Communication

Release mechanism based on polymer-drug dissolution and stability studies of paracetamol solid dispersions

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Abstract

One of the greatest challenges facing the pharmaceutical industry is the design and development of suitable delivery systems to overcome poor dissolution profile for insoluble drugs. Different formulation approaches including particulate systems, pH alterations and co solvents have been investigated in an attempt to determine the critical formulation parameters to improve dissolution and solubility of poorly soluble drugs. The present study aims to investigate formulation development of solid dispersions for model poorly soluble drug, paracetamol with an overall objective of deciphering drug release mechanisms. Solid dispersions of paracetamol in polyethylene glycol 8000 as a hydrophilic carrier showed that dissolution rate was significantly increased when compared to polymer free formulations and was controlled by the rate of polymer dissolution. The study also showed that polymer to drug ratio was another key factor affecting drug release kinetics. In addition, stability studies were performed. Hyper-differential scanning calorimetry (Hyer-DSC), fourier transform infrared spectroscopy (FTIR) and thermogravimetric analysis (TGA) were carried out as part of the quality assessment criterion during stability studies. The results concluded that solid dispersions of paracetamol were stable at room conditions.

Keywords: Dissolution studies; Solid dispersions; PEG 8000; Paracetamol; Stability studies.

Introduction

Oral drug delivery is one of the popular routes for administration and the two critical stages for generating a therapeutic outcome include sufficient drug solubility in the gastro intestinal fluids and high permeability across the epithelial cells lining the gastro intestinal tract. Majority of the drugs coming through the drug discovery pipeline suffer from poor aqueous solubility due to the deployment of non aqueous solvents in the screening of drug libraries. Thus low solubility limits absorption and results in low bioavailability. As a result, enhancement of solubility and dissolution for poorly water soluble drugs remains one of the most significant challenges facing the pharmaceutical industry. To address this problem, formulation scientists have developed different approaches including salt formation[1], particulate systems[2], pH alterations[3], co-solvents[4] and solid dispersions[5]. Formulation of solid dispersion which involves dispersion of drug in an inert hydrophilic polymer matrix has produced promising results and has resulted in the translation of products into the clinic[6].

The development of solid dispersions has been under investigation for the past couple of decades and the progression in the field can be broadly classified into three generations i) first generation (drug and crystalline carriers) ii) second generation (drug with amorphous polymer carrier) and iii) third generation solid dispersions (drug with amorphous polymer carrier and surfactant). Despite the significant improvement in the design of solid dispersion based formulations, drug release mechanisms from these solid dispersion systems has been shown to be highly complex involving several mechanisms. Majority of the published work on drug release kinetics is solely based on drug dissolution without much focus on the role of the matrix which forms the greater proportion of the formulation. Only recently, various techniques such as refractometry, optical microscopy, fluorescence, gravimetry and microviscometry have been studied to understand the kinetic behaviour of polymeric matrix. In particular, microviscometry has been successfully used for studying dissolution profile of polyethylene glycol 8000 (PEG 8000) in solid dispersions of phenacetin and phenylbutazone[7]. Another factor which has had a major impact on the commercial turnaround of solid dispersions is the chemical and physical instability of the formulation upon storage [8, 9].

The present study aims at investigating formulation development of solid dispersions for model poorly soluble drug, paracetamol with an overall objective of deciphering drug release mechanisms. PEG 8000 as a hydrophilic carrier was selected as it has high aqueous

solubility, no toxicity or immunogenicity and approved by FDA as a safe excipient for human consumption. In addition, stability studies were performed to evaluate product stability over time under the influence of environmental factors such as temperature and humidity.

2. Materials and methods

2.1. Materials

Paracetamol, phosphate buffered saline (PBS) tablets and potassium bromide, were purchased from Sigma Aldrich, UK. Polyethylene glycol 8000 (PEG 8000) was obtained from Fluka (Biochemika), U.K.

2.2. Preparation of solid dispersions and physical mixture

Solid dispersions were prepared by melt fusion containing 5%, 10% and 15% (w/w) of paracetamol in PEG 8000[10]. Paracetamol 5%, 10%, 15% (w/w) and PEG 8000 were ground for 15 min in a mortar to prepare physical mixtures at room temperature (25°C).

2.3. Drug dissolution studies

In vitro dissolution tests were performed to evaluate the dissolution of paracetamol (free drug), physical mixture and solid dispersions. The dissolution studies were carried out using Hanson Research apparatus (SRII 6 Flask dissolution test station) fitted with a validata control unit. It was also equipped with 1 Litre round bottom flasks and baskets that conform to the Apparatus 1 standards laid out in the United States Pharmacopeia[11]. The dissolution testing was carried out at 37 °C in 1000 mL of dissolution media (PBS at a pH of 7.4), rotated at 100 rpm [10]. At predetermined time points 5 mL samples were taken, filtered (0.45 μm), analyzed for drug content using UV-visible spectrophotometer and replaced with fresh 5 mL (pre-warmed to 37 °C) dissolution media after each sampling (all experiments were performed in triplicate). Experiments for dissolution studies were performed for 60 min. The dissolution vessels were covered with lids to minimize and avoid evaporation.

2.4. Polymer dissolution studies

Microviscometry was used to measure the dissolution of PEG 8000 from drug-PEG 8000 solid dispersions. The samples were measured on an Anton-Parr AMVn (Austria) version 1.612047 microviscometer, equipped with the visionlab software. The following conditions

were used for each run: temperature - 25 °C, AMVn measuring programme: Standard 50 x 4 and AMVn measuring system 15084989.

PEG 8000 was dissolved in PBS over the concentration range of 2 mg/mL to 10 mg/mL for the calibration curve. The dissolution of PEG 8000 from the drug polymer solid dispersion systems was measured using microviscometry[7] for all samples at the same time intervals as that for drug. All the measurements were done in triplicate.

2.5. Hyper-Differential scanning calorimetry (Hyper-DSC)

Perkin-Elmer Diamond DSC with a thermal analyzer, equipped with Pyris software was employed to obtain Hyper-DSC data. 2- 5 mg samples were crimped and placed on the sample furnace after weighing into a non-hermetically sealed DSC sample pan. Heat flow rate of 500 °C/min was used heat the samples from 0 °C to 300 °C. Helium was used as a purge gas. In order to derive the melting points of each peak onset temperature was measured. For reference an empty pan was crimped. All the measurements were performed in triplicate.

2.6. Infrared spectroscopy

FTIR spectrometer Pye Unicam Ltd (Cambridge, England) was used to obtain FTIR spectra. The samples were mixed thoroughly with potassium bromide at 1:100 (sample: potassium bromide) weight ratio after being ground. Pressure of 5 tons was applied for 5 min to compress the powder in order to prepare potassium bromide discs in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1} at a scan rate of 16. All the studies were performed in triplicate.

2.7. Spectrophotometric Analysis

Drug concentration was measured and determined in solution via spectrophotometric technique using quartz cuvette. Paracetamol (measured amounts) was dissolved in phosphate buffered saline (PBS) at pH 7.4. Unicam UV-visible spectrophotometer (200nm-400nm) was used to determine the wavelength for maximum absorption. A stock solution of paracetamol was prepared at 30 μg/mL in PBS (pH 7.4) for calibration. The linearity of calibration curve was obtained in the concentration range from 2 μg/mL to 14 μg/mL and analysed by UV spectroscopy at λ_{max} of 240 nm.

2.8. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was performed using a Perkin Elmer, (Pyris TGA) instrument with ThermoGravimetric Analyser. A pan base was loaded onto the mass stir up of the TGA and tared. The pan base was then loaded with known weight of sample which was evenly spread. This was then transferred onto the TGA and the furnace was raised. A typical heating run consisted of heating the sample from 30 °C to 150 °C at a rate 20 °C/min[12]. The average mass loss was calculated for each sample. All the studies were done in triplicate.

2.9. Mathematical models of release kinetics

Release of paracetamol from solid dispersions was examined after application of zero order, first order, Hixson–Crowell cube root, Higuchi model and Korsemeyer–Peppas models.

2.9.1. Zero order kinetic model

In order to analyze release kinetics, the *in vitro* release data were plotted as cumulative amount of drug released versus time. Drugs in dosage forms that tend to slowly release the drug due to non-disintegration can be measured for their dissolution profiles by applying the below equation.

$M_0 - M_t = k_0 t \quad \rightarrow (1)$

2.9.2. First order model

The data obtained was plotted as log cumulative percentage of drug remaining versus time.

$\ln(M_0/M_t) = k_1 t \quad \rightarrow (2)$

2.9.3. Higuchi model

Higuchi proposed this model which was aimed at gaining more understanding of drug release from a matrix system. The data obtained were plotted as cumulative percentage drug release versus square root of time. It can therefore be applied to monitor the drug dissolution from various pharmaceutical dosage forms.

$M_t = k\sqrt{t} \quad \rightarrow (3)$

2.9.4. Hixson-crowell model

Hixson and crowell recognized that the area of the particles is proportional to the cube root of its volume.

$(W_0)^{1/3} - (W_t)^{1/3} = kt \quad \rightarrow (4)$

2.9.5. Korsmeyer peppas model

Koremeyer et al. (1983) derived a simple relationship to observe and understand the drug release mechanism from polymeric system. *In vitro* release data was converted into the fraction of drug or polymer released from the solid dispersions and plotted against time. This plot was then fitted to the model described in peppas equation.

$M_t/M_\infty = kt^n \quad \rightarrow (5)$

where M_0 and M_t represent to the drug amount taken at time equal to zero and dissolved at a specific time, t, respectively. The term W_0 is the initial amount of drug and W_t is the remaining amount of drug at time t in the pharmaceutical dosage form. M_t/M_∞ is a fraction of drug released at time t and n is the release exponent. Where k_0, k_1 and k refer to the release rate constants determined from the linear curves of zero order, first order, Hixson Crowell cube root law, Higuchi model and Korsemeyer-Peppas respectively.

2.10. Stability Studies

The representative samples of solid dispersions were placed in a controlled temperature and humidity cabinets **(**Firlabo, 6100). The stability study was conducted according to the International Conference on Harmonization (ICH) guidelines and was carried out at 40°C±2°C/75±5% RH and 25°C/60±5% RH to simulate accelerated and room temperature conditions respectively. The physicochemical properties of these dispersions were evaluated after 0, 1 and 3 months.

3. Results and discussion

3.1. Drug-polymer dissolution studies

Dissolution profile of solid dispersion of paracetamol demonstrated that drug released faster from solid dispersions when compared to drug alone and its respective physical mix (**Fig. 1**). Solid dispersions of different poorly water-soluble drugs with hydrophilic polymer have been formulated for improving drug dissolution rate[13]. Drug release from 5% (w/w) paracetamol formulation was faster as compared to 10% and 15% (w/w) formulations over the entire duration of the study. The dissolution profiles further reveal that drug release was slower from the formulations containing high paracetamol content as compared to low paracetamol content formulations. Study by Lin and Cham[14] investigating the formulation of solid

dispersions of naproxen in PEG 6000 showed faster drug release from 5% naproxen loading as compared to 20%, 30% or 50% (w/w) drug loading. Similar results were also reported for various other drug candidates including oxazepam[15], carbamazepine[16] and zolpidem[17]. Dubois and Ford[10] suggested that lower concentrations of drug in the formulation results in polymer controlled dissolution profile which is primarily reliant on the rate of dissolution of polymer rather than the properties of the drug. The drug to polymer ratio in a solid dispersion is one of the important factors in the formulation of solid dispersions. High polymer to drug ratio can produce better wettability resulting in an enhanced solubility possibly due to a more homogenous dispersion of the drug within the polymer matrix. Characterisation of solid dispersions of paracetamol was reported in our previous paper[18] which suggested that the drug was present in an amorphous form in the formulation.

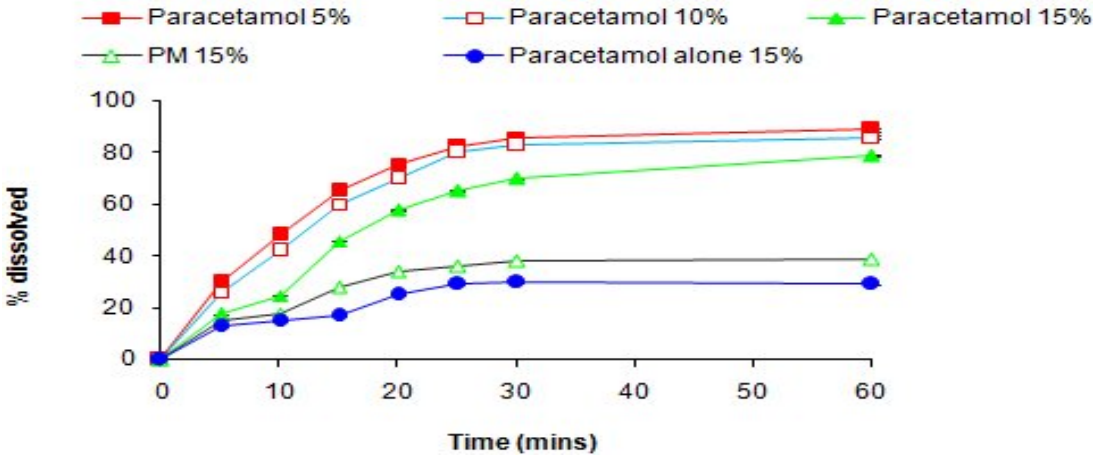

Figure 1. Dissolution profiles of paracetamol/PEG 8000 solid dispersion; 5% (w/w), 10% (w/w), 15% (w/w), 15% (w/w) physical mix (PM) and 15% (w/w) paracetamol alone is presented for comparison. Data are expressed as mean (*n* = 3).

The next phase of the work was to study the application of microviscometry to measure dissolution of the polymer at predetermined time periods. Polymer and drug release from 5% (w/w) formulation of paracetamol was 46% and 27% respectively after 5 mins (**Fig. 2**). Polymer dissolution was 100% after 30 mins as compared to 85% for paracetamol. On the other hand, formulations with 10% (w/w) paracetamol formulation demonstrated a 68% and 60% release for polymer and drug respectively after 15 mins. The percent release from 15% (w/w) solid dispersions of paracetamol was 30% and 17% for PEG 8000 and paracetamol respectively after first 5 min. Polymer dissolution was 100% after 30 mins with only 69% drug release for the same duration (**Fig. 2**).

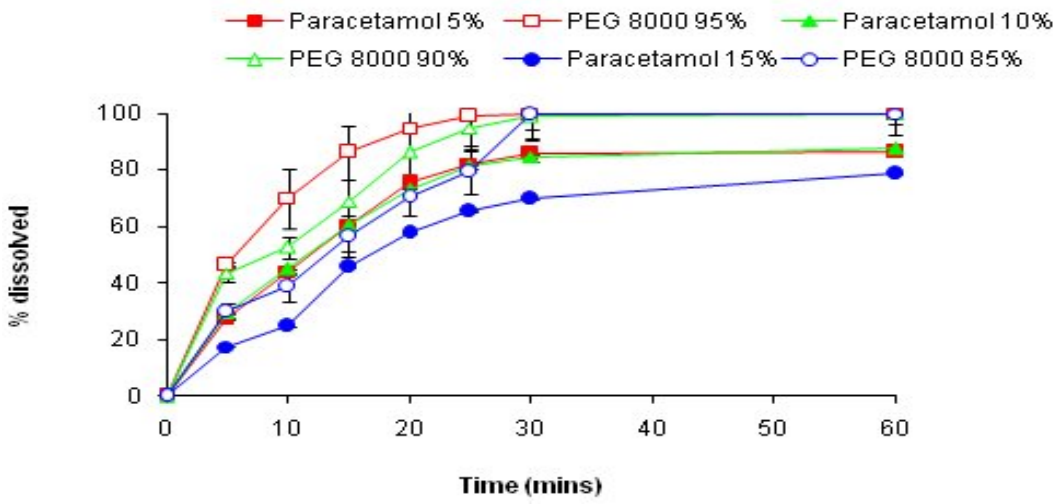

Figure 2. Dissolution of PEG 8000 and paracetamol from 5%, 10% and 15% (w/w) solid dispersion. Data are expressed as mean (*n* = 3; mean±S.D.).

The results highlight the importance of polymer dissolution in controlling drug release from solid dispersions. It can be concluded that polymer dissolution is a vital component in drug release from polymeric matrix formulation and that optimisation of polymer to drug ratios is important in the design and development of solid dispersions for poorly water soluble drugs. To further understand the release mechanism, the data was subjected to mathematical analysis to determine release/dissolution profile characteristics from the formulations.

3.2. Release kinetics studies

There is a plethora of literature available to study drug release kinetics from solid dispersions which is primarily based on properties of the drug without any focus on the role of carrier within the system. In the present work drug release kinetics and release mechanism were assessed by evaluating both carrier and drug release concurrently for the same polymeric composition and measuring polymer dissolution in addition to drug release mechanism.

The dissolution data for paracetamol and PEG 8000 were fitted into different kinetic equations including zero order, first order, Higuchi, Hixson-Crowell'S and Peppas equation. The R^2 value obtained is presented in **table 1** for various equations. The best linearity was found for Higuchi suggesting that the release of drug from polymeric matrix depends on Fickian diffusion according to Higuchi model. Similarly, Peppas equation is mostly applied to describe the release of drugs from polymeric formulations. The diffusion coefficient, n is dependent on the geometry of the formulation and n value of 0.45 indicates Fickian diffusion,

0.45<n<0.89 indicates anomalous mechanism and occurs due to a combination of Fickian diffusion and polymer relaxation. When n = 0.89, it indicates case II transport where the dominant mechanism for drug transport is due to polymer relaxation. The n value for 5% (w/w) paracetamol loading was observed to be 0.463 which increased to 0.517 for 10% (w/w) solid dispersion of paracetamol. This trend continued as the n value in the case of 15% (w/w) paracetamol loading was calculated as 0.676. On other hand, the value of n was 0.319, 0.391 and 0.554 for 95%, 90% and 85% (w/w) PEG 8000 loading respectively. From drug-polymer kinetics studies it can be concluded that polymer dissolution is the critical parameter that controls the release of the drug from the solid dispersion. The main driving force was PEG 8000 that controlled the paracetamol release from solid dispersions. This might be due to the hydrophilic nature of PEG 8000 and possibly also due to the conversion of crystalline drug into amorphous form during formulation.

Table 1. The correlation coefficient (R^2) for drug release (Equation 1-5) from each of the solid dispersions and diffusional coefficient, n, of Peppas model (Equation 5).

	R^2 Values					
Formulations	**Zero order**	**First order**	**Hixson-Crowel**	**Highuchi**	**Peppas**	**n value**
Paracetamol SD 5% (drug)	**0.627**	**0.412**	**0.750**	**0.913**	**0.876**	**0.463**
Paracetamol SD 95% (polymer)	**0.497**	**0.263**	**0.768**	**0.850**	**0.805**	**0.319**
Paracetamol SD 10% (drug)	**0.654**	**0.398**	**0.754**	**0.965**	**0.883**	**0.517**
Paracetamol SD 90% (polymer)	**0.615**	**0.291**	**0.902**	**0.811**	**0.882**	**0.391**
Paracetamol SD 15% (Drug)	**0.757**	**0.460**	**0.845**	**0.978**	**0.901**	**0.676**
Paracetamol SD 85% (polymer)	**0.743**	**0.344**	**0.890**	**0.744**	**0.920**	**0.554**

3.3. Stability studies

The last phase of the work was to evaluate the stability profile of the formulations at different conditions. Tablets comprising of solid dispersions of paracetamol were prepared and packed in aluminium foil wrapping to simulate blister packaging of the final product. Hyper-DSC, FTIR and thermogravimetric analysis (TGA) were carried out as part of the quality assessment criterion for the formulations.

Representative hyper-DSC curves for solid dispersion of paracetamol with PEG 8000 at accelerated conditions (40°C/75%RH) and room conditions (25°C) of storage are shown in **Fig.3**. The onset temperature for solid dispersions of paracetamol was 59°C (**Fig. 3a**) and after 3 months storage at room conditions (**Fig. 3c**) stayed the same as no changes were

observed in onset indicating the absence of any crystalline paracetamol. However samples stored under accelerated conditions (Fig. 3b) after 1 month revealed 4 thermal events at 52 °C, 143°C, 160°C and 183°C. The thermal event at 52°C possibly corresponds to the melting of the carrier which was lower than the onset temperature for paracetamol solid dispersions as this might be due to the high humidity at accelerated conditions resulting in water sorption by the drug. The peaks at 143°C and 160°C possibly belong to the drug, which suggests that paracetamol reverted to other polymorphic form and recrytallized at 183°C.

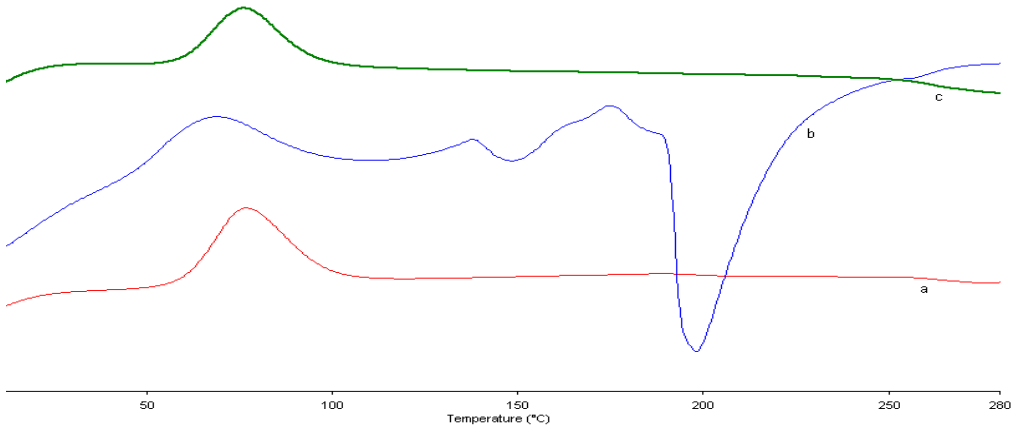

Figure 3. DSC traces of solid dispersions of paracetamol with PEG 8000 (a, t=0), stored at 40°C/75%RH (b, t=1) and at room temperature 25°C (c, t=3). t represents storage time (months).

Analysis of spectra for paracetamol solid dispersion (**Fig. 4**) showed specific absorption bands at wave number 3500, 3291, 2888, 1267, 1250, 1243, 1149 and 700cm^{-1} corresponding to the stretching associated with O-H, N-H, O-H, C-H, C-C, C-O, C-O and C-C respectively.

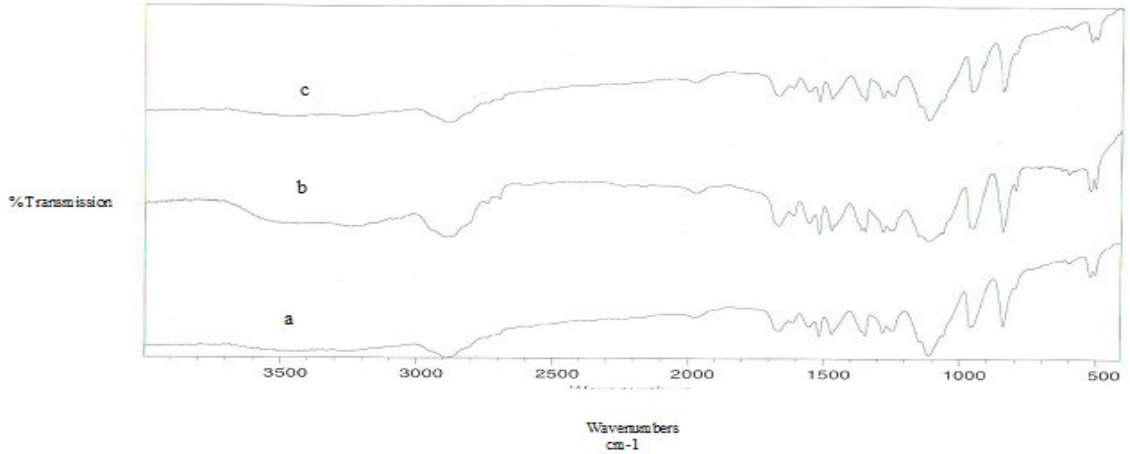

Figure 4. FTIR of solid dispersions of paracetamol with PEG 8000 (a, t=0), stored at 40°C/75%RH (b, t=1) and at room temperature 25°C (c, t=3). t represents storage time (months).

The results showed that there was no interaction (as there was no change in the spectra) after 3 months storage at room temperature (25°C) which was also further supported by Hyper-DSC studies. However changes were observed in the case of samples stored at accelerated conditions (40°C/75%RH) after 1 month at wave number 3500 and 2888cm^{-1} associated with O-H and N-H respectively.

Moisture content of the formulation was also assessed as amorphous forms of the drug have been shown to have enhanced affinity for water absorption. The moisture content of paracetamol solid dispersion was 0.54±0.29 % at the start of stability period but after 1 month storage at accelerated conditions (40°C/75%RH) increased to 9.76±0.42% (**Fig. 5**). Formulations stored at room conditions (25°C) showed similar results (0.50±0.18) after 3 months as that observed at the initial time point suggesting minimum absorption of moisture.

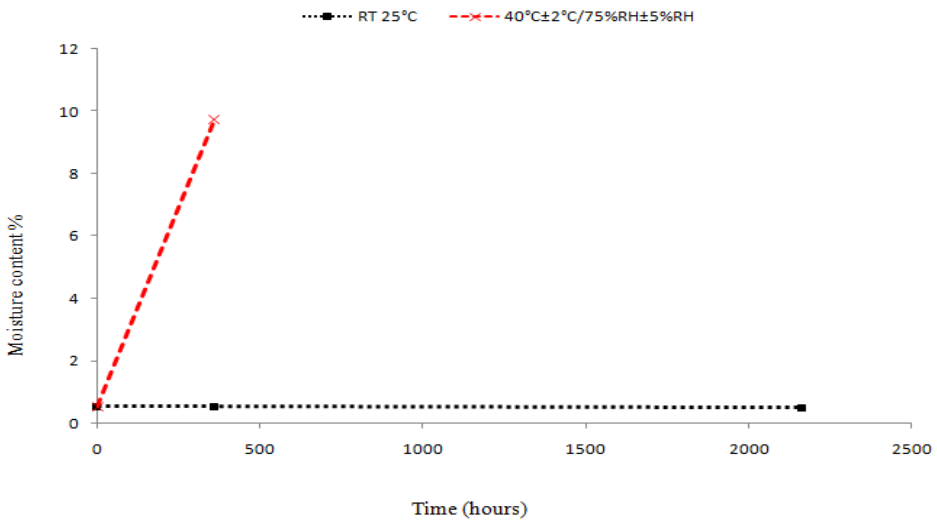

Figure 5. Moisture content of solid dispersions of paracetamol with PEG 8000 (t= 0) stored at 40°C±2°C/75%RH±5%RH (t= 1) and room temperature (RT) 25°C (t= 3). t represents storage time (months) (*n* = 3; mean±S.D.).

The differences in the thermal profile and IR spectra can be explained based on the data obtained from moisture analysis. Thermodynamically, amorphous form comprises of high energy state which is metastable and subsequently during the course of time, reconverts into more stable crystalline state. Exposure of metastable systems to high humidity and temperature may induce changes resulting in a decrease in their dissolution properties, melting point and FTIR spectra. Stability studies revealed that solid dispersions were unstable at accelerated storage conditions. This can be attributed to high temperature which enhances the movement of molecules within the matrix system causing decomposition and conversion

of amorphous drug into crystalline form possibly due to melting of the glassy amorphous cage into a stable crystalline lattice. In addition, previous research has shown that amorphous form absorb water and can cause instability of solid dispersion based formulation[19,20]. The increase in moisture content in solid polymer matrices causes drug degradation due to the plasticizing effect of water. One of the main disadvantages of amorphous form is its hygroscopic nature as compared to its crystalline counterpart. Moisture absorbed during accelerated conditions possibly acts as a plasticizer and might lower the glass transition temperature of the amorphous drug. This leads to enhanced molecular mobility and may affect both physical and chemical stability. On the other hand, solid dispersions stored at room temperature (25°C) were stable after 3 months.

Conclusion

The study highlights that optimisation of drug to polymer ratio can be used to tailor the rlease kinetics of poorly water soluble drugs from hydrophilic matrices. In addition, polymer dissolution studies can provide vital information on drug release mechanisms. The study also further reiterates previous findings that amorphous form of the drug upon exposure to temperature and moisture converts to a more stable crystalline form.

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