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Material and Tableting Properties of Theophylline Solid Dispersions

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ABSTRACT

This study was carried out to evaluate the material and tableting properties of theophylline solid dispersions (SDs) prepared by the solvent evaporation technique using Eudragit polymers (RS 100 & RSPO) as carriers. The dispersions were directly compressed into tablets using microcrystalline cellulose (MCC) as filler/binder. Compatibility studies of the prepared dispersions were conducted using FTIR, DSC and TLC while physico-technical properties of the tablets were evaluated. Results of compatibility studies revealed no chemical interaction between theophylline and the selected polymers. All the tablet properties evaluated were in conformity with the USP specifications. *In vitro* drug release was observed to be prolonged for about 24 h and the mechanism of drug release was principally by diffusion. Stability studies showed that drug content of all the tablets remained within the official specifications after three months. Overall, the material properties of the SDs were consistent with good tableting properties as confirmed by the tablets produced.

Keywords: Solid dispersion, tablets, direct compression, Eudragit®RS100, Eudragit®RS PO, drug release

1. INTRODUCTION

Solid dispersion techniques have proved to be successful interventions in the development of drug delivery systems (Verma and Rudraraju, 2014). Solid dispersions have been used to greatly improve the dissolution rate, absorption and oral bioavailability of drugs with poor aqueous solubility profile (Chris and William III, 2013) and has also been employed in the design and development of controlled release formulations (Kamlesh et al. 2012). According to Chau et al (2013) classification of solid dispersions, the fourth generation of solid dispersions serve as double target systems which not only enhance drug solubility, but also extend drug release in a controlled manner. Such studies include the report by Orugun et al (2016) which revealed that solid dispersions formulated with Eudragit® RS 100 and RSPO extended the release of theophylline for over 24 h. Similar studies have also been conducted in the last decade where drugs characterized by short biological half-life and multiple dosing regimen have been transformed into once daily dosing regimen with an extended release profile when prepared as solid dispersions (Kamlesh et al. 2012; Verma and Rudraraju, 2014).

Due to the advantages offered by tablets as a dosage form, researchers have explored the option of formulating solid dispersions into tablets. Tablets remain the undisputed and widely acceptable dosage form for very obvious reasons. Factors such as physical and chemical stability, solubility, dissolution, bioavailability, and manufacturability (Patel et al. 2016) influence the development of solid dispersions into tablets hence, the necessity of characterizing the material properties of solid dispersions to determine its suitability for tableting.

As a follow up to a previous study, where theophylline solid dispersions were developed by solvent evaporation technique using Eudragit® polymers as rate retarding carriers (Orugun et al. 2016), the present study explored the material and tableting properties of theophylline solid dispersions as well as stability studies. The principle of solid dispersion technique is based on its ability to improve the solubility of a poorly soluble drug in a given formulation. However, application of the solid dispersion technique is not limited to solubility enhancement but has been used to develop controlled release preparations when formulated using water insoluble polymers like Eudragit. Theophylline was therefore selected as the drug candidate because it meets the requirement for controlled release formulations. It is a water soluble drug that is administered 2 -3 times a day. Preparation of theophylline solid dispersions was able to extend the release of theophylline over a period of 24 h which may ensure a once daily dosing and promote patient compliance.

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2. MATERIALS AND METHODS

2.1. Materials

Theophylline (Sigma Aldrich laborchemikalien GmbH, Germany), Eudragit® RS 100, Eudragit® RSPO (Evonik Pharma Germany), Methanol, Conc. Hydrochloric acid, Acetone, Calcium chloride, Potassium Chloride (BDH Chemicals Poole, England), Monobasic Potassium Phosphate (Sigma Chemical Co., USA), Sodium Hydroxide (Merck, Germany). All other chemicals used were of analytical grade.

2.2. Formation of solid dispersions

Solid dispersions were formulated according to the method of Orugun et al. (2016).

2.3. Fourier Transform Infra-red (FT-IR) studies

The IR spectra for Theophylline, Eudragit® RS 100, Eudragit® RSPO and SDs were obtained with the Cary 630 FTIR Spectrometer (Agilent Technologies, USA) within the range of 650 – 4000 cm. Appearance, disappearance or broadening of absorption band(s) on the spectra of the solid dispersions in comparison to theophylline were used to determine possible interactions in the formulation (Poovi et al. 2013).

2.4. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) thermograms were obtained from the Phoenix Differential Scanning Calorimeter (Perkin Elmer Pyris 6 DSC model, Germany). Approximately 5 mg of sample was placed in flat-bottomed aluminium pans. Thermograms were recorded at a heating rate of 5 ^{0}C/min from 0 to 300 ^{0}C. Melting peaks, glass transition and enthalpies were calculated using the Mettler Star software and used to ascertain possible incompatibility or not between the components of the solid dispersion formulations.

2.5. Thin Layer Chromatography (TLC)

Chromatographic plates were spotted with solutions of the solid dispersions and developed in a chamber containing butanol:chloroform:acetone:ammonium solution (40:30:30:10). Afterwards, the TLC plates were air dried, viewed under UV light for spots and the R_f values were calculated (www.chem.zenkyo.h.kyoto – u.ac.jp/operation). The R_f were calculated using the formula below:

$$R_f = \frac{Migration\ distance\ of\ drug}{Migration\ distance\ of\ the\ solvent} \quad \ldots\ldots\ldots 1$$

2.6. Dilution Potential

Powder mixtures of MCC and SDs were prepared in the following ratios: 20:80, 30:70, 40:60, and 50:50 and compressed into tablets on the Single Punch Tablet Press (Erweka, Germany). These tablets were evaluated for crushing strength and friability to determine the optimal carrying capacity (dilution potential) for the SDs. The mixture which gave the optimized tablet properties in terms of superior crushing strength and minimal friability was chosen as the formula for tablet formulation (Table 1).

2.7. Tableting

Tablets of SDs and PD were prepared by direct compression using MCC as the sole excipient. Tablets weighing either 420 or 500 mg were compressed on the Single Punch Tablet Press. The tablets were kept for 24 h to allow for elastic recovery and the properties evaluated afterwards. The formula for tablet formulation is given in Table 1 below.

2.8. Physicotechnical properties of tablets

The tablets were evaluated for the following parameters;

2.8.1. Weight Variation test

The mean weight of ten (10) tablets sampled randomly from each batch was determined and recorded with its standard deviation.

2.8.2. Crushing strength

The crushing strength of five (5) tablets from each batch was determined using the Monsanto hardness tester (Monsanto Chemical Co., USA. The mean of the determinations was then recorded for each batch.

2.8.3. Friability

Ten (10) tablets were weighed and placed into the friabilator (Erweka, Germany) and allowed to rotate at 25 rpm for 4 min. At the end of 4 min, the tablets were taken out, dusted and re-weighed. The percentage weight loss was expressed as friability using the equation below:

$$\% \text{ friability} = \frac{W_i - W_f}{W_i} \times 100\ \% \ldots\ldots\ldots 2$$

where w_i = Initial weight and w_f = Final Weight

2.8.4. Disintegration time

The disintegration test was conducted according to USP (2011). Six tablets were placed in a disintegration tester (Type ZT3, Erweka, Germany) filled with distilled water at 37 ± 0.2 ^{o}C. The time taken for all the particles of the tablet to pass through the disintegration mesh was noted and the mean of six determinations was recorded for each batch.

2.8.5. In vitro dissolution studies

The drug release profile for the prepared tablets from SDs was determined as described in the USP (2011) using dissolution apparatus type II (Universal dissolution tester, UDT 804, United States). Drug release studies was carried out in 900 ml of simulated gastric fluid (SGF) without pepsin (pH 1.2) as dissolution medium for 24 h at 37± 0.5 ^{0}C and stirred at a rate of 50 rpm. One tablet was placed in the basket and at predetermined time intervals; 2 ml samples were withdrawn and replaced with equivalent volume of the fresh medium at the same temperature to maintain sink conditions throughout the study. The samples withdrawn were filtered through a 0.45 µm Whatman filter paper and assayed

spectrophotometrically at 271 nm (UV-1800 Shimadzu, Japan). For the purpose of comparison, the dissolution of pure theophylline tablet was also carried out. The entire dissolution procedure was repeated using simulated intestinal fluid (SIF) without pancreatin (pH 7.4) as the dissolution medium. The experimental set up is displayed in Figure 2.

2.9. Kinetic studies

Data from the *in vitro* studies were fitted into different kinetic models including zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models to determine the best kinetic fit and mechanism of release.

2.10. Stability studies

This study was conducted using the optimized tablet formulations. Tablets were stored at room temperature (25 ± 2 ^{o}C) in a desiccator for 3 months, after which they were evaluated for presence and content of theophylline.

3. RESULTS

3.1. Percentage yield and solubility of solid dispersions

The percentage yield of SD4, SD5, SD9 and SD10 ranged from 63.7 – 81.8 % and was observed to decrease as the concentration of polymer increased as reported in an earlier study (Orugun et al. 2016). The solubility of theophylline in SDs also decreased as the content of polymer increased. Notwithstanding, the entrapment efficiency (EE) of SDs increased with increasing concentration of polymer. Based on the solubility profile, four SDs namely SD4, SD5, SD9, and SD10 were selected for further studies.

3.2. Fourier transform Infra-Red (FT-IR)

The infrared spectra of theophylline, Eudragit® RS 100 and solid dispersions are presented in Figure 2(A). Typical IR bands of theophylline occurring at 1453.41cm^{-1}, 1568.18 cm^{-1}, 1674.27 cm^{-1} and 3399.65 cm^{-1} corresponds to C-H stretching, C=N stretching, C=O stretching in amines and N-H stretching respectively. Spectrum of Eudragit® RS 100 show peaks at 1726.35 cm^{-1} attributed to C=O stretching in esters, peaks at 1456.30cm^{-1} indicate C-H stretching in alkanes while a broad peak at 1159.26 cm^{-1} indicate C-O stretching in esters and a peak at 1017.48 cm^{-1} indicates C-N stretching. The spectrum of Eudragit® RSPO in Figure 2(B) was observed to be similar to that of Eudragit® RS 100 indicating similarity in their chemical structure. On the other hand, the IR spectra of theophylline solid dispersions (Figures 2A and 2B) were observed to reflect characteristic IR bands of theophylline and the corresponding polymer.

3.3. Differential Scanning Calorimetry (DSC)

The DSC thermogram for pure theophylline, Eudragit® RS 100 and SD4 displayed in Figure 3(A) shows an endothermic peak at 390.5 ^{0}C corresponding to the melting peak of the polymer while that of theophylline was observed to be at 275.1 °C. Disappearance of the melting peak of theophylline in the thermograms of SD4 and SD9 (Figure 3B) reveal the amorphous nature of theophylline in these formulations.

3.4. Thin Layer Chromatography (TLC)

The distance which the drug migrated, relative to the solvent system is displayed in Table 2 as retention factor (R_f) values; the results confirm that polymers moved with the solvent front (www.chem.zenkyo.h.kyoto-u.ac.jp/operation).

The number of spots obtained after separation of SD4, SD5, SD9 and SD10 represents the number of components that constitutes these formulations.

3.5. Dilution Potential

The result of the carrying capacity (dilution potential) of MCC in the formulation of solid dispersion tablet is presented in Table 3 below. The crushing strength of the tablets increased as the content of MCC increased with a corresponding decrease in friability. The minimum ratio of 40 % MCC in the powder mixture produced tablets with acceptable crushing strength and friability.

3.6. Physico-technical properties

The tablet properties of solid dispersion and pure drug evaluated are given in Table 4. Crushing strength values ranged from 85.6 – 118.3 N with the solid dispersion formulations (SD4, SD5, SD9, SD10) having the highest values due mainly to the binding properties of Eudragit polymers. The friability parameter did not exceed 1 % for all the batches. The thickness data obtained was consistent with mean weight recorded for each batch of tablets. Disintegration time exceeded 8 h for all batches including the pure drug suggesting that MCC has poor disintegrating functionality and will be most suitable as a sustained release agent.

3.7. Dissolution Studies for Tablets

The drug release from the various tablets of SDs formulated with Eudragit® RS 100 and RSPO in SIF and SGF is depicted in Fig. 4. The graph shows that the maximum release of tablets from SDs was found to be 98.82 % in 24 h (SIF) and 95.84 % in 24 h (SGF). The plot shows that the pattern of release of theophylline from solid dispersion tablets was sustained over a period of 24 h as compared to tablets containing pure drug where drug release was faster and maximum drug release was attained at ≈ 8 h.

3.8. Kinetics of drug release

Table 5 summarizes the release kinetic parameters and correlation coefficients (R^2) calculated for the investigated formulations. The *in vitro release* data indicates that the release of theophylline from the solid dispersion tablets and pure drug tablet is most fitted to diffusion-controlled mechanism (Higuchi model) based on the higher correlation coefficient. Korsmeyer-Peppas model was applied to give more insights on other drug release mechanisms.

Table 1. Tablet formula for solid dispersions and pure drug

Formulation	Amount of solid dispersion per tablet (mg)	Amount of MCC per tablet	Total weight of tablet
SD4/SD9	250	170	420
SD5/SD10	300	200	500
PD1	50	370	420
PD2	50	450	500

Key:
SD4: Theophylline: Eudragit® RS 100 (1:4) SD9: Theophylline: Eudragit® RSPO (1:4)
SD5: Theophylline: Eudragit® RS 100 (1:5) SD10: Theophylline: Eudragit® RSPO (1:5)
PD1 and PD2: Pure Theophylline tablet of 420 mg and 500 mg weights respectively

Table 2. Thin layer chromatography (TLC) of theophylline, polymers and solid dispersions

Formulations	Theophylline	Eudragit® RS 100	Eudragit® RSPO	Number of Spots	Rf Values
Pure theophylline	+	-	-	1	0.314
Eudragit® RS 100	-	+	-	1	1
Eudragit® RSPO	-	-	+	1	1
SD4	+	+	-	2	0.314, 1
SD5	+	+	-	2	0.316, 1
SD9	+	-	+	2	0.314, 1
SD10	+	-	+	2	0.315, 1

Key: + = present - = absent

Table 3. Dilution Potential

Binary Mix (MCC: SD)	Crushing Strength (N)	Friability (%)
20:80	50 ± 1.00	1.67 ± 0.02
30:70	65 ± 0.10	1.33 ± 0.30
40:60	100 ± 1.00	0.67 ± 0.03
50:50	110 ± 0.20	0.53 ± 0.15

Table 4. Physico-technical properties of tablets

Parameters/Batches	TSD4	TSD5	TSD9	SD10	TPD1	TPD2
Weight (mg)	416.67 (0.7)	494.44 (0.7)	421.11 (0.1)	503.67 (0.7)	418.25 (0.6)	502.15 (0.5)
Thickness (mm)	3.81 (0.1)	4.36 (0.1)	3.78 (0.1)	4.37 (0.04)	3.83 (0.03)	4.45 (0.1)
Crushing strength (N)	108.3 (0.8)	113.3 (0.6)	108.3 (0.8)	118.3 (0.8)	85.6 (0.4)	92.5 (0.3)
Friability (%)	0.80	0.67	0.79	0.65	0.90	0.85
Disintegration time (h)	> 8	> 8	> 8	> 8	> 8	> 8

Key:
TSD4: Theophylline: Eudragit RS 100 (1:4) TSD5: Theophylline: Eudragit RS 100 (1:5)
TSD9: Theophylline: Eudragit RSPO (1:4) TSD10: Theophylline: Eudragit RSPO (1:5)
TPD1: Pure Theophylline tablet TPD2: Pure Theophylline tablet

Table 5. Kinetics of theophylline release from solid dispersion tablets according to different kinetic models

Formulations	Correlation Coefficient (R^2)					Korsemeyer-Peppas (n)
	Zero-order	First-order	Higuchi	Hixson- Crowell	Peppas	
TSD4a	0.604	0.320	0.863	0.206	0.614	0.448
TSD4b	0.663	0.131	0.896	0.113	0.893	0.446
TSD5a	0.626	0.147	0.872	0.126	0.639	0.446
TSD5b	0.687	0.885	0.903	0.189	0.650	0.452
TSD9a	0.627	0.192	0.867	0.195	0.647	0.450
TSD9b	0.713	0.163	0.913	0.173	0.655	0.458
TSD10a	0.635	0.156	0.866	0.169	0.666	0.457
TSD10b	0.724	0.147	0.911	0.753	0.688	0.467

Key:
TSD4a – Theophylline: Eudragit RS 100 (1:4) in SIF TSD5a – Theophylline: Eudragit RS 100 (1:5) in SIF
TSD9a– Theophylline: Eudragit RSPO (1:4) in SIF TSD10a– Theophylline: Eudragit RSPO (1:5) in SIF
TSD4b – Theophylline: Eudragit RS 100 (1:4) in SGF TSD5b– Theophylline: Eudragit RS 100 (1:5) in SGF
TSD9b – Theophylline: Eudragit RSPO (1:4) in SGF TSD10b – Theophylline: Eudragit RSPO (1:5) in SGF

Table 6. Drug content of solid dispersion tablet after three months of storage

Formulation	Drug Content (mg)	
	Initial	Final
TSD4	85.67 ± 1.53	85.00 ± 0.45
TSD5	91.33 ± 2.08	90.85 ± 0.15
TSD9	77.67 ± 1.53	77.13 ± 0.20
TSD10	86.33 ± 1.16	85.97± 0.35

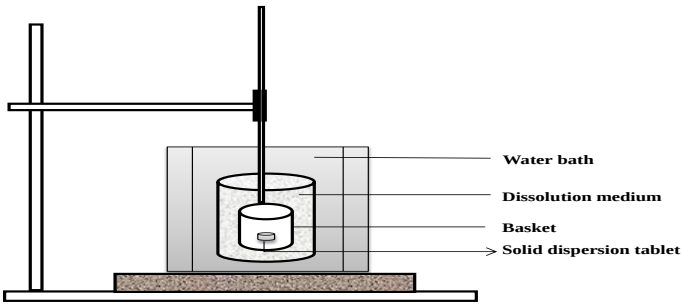

Figure 1. Dissolution setup for formulated solid dispersion tablet

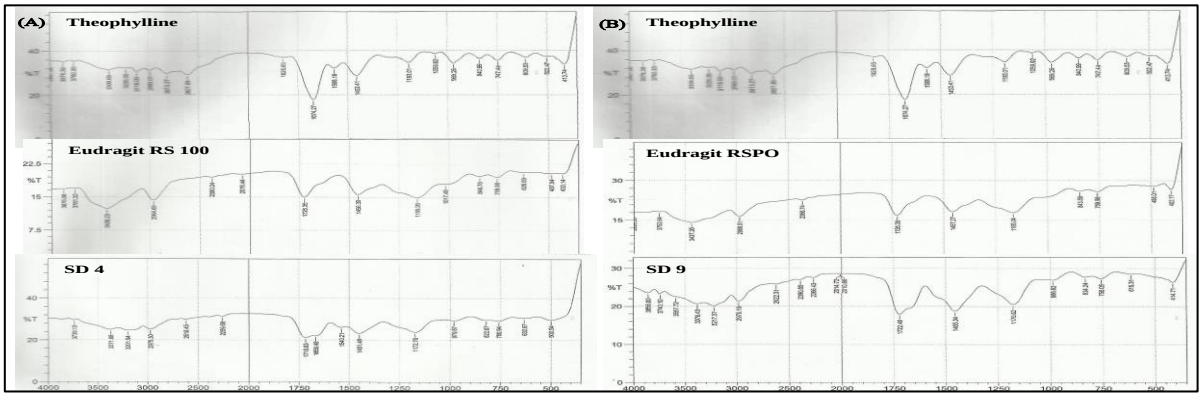

Figure 2. FT-IT spectra of (A) Theophylline, Eudragit RS 100 and SD4 and (B) Theophylline, Eudragit RSPO and SD9

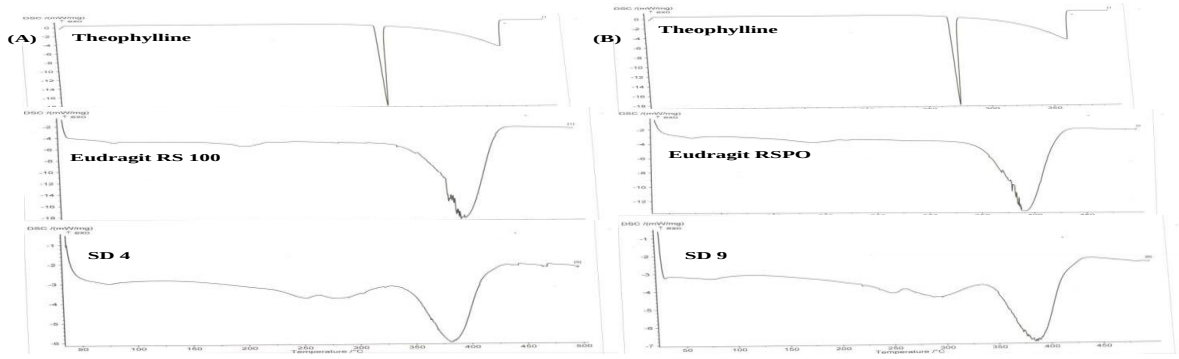

Figure 3. DSC thermograms of (A) Theophylline, Eudragit® RS 100 and SD4 and (B) Theophylline, Eudragit® RSPO and SD9

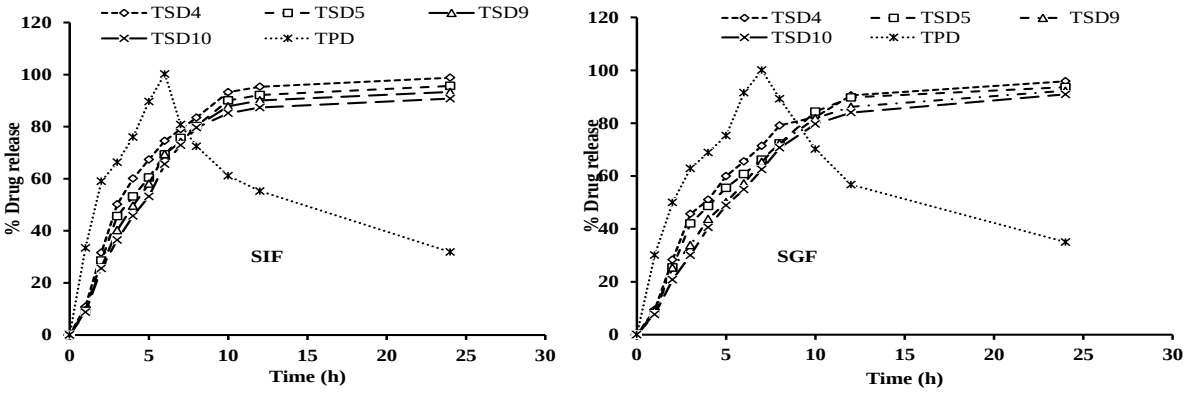

Figure 4. Dissolution profile of theophylline and theophylline solid dispersion tablets in SIF and SGF media

The diffusion exponent of Peppas model was found to be < 0.5 indicating that a Fickian mechanism is dominant and controls drug release from the different formulations.

3.9. Stability studies

The results of the stability studies carried out on the solid dispersion tablets of theophylline are presented in Table 6. The results show that the original properties of the solid dispersions at the time of production were preserved and sustained after three months of storage. There was no significant difference in the change in drug content after three months of storage at 25 ± 2 °C and 75 % RH.

4. DISCUSSION

4.1. Fourier transform Infra-Red (FT-IR)

The infrared spectra of theophylline, Eudragit® and solid dispersions are presented in Figure 2(A). Typical IR bands of theophylline occurring at 1453.41cm^{-1}, 1568.18 cm^{-1}, 1674.27 cm^{-1} and 3399.65 cm^{-1} corresponds to C-H stretching, C=N stretching, C=O stretching in amines and N-H stretching respectively and are consistent with the IR spectra of theophylline reported in other studies (Uhumwangho and Ramana 2011). IR Spectrum of Eudragit®RS 100 show peaks at 1726.35 cm^{-1} attributed to C=O stretching in esters, peaks at 1456.30cm^{-1} indicate C-H stretching in alkanes while a broad peak at 1159.26 cm^{-1} indicate C-O stretching in esters and a peak at 1017.48 cm^{-1} indicates C-N stretching. The IR spectrum of Eudragit® RSPO in Figure 2(B) was observed to be similar to that of Eudragit®RS 100 indicating similarity in their chemical structure. On the other hand, the IR spectra of theophylline solid dispersions (Figures 2A and 2B) were observed to reflect characteristic IR bands of theophylline and the corresponding polymers although the intensity of absorption were either increased or decreased and this could be attributed to the presence of the polymers in the dispersions. Super-imposing the solid dispersion spectra on the reference samples; drug and polymers did not reveal any new peak formed as a result of a new chemical group.. This confirms that there is no chemical interaction or complex formation between theophylline and the polymers employed as has also been reported by Uhumwangho and Ramana (2011).

4.2. Differential Scanning calorimetry (DSC)

The DSC thermogram for pure theophylline, Eudragit®RS 100 and SD4 are presented in Figure 3(A). A sharp endothermic peak was observed at 275.1 °C and this corresponds to its melting peak. However, this peak is similar to 273 ^{0}C reported by Lin et al. 2013. This peak displays high intensity which is characteristic of its crystalline form. Thermograms of solid dispersion formulations were also observed to have those endothermic peaks but with some changes in characteristic peaks shown by the individual components as have been reported earlier (Nayak and Jain, 2011). Disappearance of the melting peak of theophylline in the thermograms of SD4 and SD9 (Figure 3B) reveal the amorphous nature of theophylline in these formulations due to the solid dispersion technique. This concurs with the findings of Itishree et al. (2011) who reported a lowering of the melting point of piroxicam when prepared as a solid dispersion due to its conversion to the amorphous form.

The endothermic peak of the solid dispersion formulations lost their sharpness and distinctive appearance giving an indication that no possible interaction was found between the drug and polymers. Furthermore, it shows that there was homogeneous dissolution of drug in the polymer (Kulkami et al. 2012).

4.3. Thin Layer Chromatography (TLC)

The distance which the drug migrated relative to the solvent system is displayed in Table 2 as retention factor (R_f) values and the results confirm that polymers moved with the solvent front

(www.chem.zenkyo.h.kyoto-u.ac.jp/operation).
The number of spots obtained after separation of SD4, SD5, SD9 and SD10 represents the number of components that constitutes these formulations.
Previous work where TLC was used to ascertain the interaction between drug and polymer has proven TLC to be an alternative investigative tool where others are not available (Zawar et al. 2011). The principle behind this is that the developing solvent is drawn into the silica gel when a TLC plate end is dipped into the solvent system and the sample compound dropped at the starting point moves on the plate along with the developing solvent. This brings about repeated absorption and desorption of the sample compound by the silica gel. Less polar compounds are adsorbed weakly unto the silica gel and thus move faster than the polar compounds. In this study, the polymers, Eudragit®RS 100 and RSPO) were observed to move quickly on the plate while pure theophylline, a more polar compound was observed to move slowly. The separation of the solid dispersion into two distinct spots; one for the polymer and the other for theophylline, confirms the absence of chemical interaction between the drug and the polymer.

4.4. Dilution Potential

The dilution potential of an excipient is defined as the extent to which it can compress a poorly compressible drug and still retain its compressibility; thus, it is an indication of its drug loading capacity. A directly compressible adjuvant should have high dilution potential so that the final dosage form would have a minimum acceptable weight (Gohel and Jogani, 2005).
The result of the carrying capacity (dilution potential) of MCC in the formulation of solid dispersion tablet is presented in Table 3 below. Microcrystalline cellulose used as the direct compression excipient had high dilution capacity such that 40 % was sufficient to compress the solid dispersions with desirable results. This can be linked to its low bulk density (which imparts high covering capacity), broad particle size distribution (which allows optimum packing density), and its superior binding capacity (Chowhan, 1998). Therefore, the batch minimum ratio of 40 % MCC in the powder mixture was incorporated to produce sufficient tablets which were then subjected to physical evaluation.

4.5. Physico-technical properties of tablets

The average weight for all the tablets ranged between 416.67 and 503.67 mg which fall within the acceptable range for tablets weighing ≥ 324mg (B.P 2002). This shows that there was uniform filling of the die cavity due to adequate powder flow. Tablet diameter fell between 11.99 and 12.01 mm while tablet thickness ranged from 3.78 - 4.37 mm. This has been attributed to the compression force applied as well as the compressibility of the material.
Crushing strength is the applied load that just fractures the tablet. Although, a tablet is expected to be hard, it is also expected to disintegrate and release the drug in it for absorption, thus a minimum requirement of 40 N is said to be satisfactory (Allen et al. 2005). This could however differ from the norm depending on the type of excipient used and the intent of the formulation (Odeku and Itiola, 2003) for example; materials that deform plastically would normally produce tablets with high crushing strength. Application of pressure unto a powder bed leads to volume reduction, closer packing of particles in the compact and greater bonding; subsequently giving rise to strong tablets (Korhonen et al. 2002). The results show that the tablets produced were hard with crushing strength between 108.3 and 113.3 N as shown in Table 4.
Tablet friability is a measure of the weakness of the tablets and thus gives an indication of the likely damage that would occur in the tablet. Generally, the values of ≤ 1% are considered to be satisfactory and all the tablets had values between 0.65 and 0.8 %. The disintegration time for all the tablets was greater than 8 h and can be attributed to the fact that MCC forms very strong interparticulate bonds even at low compression pressure (Balami, 1991) with simultaneous reduction in porosity thus, reducing the uptake of water that aids disintegration. Furthermore, the polymers employed in this study, have low content of charged groups making them less permeable to fluids and ultimately less swelling ability (Apu et al. 2009).

4.6. *In vitro* dissolution studies

In this study the "*Drug burst*" phenomenon was observed from the pure theophylline tablet, however this was more rapid in SIF than in SGF and is in contrast to the studies by Aiman (2013) where dissolution of theophylline showed greater release in SGF. This has been attributed to the increase in solubility of theophylline at higher pH (Tiekink et al. 2010).
On the other hand, drug dispersion in the polymer matrices strongly influenced their dissolution rate which appeared slower and more gradual than that of the pure drug. The presence of the polymer reduced the massive initial drug dissolution observed with pure theophylline. As the proportion of the polymers increased, the permeability of water in the formulation decreased and sustained release pattern was observed. Eudragit® RS 100 and Eudragit®RSPO are methacrylic acid polymers which exhibit pH independent swelling as such are widely used as wall material for sustained release formulations due to their bio compatibility, good stability and easy fabrication (Marwa et al. 2012).

They are insoluble in water and digestive juices but swell and have low permeability which means that the drug would be released by diffusion (Kibbe 2000). Therefore, the drug permeability profile of these polymers is basically independent of the pH of the digestive tract (Apurba et al. 2009).

In solid dispersions, the drug forms a complex with an inert insoluble carrier in solid state and availability of the drug depends on the solubility of the polymer and the absorption rate of the drug. Slow drug release with Eudragit®RS polymers can therefore be attributed to the low permeability of the polymers which pose a significant hindrance to fluid penetration and passive drug diffusion (Shivakumar et al. 2008). Tablets containing Eudragit®RSPO were observed to extend drug release farther than those containing Eudragit RS®100 (Figure 4).

4.7. Kinetics of drug release

In order to gain an understanding of the kinetics of drug release, the results of the *in vitro* drug release were fitted into five kinetic models including; zero-order, first-order, Higuchi, Hixson Crowell and Korsmeyer Peppas models. The model with the highest coefficient indicates the appropriate model which describes the possible mechanism of drug release.

The most predominant release model for all the formulations prepared was the Higuchi model (Table 5). This model is based on the hypothesis that drug diffusion takes place in one dimension, that drug particles are smaller than the system thickness, that matrix swelling and dissolution are negligible and perfect sink conditions are attained in the release environment (Suvakanta et al (2010). Korsmeyer Peppas model on the other hand describes the relaxation process of the polymer which occurs when the polymer imbibes fluid. When the exponent 'n' is 0.45, drug release is said to be diffusion–controlled (Fickian diffusion) while 'n' values $\geq$ 0.89 indicate swelling – controlled drug release (Case II or super case II transport). When the values are between 0.45 and 0.89, anomalous or non–Fickian diffusion, which is the super imposition of both mechanisms of drug release dominates (Siepmann and Peppas, 2001),

The release mechanism of all the formulations was by anomalous or non–Fickian diffusion as indicated by the 'n' values which were between 0.446 – 0.467 (Table 5). Fassihi and Ritschel (1993) observed a similar result with matrix tablets of theophylline. This implies that drug release was by the combination of Eudragit matrix erosion and diffusion through the matrix formulations.

4.8. Stability studies

The results of the stability studies (storage at 25 ± 2 °C and 75 % RH) carried out on the solid dispersion tablets of theophylline are presented in Table 6. The results show that the drug content in the solid dispersions at the time of production was preserved and within the specified limit after three months of storage. This shows that solid dispersion would show good extended release characteristics with storage.

5. CONCLUSION

Theophylline SDs prepared using Eudragit polymers were successfully formulated into tablets with MCC as filler/binder. The components of the SDs were found to be compatible as confirmed with FT-IR. The solubility of theophylline was enhanced in the SD due to the conversion from crystalline state to amorphous state (DSC). The tablet formula incorporating SDs was determined based on the dilution capacity of MCC and was found to be a minimum of 40 % of the entire formulation. Tableting properties of crushing strength and friability were in agreement with USP standards. The mechanism by which drug was released from the tablet matrix during dissolution was principally by diffusion. The tablets were found to be stable after three months of storage without any significant change in the drug content. This study has proven the usefulness of formulating SDs into suitable dosage forms like tablets.

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