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Solubility and dissolution optimization of paracetamol using *in situ* micronization by solvent change method

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Abstract

Dissolution is an important preceding step for the absorption of drugs in class II of the Biopharmaceutics Classification System (BCS) resulting in poor bioavailability. This current study was directed at determining the outcome of *in situ* micronization technique on the dissolution and solubility profiles of paracetamol. Six formulations of paracetamol microcrystals were produced by the solvent change method using HPMC and PVP K30 as stabilizing agents. The solubility, percentage drug content, and dissolution patterns of the produced microcrystals were all tested. The study disclosed that paracetamol solubility was increased up to 5-fold in the PVP K30 stabilized paracetamol microcrystal and a 4.5-fold increase for HPMC stabilized paracetamol microcrystal. The time course of dissolution was improved significantly from 0.6%/min for plain paracetamol to 1.1%/min and 1.2%/min for HPMC and PVP K30 stabilized paracetamol microcrystal respectively. Formulation P6, with 0.08 g of PVP K30 as stabilizing agents and an anti-solvent to solvent ratio of 1:6 was the optimized formulation having a 5-fold solubility increase, 98.3% content of active and 95.32% drug release in 60 minutes. The solvent change strategy of the *in situ* micronization technique could be used for the augmentation of solubility and dissolution of paracetamol.

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Introduction

Active pharmaceutical ingredients (API) belonging to class II and class IV of the Biopharmaceutics Classification System (BCS) exhibit poor solubility in aqueous vehicles. The majority of drugs are poorly water-soluble compounds and fall under these classes (Filippos and Yunhui, 2008). Dissolution is the rate-determining step for the drug absorption of both class II and class IV compounds resulting in poor bioavailability. Some potential drugs are neglected in pharmacological screenings due to limited aqueous solubility and bioavailability (Rasenack and Muller, 2002a). The physicochemical properties of drugs exhibiting poor solubility in aqueous medium can be optimized to improve oral bioavailability. Several formulation approaches have been proven to boost the solubility and dissolution properties of poorly aqueous-soluble drugs such as complexation with cyclodextrins, solid dispersion, salt formation, particle size reduction, use of surfactants, co-solvency, hydrotrophy etc. One dependable way to optimize the dissolution profile is micronization, a comminution technique where the resulting size distribution of the particles is less than 10 µm. (Rasenack *et al*., 2004; Jalay, 2011).

The administering of a drug in micron size is a well-known method to improve the bioavailability of poorly water-soluble drug substances with remarkable effects on solubility, dissolution and release properties (Kawashima, 2001; Miranda *et al*., 2007; Mullarney and Leyva, 2009; Koennings *et al*., 2007; Yohei *et al*., 2011). Comminution or micronization of hydrophobic drugs increases absolute surface area but reduces the effective surface area for wetting leading to floatation as seen in dry milling (Rasenack *et al*., 2004). Consequently, the dissolution time course of the comminuted products may not increase as desired (Sharma *et al*., 2009; Leena and Jouni, 2010). *In situ* micronization process can be applied for boosting the dissolution rate of hydrophobic substances whose hydrophobic surfaces are retained when micronized. The deployment of stabilizing agents (hydrophilic polymers) in the process improves the wetting attributes and consequently the dissolution rate (Varshosaz *et al*., 2008; Rasenack *et al*., 2002a; Rasenack *et al*., 2002b).

In situ micronization requires simple equipment, and micron-sized crystals are derived *in situ* within its production without the necessity for additional particle size reduction unlike in spray drying, milling, and supercritical fluid requiring purpose-built equipment, where extrinsic experimental conditions like mechanical force, pressure and temperature are needed, making the process more capital intensive (Rasenack and Muller, 2002a; Rasenack *et al*., 2002a; Chiou and Langrish, 2008; Sunday and Simon, 2006; Masoud and Sima, 2007; Pasquali *et al*., 2006; Rasenack and Muller, 2004; Deelip *et al*., 2010). The limitations of SCF technologies, milling, and spray drying such as non-homogeneous distribution of the size of particles resulting from the agglomeration, amorphous regions, mechanical activation due to comminution decrease the functional surface accessible for dissolution (Brodka *et al*., 2003; Irngartinger *et al*., 2004; Sunday and Simon, 2006; Fang *et al*., 2009; Yohei *et al*., 2011). The *in situ* micronization technique can circumvent these challenges by the use of stabilizing agents to boost the wetting ability and stability of the microcrystals (Rasenack and Muller, 2002a; Kim *et al*., 2003; Rasenack *et al*., 2003; Varshosaz *et al*., 2008; Amal *et al*., 2012).

In situ micronization can be achieved by either the Solvent change or pH shift method (Rasenack and Muller, 2002c; Steckel *et al*., 2003). The Solvent change procedure which applies to both hydrophilic and hydrophobic drugs requires precipitation amid protective hydrophilic polymers acting as a stabilizing agent, followed by drying. Gliclazide, budesonide, ibuprofen and prednisolone microcrystals were formulated by solvent change procedure (Rasenack *et al*., 2003; Steckel *et al*., 2003; Rasenack *et al*., 2004; Varshosaz *et al*., 2008). The pH shift procedure is for drugs showing pH-dependent solubility. The pH of the system is changed slowly from alkaline to acidic or acidic to alkaline using 0.1 N NaOH or 0.1 N HCl.

Aggregation during pH change can be averted by using a high-speed homogenizer for effective micro crystallization. Gliclazide and indomethacin microcrystals have been formulated by the pH shift procedure (Sung *et al.*, 2003; Gibson, 2001; Roya *et al.*, 2009; Mauludin *et al.*, 2009). The microcrystal formed by this approach can be applied in liquid preparations without Ostwald ripening, with reduced sedimentation rate and easy redispersibility. It can also be applied in respiratory drug delivery systems as dry powder inhalers (DPI) or aerosols due to enhanced aerodynamic properties (Steckel *et al.*, 2003; Rasenack and Muller, 2002c).

Paracetamol is a BCS class II drug with variability in bioavailability ranging from 63-89% for oral, and 24-98% for rectally administered preparations which can make the onset and duration of action unpredictable (Mattia and Colluzi, 2009).

The *in situ* micronization technique has been successfully used in enhancing the solubility and dissolution of many drugs including non-steroidal anti-inflammatory drugs (NSAIDs). The rationale for this study is the fact that paracetamol is one of the most commonly used over-the-counter (OTC) medicines today, but there is very little study on the use of this technique on paracetamol. Thus, this study aimed to investigate the outcome of *in situ* micronization on the dissolution and solubility of paracetamol.

Materials and methods

Materials

Paracetamol B.P (BDH, Poole, England), Hydroxypropylmethylcellulose, HPMC (TNJ Chemical Industry Co. Ltd), Polyvinylpyrrolidone, PVP K30 (Guangdong Guanghua Sci-Tech. Co. Ltd, China). All other chemicals and reagents used were of analytical grade.

Preparation of paracetamol microcrystals

The process was carried out by the solvent change method, using HPMC and PVP K30 as stabilizing agents. An organic solution of the paracetamol, 0.5 g in 10 ml of ethanol was made. Then an aqueous solution containing 0.02 g of HPMC or PVP K30 in a little quantity of distilled water (anti-solvent to the drug solution) was added rapidly stirring at 1200 rpm in a magnetic stirrer. The mixture was stirred for 30 minutes and then slowly cooled in an ice bath. This caused supersaturation of the paracetamol and subsequent nucleation and crystal growth. The microcrystals were obtained by filtration using a filter paper followed by three consecutive washings with cold water to remove any non-absorbed excipient and dried in an oven at 45°C until a constant mass is obtained (Nighute and Bhise, 2009). Six (6) formulations (F1-F6) were prepared using different anti-solvent to solvent ratios as presented in Tables 1 and 2.

Evaluation of Paracetamol Microcrystals

Solubility

Excessive quantities of plain paracetamol (P0), and paracetamol microcrystal (P1-P6) were placed into flasks containing 10 ml of purified water respectively. The flasks were sonicated at 25 ˚C for 1 h, stirred and agitated for 2 days at 25 ˚C. The suspensions were filtered using a 0.45 µm filter, diluted suitably and spectrophotometrically (UV-3200, LabIndia, Mumbai, India) and analyzed at 245 nm (Daravath *et al.*, 2017).

Drug Content

A 100 mg quantity of paracetamol powder was weighed and dissolved in 10 ml ethanol and then made up to a volume of 100 ml with 0.1 N HCl to give 1000 µg/ml of concentrated stock solution (working standard). From the working standard solution, 10 ml was diluted to 100ml with 0.1 N HCl giving 100 µg/ml of solution (Dilution 1). From dilution 1, Aliquots of 0.2, 0.4, 0.6, 0.8, 1 and 1.2 ml were pipetted out into a 10 ml volumetric flask respectively. The volumes were made up to the 10 ml mark with 0.1 N HCl solution. These gave dilutions of 2, 4, 6, 8, 10 and 12 µg/ml concentrations of Paracetamol respectively. The absorbances were measured in the UV-visible spectrophotometer at 245 nm using and a graph of concentration versus absorbance was plotted (Buddha and Raja, 2009).

In vitro dissolution studies

In vitro dissolution studies of plain paracetamol and paracetamol microcrystals were conducted with the USP type II apparatus (paddle method). The dissolution evaluation was performed using 900 ml saliva stimulated fluid buffer of pH 6.8 as dissolution medium at 37±0.5°C with 75 rpm speed (Kausalya *et al.*, 2011). Samples of each formulation equivalent to 60 mg of the drug were introduced into the dissolution medium. The sample of 1ml aliquots was withdrawn periodically (15, 30, 45 and 60 min) and filtered. The withdrawn sample was replaced after each withdrawal to maintain the sink condition. The filtered solutions were analyzed for their drug content by using a UV spectrophotometer at a wavelength of 245 nm. The percentage of drug dissolved at various time intervals was calculated by plotting time on the X-axis against the percentage of cumulative drug release on the Y-axis.

Scanning Electron microscopy (SEM)

The morphology of the microcrystals was investigated by an SEM microscope (JSM 6303A, Joel, Tokyo, Japan).

Drug– Excipient compatibility

FTIR analysis

The Potassium Bromide (KBr) procedure was adopted for the analysis; 5 mg of the sample under test was ground to a fine powder and mixed with dry KBR powder. The sample was then placed in an evacuable KBr die and a 13 mm clear disk was pressed in a hydraulic press to form a KBr pellet. The pelletized sample which was formed inside the evacuated chamber in the cell holder (Universal Demountable Cell) was placed into the FTIR machine (FTIR SYSTEM, Spectrum BX, PerkinElmer, England) and scanned at a range of 350 – 4000 nm. After a while, the spectrum was displayed on the computer screen.

Results and discussion

Solubility test

The finding of the solubility test on plain paracetamol, HPMC and PVP K30 stabilized paracetamol microcrystals is presented in Fig. 1. The result revealed that the *in situ* micronization technique gave rise to a significant boost in solubility of 2-5 fold compared to the solubility of plain paracetamol. Paracetamol microcrystal formulation P4 (1:2) and P6 (1:6) both stabilized with PVP K30 showed a 5-fold rise in solubility than the corresponding ratios of HPMC stabilized formulation P1 (1:2) and P3 (1:6) with 4.5-fold and 3.5-fold increase respectively.

This is similar to the result from the study by Talari *et al.*, 2009 in which the solubility of recrystallized gliclazide in the presence of PVP K30 as a stabilizer was increased 20-fold using the *in situ* micronization approach.

Table 1. Composition of different formulations of paracetamol microcrystals.

Formulations	Paracetamol (g)	Solvent (ethanol) (ml)	HPMC (g)	PVP K30 (g)	Anti-solvent (water) (ml)
P1	0.5	10	0.02	---	20
P2	0.5	10	0.04	---	40
P3	0.5	10	0.08	---	60
P4	0.5	10	---	0.02	20
P5	0.5	10	---	0.04	40
P6	0.5	10	---	0.08	60

Drug content test

The result of the drug content of the paracetamol microcrystals is presented in Table 3. Formulations P1–P6 complied with the test because the individual contents fell within the official range of 85 – 115%. The values ranged from 95 – 98% (Table 3). The European Pharmacopoeia (Ph. Eur) states that a batch falls short of the standard if more than one individual content is outside the limit of 85 – 115% or if one is outside the limit of 75 – 125% of the average

content (European Pharmacopoeia, 2002). The quantities of carriers incorporated in the various formulations showed some effect on the drug content of the microcrystals as revealed in Table 3. Formulations P3 and P6 showed higher drug contents of 98 and 98.3% respectively and these are formulations with ratios of 1:6 of carriers HPMC and PVP K30 respectively.

Table 2. Solvent to Anti-Solvent Ratios of the different Paracetamol Formulation**.**

Formulation	Solvent to Anti-solvent ratio
P1	1:2
P2	1:4
P3	1:6
P4	1:2
P5	1:4
P6	1:6

Table 3. Content of Paracetamol microcrystals.

Formulation	% Content of drug
P1	95.23
P2	96.07
P3	98.22
P4	96.59
P5	97.44
P6	98.29

Dissolution studies test

The results of the evaluation are presented in Figures 2, 3 and 4. Fig. 2 shows a comparison of the dissolution rates of plain (untreated) paracetamol P0 and paracetamol microcrystal P1 and P4 stabilized with corresponding ratios of HPMC and PVP K30 respectively.

The maximum concentration of plain paracetamol (P0) released in 60 minutes was about 36% (dissolution rate of 0.6%/min) compared to P1 with 68% release (dissolution rate of 1.1%/min) and P4 with 71% release (dissolution rate of 1.2%/min) of HPMC and PVP K30 stabilized paracetamol microcrystal respectively.

The double-fold increase in the dissolution rate from 0.6%/min (untreated paracetamol) to 1.2%/min (PVP K30 stabilized) is corroborated by the findings of Talari *et al.*, 2009 in which there was a similar double-fold increase in dissolution efficiency of PVP K30 stabilized gliclazide as against untreated gliclazide Fig. 3 shows a comparison of the dissolution rates of plain (untreated) paracetamol P0 and paracetamol microcrystal P2 and P5 stabilized with corresponding ratios HPMC and PVP K30 respectively.

The maximum concentration of pure paracetamol (P0) released in 60 minutes was about 36% (rate of dissolution 0.6%/min) compared to P2 with 74% release (rate of dissolution 1.2%/min) and P5 with 86% release (rate of dissolution 1.4%/min) of HPMC and PVP K30 stabilized paracetamol microcrystal respectively.

Fig. 4 shows a comparison of the dissolution rates of plain paracetamol P0 and paracetamol microcrystal P3 and P6 stabilized with corresponding ratios HPMC and PVP K30 respectively.

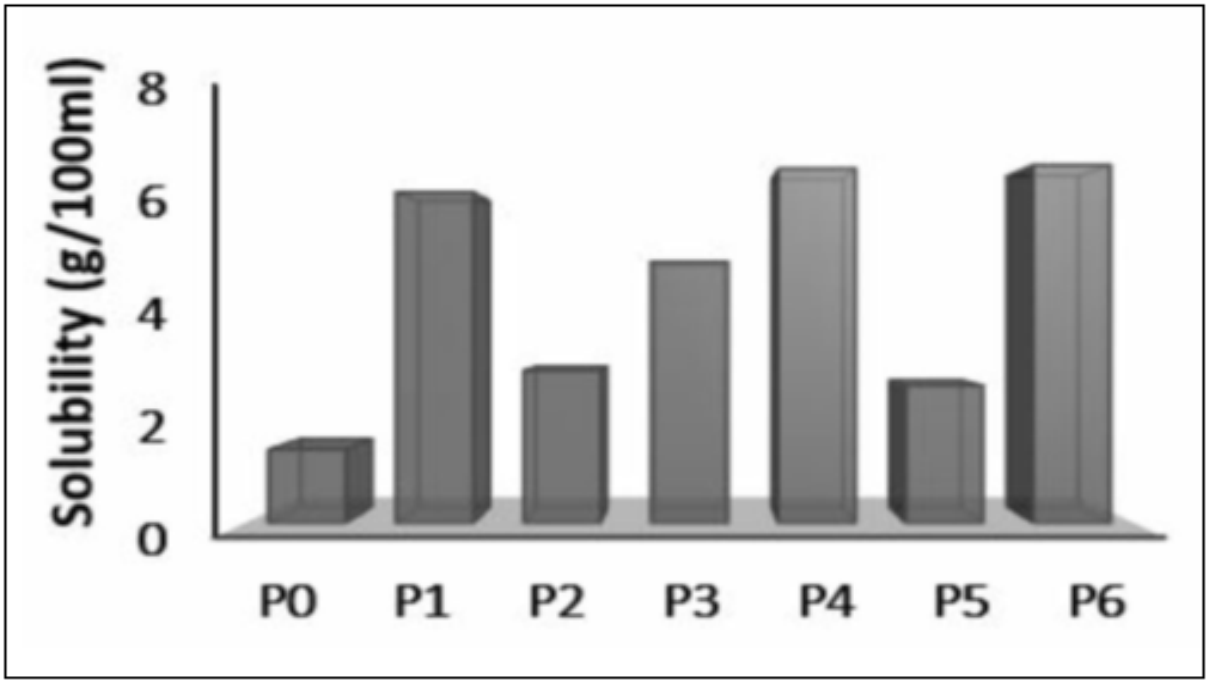

Fig. 1. Solubility of plain paracetamol P0 and *in situ* micronized formulations (P1-P5).

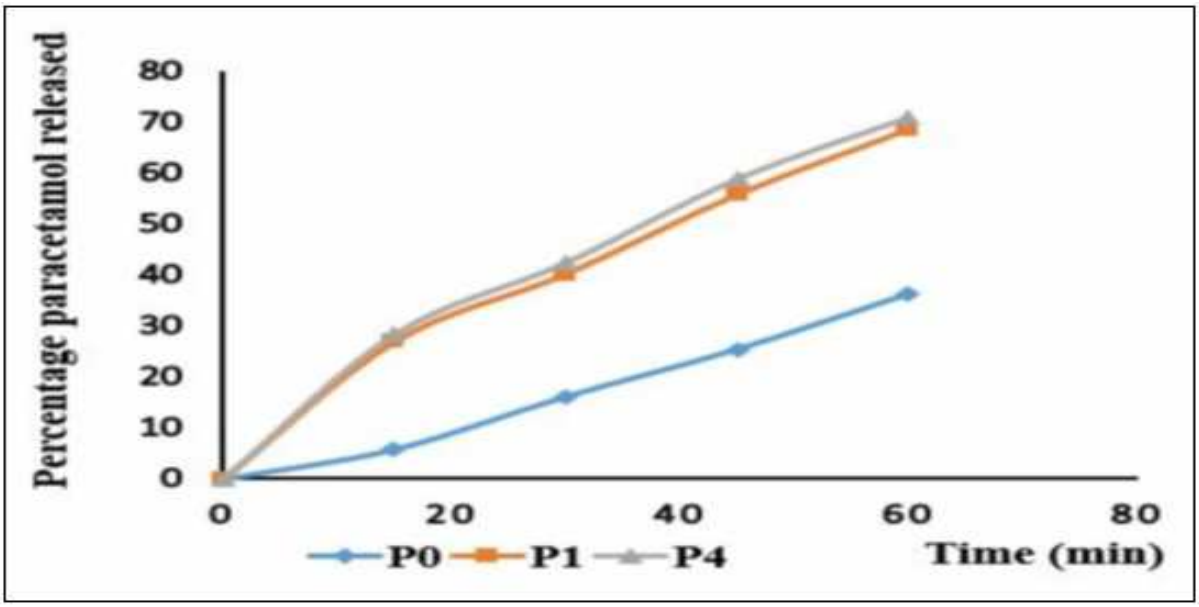

Fig. 2. Dissolution curves of plain paracetamol P0 and paracetamol microcrystal formulations P1 (HPMC-stabilized) and P4 (PVP K30 stabilized).

The maximum concentration of pure paracetamol (P0) released in 60 minutes was about 36% (dissolution rate of 0.6%/min) compared to P3 with 82% release (dissolution rate of 1.4%/min) and P6 with 95% release (dissolution rate of 1.6%/min) of HPMC and PVP K30 stabilized paracetamol microcrystal respectively.

The solvent change approach of the *in situ* micronization process resulted in significant improvement of the dissolution rate of paracetamol as revealed in the result of the dissolution studies.

The increased dissolution rate recorded above with the *in situ* micronized formulations irrespective of the type of stabilizer used is in line with the research submissions of Talari *et al.*, 2009; Maximiano *et al.*, 2011 and Noor *et al.*, 2019.

FTIR analysis

The findings of the drug-excipient compatibility test are revealed in the FT-IR Spectroscopy result. The FT-IR spectra of plain paracetamol powder and paracetamol microcrystal with HPMC and PVP K30 as stabilizing agents are presented in Figures 5, 6 and 7 respectively. The spectrum of plain paracetamol showed major infra-red (IR) bands in the fingerprint region around 680-1222 cm $^{-1}$ due to C-C, C-O and C-N stretch and in the functional group region around 1435-1610 cm $^{-1}$ due to C=N, C=C and C=O stretch (Devineni *et al.*, 2015).

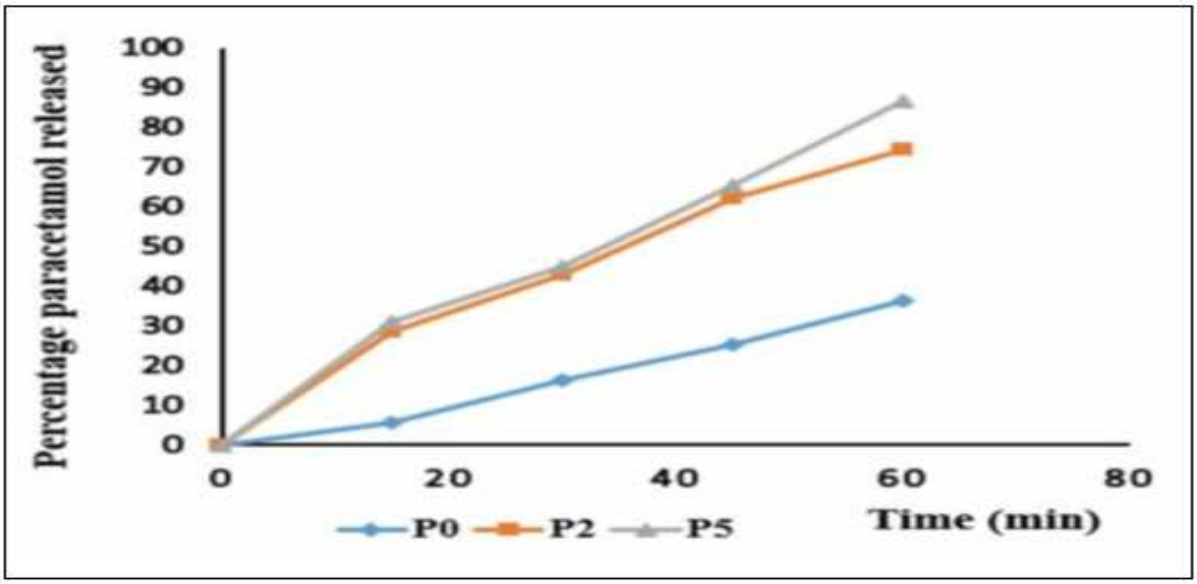

Fig. 3. Dissolution curves of plain paracetamol P0 and paracetamol microcrystal formulations P2 (HPMC-stabilized) and P5 (PVP K30 stabilized).

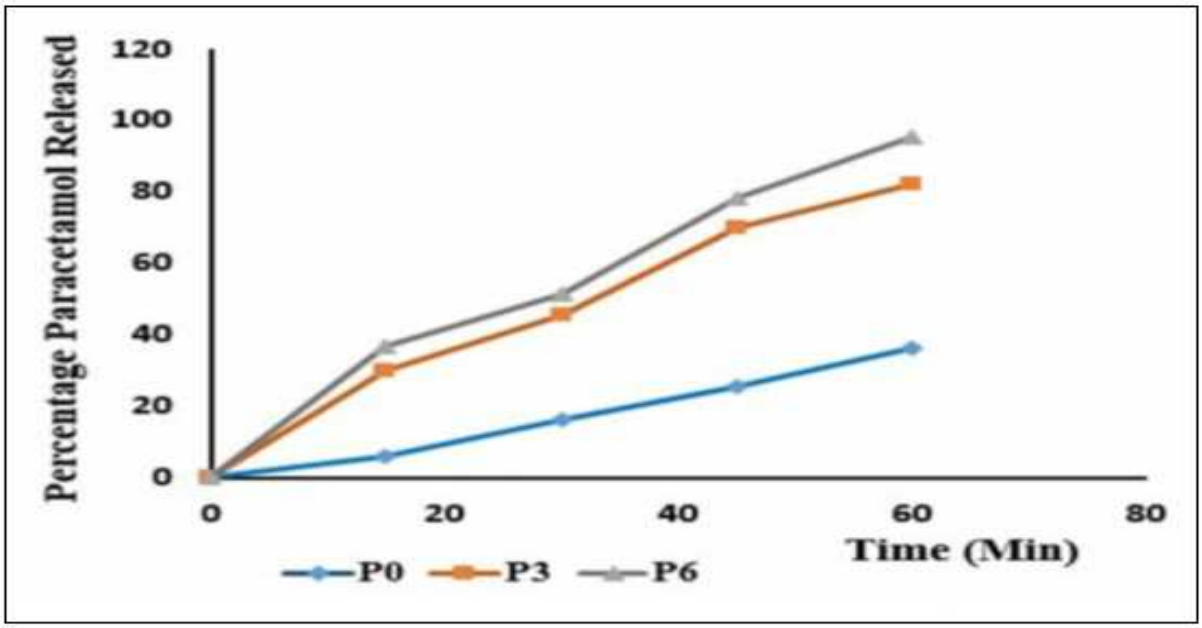

Fig. 4. Dissolution curves of plain paracetamol P0 and paracetamol microcrystal formulations P3 (HPMC-stabilized) and P6 (PVP K30 stabilized).

The spectra of paracetamol microcrystal with HPMC and PVP K30 as stabilizing agents showed the major bands as seen in the spectrum of paracetamol powder but with weak intensity. The spectrum of paracetamol microcrystal with HPMC and PVP K30 as stabilizing agents showed that there were no interactions

between paracetamol and the excipients (HPMC and PVP K30) used in the *in situ* micronization process since there was no appearance of a new peak, and/or disappearance of original drug or excipient peak which would be indicative of drug - excipient interaction.

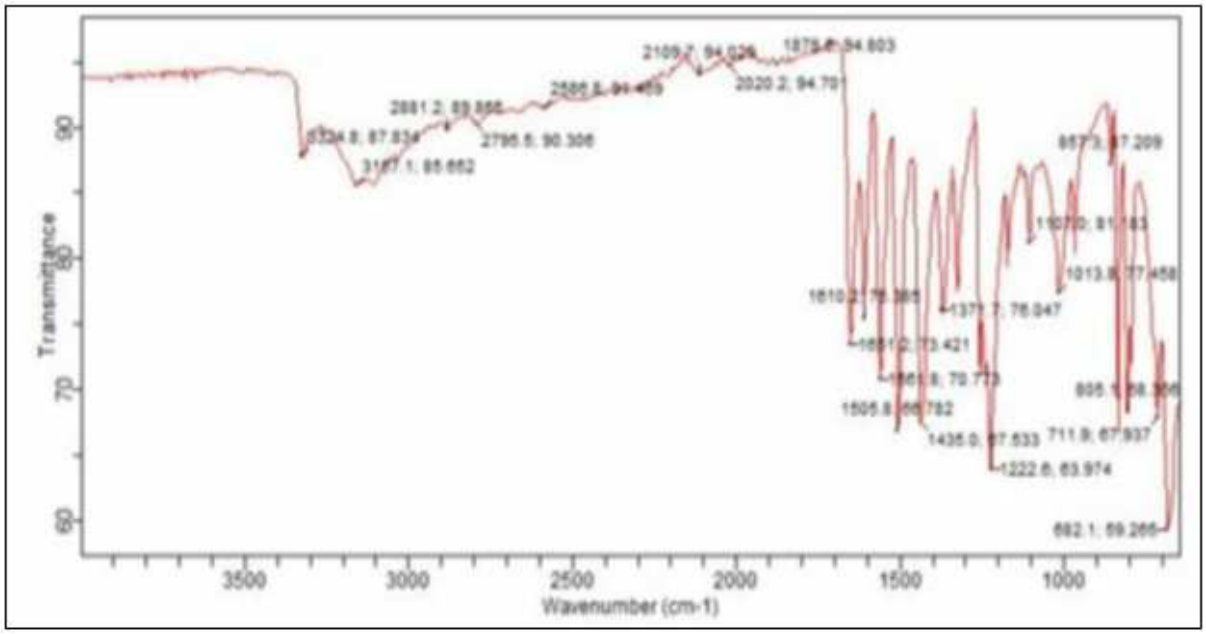

Fig. 5. FTIR Spectrum of plain paracetamol P0.

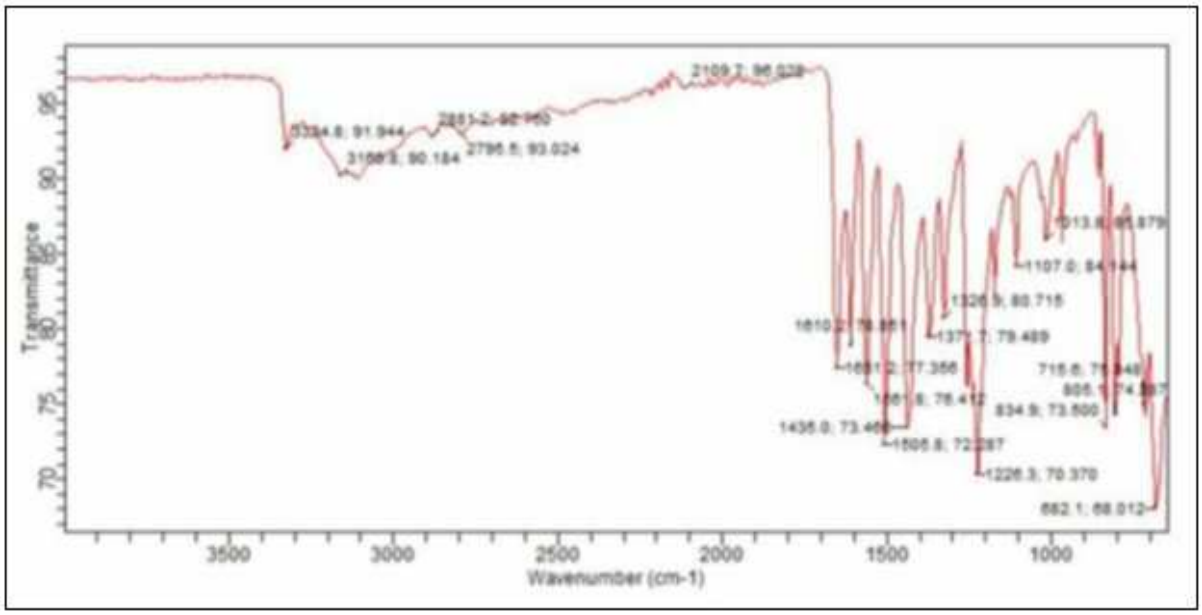

Fig. 6. FTIR Spectrum of paracetamol microcrystal (P1), HPMC as a stabilizer.

SEM analysis

The result of the SEM backscattered electron images is presented in Figures 8a, 8b and 8c. SEM evaluation was performed to study the size and morphology of the microcrystals of paracetamol. The SEM image of untreated paracetamol P0 reveals that paracetamol existed as elongated rod-like irregularly shaped crystals of various sizes as depicted in Fig. 8a and similarly described by Simek *et al.*, 2016. The SEM image of the HPMC stabilized paracetamol microcrystal (P1) in Fig. 8b reveals micro-sized more regularly shaped crystals and some aggregated particles with some changes in the rod-like shape seen in Fig. 8a.

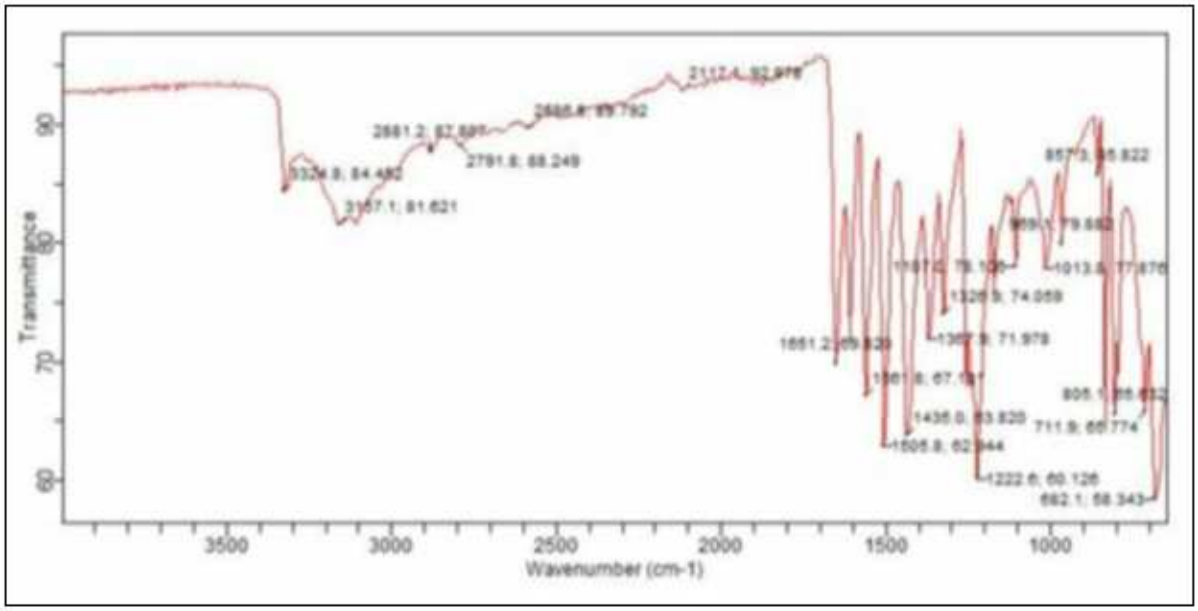

Fig. 7. FTIR Spectrum of *in situ* paracetamol microcrystal (P6), PVP K30 as stabilizer.

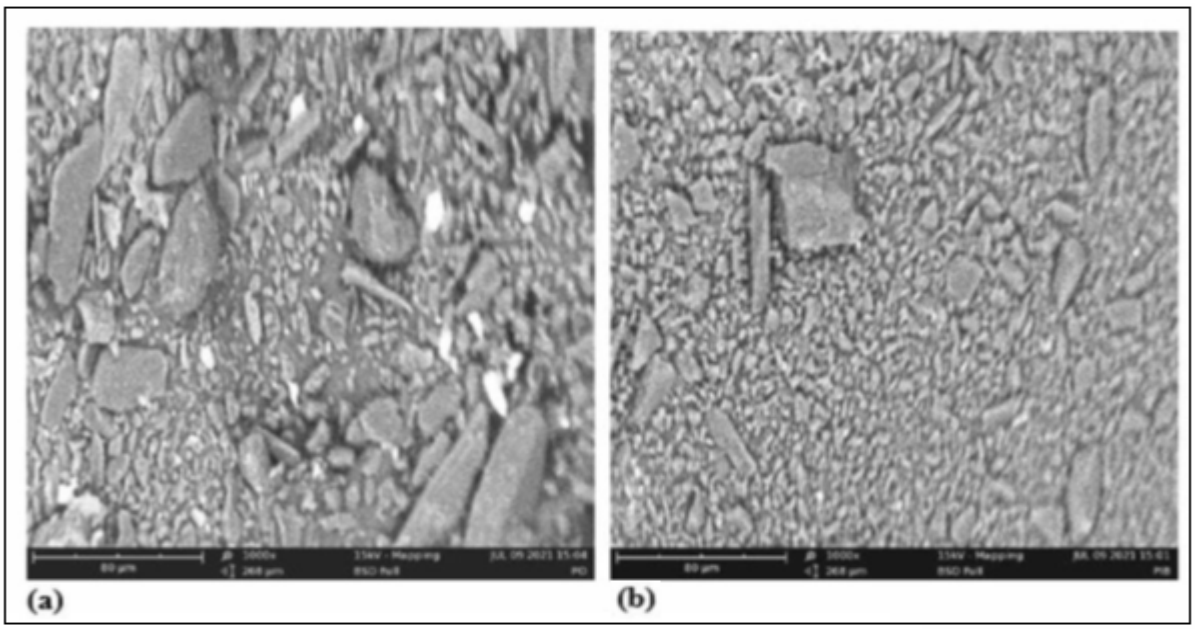

Fig. 8. (a) SEM image of paracetamol P0 (b) SEM image of HPMC stabilized paracetamol microcrystal (P1).

Conclusion

Preparation of paracetamol microcrystals was successfully carried out by solvent change method of the *in situ* micronization technique using HPMC and PVP K30 as stabilizing agents. Formulation P6, containing 0.08g of PVP K30 as stabilizing agents with a 1:6 ratio of solvent to anti-solvent (v/v) was the optimized formulation having the greatest solubility increase (5-fold), highest % drug content (98.3%) and highest drug release (95.32% within 60 minutes). The enhanced dissolution rates are attributed to the reduction of the particle size, change in crystal habit, formation of hydrophilic surface and the increased wettability due to adsorption of PVP K30 onto the surface of the paracetamol.

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