed.), 1985. Lange's Handbook of Chemistry, 13th ed.McGraw-Hill, Inc., New York.

Evstigneev, M.P., Evstigneev, V.P., Santiago, A.A., Davies, D.B., 2006. Effect of a mixture of caffeine and nicotinamide on the solubility of vitamin (B_2) in aqueous solution. Eur. J. Pharm. Sci. 28, 59–66.

FDA, 2015. Dissolution Methods. www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm/ (accessed 23.02.18).

Fouad, E.A., El-Badry, M., Alanazi, F.K., Arafah, M.M., Al-Ashban, R., Alsarra, I.A., 2010. Preparation and investigation of acetyl salicylic acid-caffeine complex for rectal administration. Pharm. Dev. Technol. 15, 249–257.

Freitag, G., 2001. Guidelines on dissolution profile comparison. Drug Inform. J. 35, 865–874.

Fridgeirsdottir, G.A., Harris, R., Fischer, P.M., Roberts, C.J., 2016. Support tools in formulation development for poorly soluble drugs. J. Pharm. Sci. 105, 2260–2269.

Gabr, M.M., Mortada, S.M., Sallam, M.A., 2018. Carboxylate cross-linked cyclodextrin:a nanoporous scaffold for enhancement of rosuvastatin oral bioavailability. Eur. J. Pharm. Sci. 111, 1–12.

Gibson, C.M., Fowler, P.W., 2014. Aromaticity of caffeine, xanthine and the dimethyl xanthines. Tetrahedron Lett. 55, 2078–2081.

Goel, H., Kaur, G., Tiwary, A.K., Rana, V., 2010. Formulation development of stronger and quick disintegrating tablets: A crucial effect of chitin. Yakugaku Zasshi 130, 729–735.

Griswold, J., Dinwiddie, J.A., 1942. Vapor-liquid equilibrium of methanol-ethanol-water. Ind. Eng. Chem. 34, 1188–1191.

Gupta, A., Mishra, P., Shah, K., 2009. Simple UV spectrophotometric determination of rosuvastatin calcium in pure form and in pharmaceutical formulations. E-J. Chem. 6, 89–92.

Guttman, D., Higuchi, T., 1957. Reversible association of caffeine and of some caffeine homologs in aqueous solution. J. Am. Pharm. Assoc. Sci. Ed. 46, 4–10.

Hadkar, U.B., 2007. Complexation. In: Hadkar, U.B. (Ed.), Physical Pharmacy. Nirali Prakashan, Pune, India, pp. 37–38.

Hampp, A., 1996. The extraction of caffeine from tea: A modification of the procedure of Murray and Hansen. J. Chem. Educ. 73, 1172.

Haynes, W.M. (Ed.), 2013. CRC Handbook of Chemistry and Physics. 94th ed. CRC Press, Boca Raton (FL), pp. 3–90.

He, H., Ma, D., Brooks Crone, L., Butawan, M., Meibohm, B., Bloomer, R.J., Yates, C.R., 2017. Assessment of the drug-drug interaction potential between theacrine and caffeine in humans. J. Caff. Res. 7, 95–102.

Higuchi, T., Kristiansen, H., 1970. Binding specificity between small organic solutes in aqueous solution: classification of some solutes into two groups according to binding tendencies. J. Pharm. Sci. 59, 1601–1608.

Hodgdon, T.K., Kaler, E.W., 2007. Hydrotropic solutions. Curr. Opinion Colloid Interfac. Sci. 12, 121–128.

Kalepu, S., Nekkanti, V., 2015. Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm. Sinica B. 5, 442–453.

Kamble, P.R., Shaikh, K.S., Chaudhari, P.D., 2014. Application of liquisolid technology for enhancing solubility and dissolution of rosuvastatin. Adv. Pharm. Bull. 4, 197–204.

Kamel, A.O., Mahmoud, A.A., 2013. Enhancement of human oral bioavailability and in vitro antitumor activity of rosuvastatin via spray dried self-nanoemulsifying drug delivery system. J. Biomed. Nanotechnol. 9, 26–39.

Kapse Vidya, N., Chemate, S.Z., Dharashive, V.M., 2016. Formulation development and solubility enhancement of rosuvastatin calcium tablet prepared by complexation with β- cyclodextrin by kneading method. Int. J. Pharm. Sci. Rev. Res. 7, 4882–4892.

Kapure, V.J., Pande, V.V., Deshmukh, P.K., 2013. Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique. J. Pharm. 9 pages. DOI:10.1155.

Khinchi, M.P., Gupta, M.K., Bhandari, A., Agrawal, D., 2011. Modified polysaccharides as fast disintegrating excipients for orally disintegrating tablets of fexofenadine HCl. Der Pharmacia Lettre. 3, 108–118.

Kolhe, P., Kannan, R.M., 2003. Improvement in ductility of chitosan through blending and copolymerization with PEG: FTIR investigation of molecular interactions. Biomacromolecules 4, 173–180.

Kuhad, A., 2017. Cyclodextrin Complexes of Rosuvastatin Calcium. Lambert Academic Publishing, Chisinau (Moldova).

Kulkarni, N.S., Ranpise, N.S., Mohan, G., 2015. Development and evaluation of solid self nano-emulsifying formulation of rosuvastatin calcium for improved bioavailability. Trop. J. Pharm. Res. 14, 575–582.

Kumar, K.M., Anil, B., 2013. Solubility and dissolution enhancement: Technologies and research emerged. J. Biol. Sci. Opin. 1, 105–116.

Kumar, P.T., Mishra, J., Podder, A., 2016. Design, fabrication and evaluation of rosuvastatin pharmacosome - A novel sustained release drug delivery system. Eur. J. Pharm. Med. Res. 3, 332–350.

Kumar, P., Singh, C., 2013. A study on solubility enhancement methods for poorly water soluble drugs. Am. J. Pharmacol. Sci. 1 (4), 67–73.

Laza-Knoerr, A.L., Gref, R., Couvreur, P., 2010. Cyclodextrins for drug delivery. J. Drug Target. 18, 645–656.
Lennernas, H., Fager, G., 1997. Pharmacodynamics and pharmacokinetics of the HMG-21 CoA reductase inhibitors, similarities and differences. Clin. Pharmacokinet. 32, 403–425.
Lim, L.Y., Go, M.L., 2000. Caffeine and nicotinamide enhances the aqueous solubility of the antimalarial agent halofantrine. Eur. J. Pharm. Sci. 10, 17–28.
Linglei, J., Huang, Y., Zhang, Q., He, H., Xu, Y., Mei, X., 2014. Preparation and solid-state characterization of dapsone drug-drug co-crystals. Crystal Growth Des. 14, 4562–4573.
Lipinski, C.A., 2000. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Meth. 44, 235–249.
Liu, R., 2018. Introduction. In: Liu, R. (Ed.), Water-Insoluble Drug Formulation. third ed. CRC Press, Boca Raton, FL, pp. 1–6.
Loftsson, T., Duchene, D., 2007. Cyclodextrins and their pharmaceutical applications. Int. J. Pharm. 329, 1–11.
Mostafa, N.M., Badawey, A.M., Lamie, N.T., Abd El-Aleem, A.E.A.B., 2014. Selective chromatographic methods for the determination of rosuvastatin calcium in the presence of its acid degradation products. J. Liq. Chromatogr. Relat. Technol. 37, 2182–2196.
Murray, S.D., Hansen, P.J., 1995. The extraction of caffeine from tea: An old undergraduate experiment revisited. J. Chem. Educ. 72, 851.
Nainwal, P., Singh, A., Nanda, D., Jain, D.A., 2011. A comparative solubility enhancement study of rosuvastatin using solubilization techniques. Indian J. Pharm. 2, 13–16.
Neuberg, C., 1916. Hydrotropy. Biochem. Z. 76, 107–109.
Nidhi, K., Indrajeet, S., Khushboo, M., Gauri, K., Sen, D.J., 2011. Hydrotropy: A promising tool for solubility enhancement: A review. Int. J. Drug Dev. Res. 3, 26–33.
Nissen, S.E., Nicholls, S.J., Sipahi, I., Tuzcu, E.M., 2006. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. J. Am. Med. Assoc. 295, 1556–1565.
Noor, R., Hasan, S.M.F., Hassan, F., Rehman, A., 2017. Formulation and dissolution enhancement of meloxicam tablets using polyvinylcaprolactam-polyvinyl acetate- polyethylene glycol graft copolymer and povidone in combination. Pak. J. Pharm. Sci. 30, 407–414.
O'Neil, M.J. (Ed.), 1985. The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals. Royal Society of Chemists, Cambridge, UK, p. 289.
Onoue, S., Kojo, Y., Aoki, Y., Kawabata, Y., Yamauchi, Y., Yamada, S., 2012. Physicochemical and pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability. Drug Metab. Pharmacokinet. 27, 379–387.
Paradkar, M.M., Irudayaraj, J.M.K., 2002. Rapid determination of caffeine content in soft drinks using FTIR-ATR spectroscopy. Food Chem. 78, 261–266.
Palani, K., Christopher, G.V.P., Kesavan, S.K., 2015. Enhancement of rosuvastatin calcium bioavailability applying nanocrystal technology and in-vitro, in-vivo evaluations. Asian J. Pharm. Clin. Res. 8, 88–92.
Paramita, V.D., Kasapis, S., 2019. Molecular dynamics of the diffusion of natural bioactive compounds from high-solid biopolymer matrices for the design of functional foods. Food Hydrocolloids 88, 301–319.
Ponnuraj, R., Janakiraman, K., Gopalakrishnan, S., Jeyakumar, H.J., Venkateswarlu, V., Narayanan, D.S., 2015. Formulation and characterization of rosuvastatin calcium nanoparticles. Indo Am. J. Pharm. Res. 5, 767–779.
Rajam, K., Rajendran, S., Nazeera Banu, N., 2013. Effect of caffeine-Zn^{2+} system in preventing corrosion of carbon steel in well water. J. Chem. available at: http://dx.doi.org/10.1155/2013/521951 and https://www.hindawi.com/journals/jchem/2013/521951/ 521951.
Renner, B., Clarke, G., Grattan, T., Beisel, A., Mueller, C., Werner, U., Kobal, G., Brune, K., 2007. Caffeine accelerates absorption and enhances the analgesic effect of acetaminophen. J. Clin. Pharmacol. 47, 715–726.
Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Controlled Rel. 5, 23–36.
Rohini, P., 2013. Formulation and evaluation of orally disintegrating tablets of rosuvastatin. Global J. Pharmacol. 7, 249–257.
Rohini, P., Pavani, A., Raja Reddy, R., 2014. Formulation and evaluation of orally disintegrating tablets of rosuvastatin. Int. J. Pharm. Sci. Rev. Res. 24, 209–214.
Rosin, J., 1946. U. S. P. Melting point reference standards. J. Am. Pharm. Assoc. Sci. Ed. 35, 55–58.
Roy, B.K., Moulik, S.P., 2003. Effect of hydrotropes on solution behavior of amphiphiles. Curr. Sci. 85, 1148–1155.
Ryu, S.R., Noda, I., Jung, Y.M., 2010. What is the origin of positional fluctuation of spectral features: true frequency shift or relative intensity changes of two overlapped bands? Appl. Spectrosc. 64, 1017–1021.
Salih, O.S., Samein, L.H., Ali, W.K., 2013. Formulation and in vitro evaluation of rosuvastatin calcium niosomes. Int. J. Pharm. Pharm. Sci. 5, 525–535.
Sambath, L., Muthu, A.K., Kumar, M.A., Phaneendra, K., 2013. Physicochemical characterization and in-vitro dissolution behavior of gliclazide-Soluplus solid dispersions. Int. J. Pharm. Pharm. Sci. 5, 204–210.
Sarfraz, R.M., Ahmad, M., Mahmood, A., Akram, M.R., Abrar, A., 2017. Development of β- cyclodextrin-based hydrogel microparticles for solubility enhancement of rosuvastatin: An in vitro and in vivo evaluation. Drug Des. Dev. Ther. 11, 3083–3096.
Sathe, P., Tsong, Y., Shah, P., 1996. In vitro dissolution profile comparison: Statistics and analysis, model dependent approach. Pharm. Res. 13, 1799–1803.
Satyanarayana, T., Someshwar, K., 2006. Rosuvastatin calcium immediate release tablets. Int. J. Chem. Pharm. Sci. 4, 204–214.
Scott, L.J., Curran, M.P., Figgitt, D., 2004. Rosuvastatin, a review of its use in the management of dyslipidemia. Am. J. Cardiovasc. Drugs. 4, 117–138.
Shakeel, F., Faisal, M.S., 2010. Caffeine: A potential complexing agent for solubility and dissolution enhancement of celecoxib. Pharm. Biol. 48, 113–115.
Shamma, R.N., Basha, M., 2013. Soluplus®: A novel polymeric solubilizer for optimization of carvedilol solid dispersions: Formulation design and effect of method of preparation. Powder Technol. 237, 406–414.
Shankar, K.R., Chowdary, K.P.R., 2013. Factorial studies on enhancement of solubility and dissolution rate and formulation development of efavirenz tablets employing ß-cyclodextrin and Soluplus. BioMedRx. 1, 299–303.
Shargel, L., Wu-Pong, S., Andrew, Y.U. (Eds.), 2012. Applied Biopharmaceutics & Pharmacokinetics. 6th ed. McGraw Hill, New York.
Shekhawat, P.B., Pokharker, V.B., 2017. Understanding peroral absorption: Regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles. Acta Pharma. Sinica B. 7, 260–280.
Siepmann, J., Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv. Drug Deliv. Rev. 48, 139–157.
Silverstein, R.M., Bassler, G.C., Morrill, T.C., 1981. Spectrometric Identification of Organic Compounds. Wiley, New York.
Siriwardane, R.V., Woodruff, S., 1995. Interaction of oxygen with zinc sulfide. Ind. Eng. Chem. 34, 699–702.
Stegemann, S., Leveiller, F., Franchi, D., de Jong, H., Linden, H., 2007. When poor solubility becomes an issue: from early stage to proof of concept. Eur. J. Pharm. Sci. 31, 249–261.
Sweetman, S.C. (Ed.), 2009. Martindale: The complete drug reference. 36th ed. The Pharmaceutical Press, London.
Szejtli, J., 1997. Utilization of cyclodextrins in industrial products and processes. J. Mater. Chem. 7, 575–587.
Szejtli, J., 2004. Past, present and future of cyclodextrin research. Pure Appl. Chem. 76, 1825–1845.
Tsutsumi, H., 2012. Study of stereochemical structures of complex of tea catechins and caffeine. Yakugaku Zasshi 132, 925–931.
United States Pharmacopoeia/National Formulary (USP 30/NF 25), 2007. The United States Pharmacoepial Convention, Rockville, MD.
Urbanetz, N.A., 2006. Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. Eur. J. Pharm. Sci. 28, 67–76.
U.S. Food & Drug Administration, Rockville, MD. The Biopharmaceutics Classification System (BCS) Guidance. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm (accessed 14.03.16).
Velivela, S., Mayas, V., Guptha, R.M., Pati, N.B., Ramadevi, C., 2016. Formulation development and evaluation of rosuvastatin calcium immediate release tablets. Eur. J. Pharm. Med. Res. 3, 351–358.
Venkatesh, N., Spandana, K., Sambomoorthy, U., Suresh, K., 2014. Formulation and evaluation of fast dispersible tablet of rosuvastatin using a cyclodextrin complexation method. IJMPR 2, 785–793.
Yasir, M., Asif, M., Kumar, A., Aggarval, A., 2010. Biopharmaceutical classification system: An account. Int. J. Pharm. Tech. Res. 2, 1681–1690.
Yu, H., Xia, D., Zhu, Q., Zhu, C., Chen, D., Gan, Y., 2013. Supersaturated polymeric micelles for oral cyclosporine A delivery. Eur. J. Pharm. Biopharm. 85, 1325–1336.
Zughul, M.G., Badwan, A.A., 1997. Rigorous analysis of SL-type phase solubility diagrams to obtain individual formation and solubility product constants for both SL- and S_2L-type complexes. Int. J. Pharm. 151, 109–119.