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Sustained Release Solid Dispersions of Pentoxyfylline: Formulation and Optimization

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Abstract

Objective: The purpose of the study is to formulate and optimize sustained release solid dispersions of pentoxyfylline using a combination of eudragit polymers and ethyl cellulose.

Methods: Solid dispersions were formulated by solvent evaporation method. Preliminary batches were formulated using various drug to polymer ratio; with eudragit S100 and L100 (1:1 to 1:5 ratio), and with ethyl cellulose (1:1 to 1:3 ratio) and evaluated for solubility analysis. Based on results of preliminary batches, Box Behnken design was further applied and three factors (X_1- concentration of Eudragit S100, X_2- concentration of Eudragit L100, X_3- concentration of Ethyl Cellulose) were selected with three levels (+1, 0, -1). Multiple linear regression was applied to generate polynomial equations and statistical evaluation. Prepared solid dispersions were investigated for sustained release properties via *in vitro* dissolution studies. Fourier transform infrared spectroscopic analysis (FTIR), X-ray diffraction analysis (X-RD), Differential scanning calorimetry (DSC) studies were carried out to evaluate drug polymer interactions. Scanning Electron Microscopy (SEM) analysis of optimized solid dispersion was carried out to evaluate surface morphology of the particles.

Results: Batch F5 showed maximum sustained release (65.46% in 24 h) characteristics out of all solid dispersions. DSC studies indicated drug integrity when mixed with the polymeric carriers. FTIR and X-RD studies also ruled out any drug polymer interaction. A change in crystalline habit was observed in solid dispersion particles (F5 batch) as seen in SEM micrographs. Polynomial mathematical model generated using multiple regression analysis was found to be statistically significant ($p<0.05$).

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Conclusion: Release retarding effect was found to be dependent on polymer concentration. Therefore, an optimized combination may lead to better sustaining effect.

Keywords: solid dispersion, eudragits, solubility studies, dissolution, scanning electron microscopy.

1. INTRODUCTION

Extended release (ER) drug delivery systems are developed to moderate the drug release characteristics to achieve specific goals that cannot be accomplished with conventional drug delivery systems. Potential therapeutic benefits of an appropriately designed ER dosage form include improved efficacy, reduced adverse effects, low cost, flexible release characteristics, increased convenience and patient compliance (Qui *et al.* 2000; Colombo *et al*. 2003). The solid dispersion approach is commonly used to improve the dissolution properties of poorly water-soluble drugs using hydrophilic polymeric carriers as dispersing agents. Several studies have been reported on solid dispersions using water-insoluble carriers to produce sustained release dosage forms of highly water soluble drugs (Zijlstra *et al.* 2007; Droogge *et al.* 2004; Nagarsenker *et al.* 2000). Solid dispersion technique is widely used in the preparation of matrices with insoluble polymers for the production of sustained-release dosage forms (Katikaneni *et al.* 1995). Among the existing matrix forming polymers, methacrylic resins (Eudragit®) appear predominantly attractive due to their chemical stability, compactibility and variability in physicochemical parameters(Rodriguez *et al.*1993). The most interesting among acrylic polymers are Eudragit RL (highly permeable) and Eudragit RS (less permeable). Both are neutral copolymers of poly ethylacrylate (methyl methacrylate and trimethyl aminoethyl methacrylate chloride). These are insoluble in water and digestive juices, though both swell and are permeable (Tiwari *et al.* 2009). The release retarding characteristics of methacrylic acid copolymers (Eudragit® L and S) and amino methacrylate (Eudragit® RL and RS) in solid dosage forms has been revealed through various experimental evidences (Kidokoro *et al.* 2001; Zhu *et al.* 2000; Palmieri *et al.* 2000; Bruce *et al.* 2000). The sustained release solid dispersion presents various possible advantages for poorly bioavailable drug candidates and can be delivered proficiently there by enhancing their bioavailability. The decreased dissolution rate of drug in insoluble carrier matrices helps in prolonging the duration of time during which the drug is released. Therefore, these systems are appropriate for designing sustained release dosage forms (Gurnasinghani *et al.* 1989; Aceves *et al.* 2000; Goracinova *et al.* 1995; Pignatello *et al.* 2001).

Box–Behnken design is an experimental design used for response surface methodology and was introduced by George Box and Donald Behnken in 1960. This is an autonomous quadratic design and does not contain an embedded factorial or fractional factorial design. In this design, the treatment combinations are at the middle points of edges of the process space and at the centre and it require 3 levels (-1, 0, +1) of each factor. Pentoxyfylline (PX) is a derivative of tri-substituted xanthine. Chemically it is 1-(5oxohexyl)-3, 7-dimethylxanthine, and is a hemorrheologic agent (an agent that affects blood viscosity). Pentoxyfylline is having solubility in water and ethanol. PX is a xanthine derivative used in the treatment of peripheral vascular disease (Thube *et al*. 2010). It has very short half-life of 0.4 to 0.8 h due to which the frequency of administration is very much high (Moffat *et al*. 2011). Thus the present drug may serve as an ideal candidate for sustained release action. In the present investigation, attempts would be made to sustain the release of highly water soluble drug Pentoxyfylline using solid dispersion technique employing release retardants like Eudragit L100, Eudragit S100 and Ethyl cellulose (EC).

2. MATERIALS & METHODS

2.1 Materials

Pentoxyfylline was obtained as a gift sample from Bakul Pharma Pvt. Ltd., Mumbai (India). Eudragit L100 and Eudragit S100 were procured from Evonik Rohm Pharma Polymers. Mumbai (India) as gift samples. Ethyl Cellulose was purchased from LOBA Chemie Laboratory reagents Pvt.Ltd., Mumbai (India). All other reagents were of suitable analytical grades and were used as received.

2.2 Methods

2.2.1 Preparation of solid dispersions (preliminary batches)

Solid dispersions of Pentoxyfylline were prepared by using solvent evaporation method. The drug and the polymers were weighed separately. The drug (100mg) was dissolved in 50ml ethanol. In a separate volumetric flask, the polymers (Eudragit L100, Eudragit S100 and Ethyl Cellulose) were dissolved in 50ml ethanol. After obtaining clear solution of drug and polymer, drug solution was added to the polymer solution under constant stirring using magnetic stirrer (Remi Instruments, India) at 500 rpm for 10 min. Then the mixture was transferred to rotary evaporator (Perfit, India) to evaporate the solvent. The residue obtained was dried overnight in the oven. The dried dispersion powder was then pulverized and sieved through a # 16 mesh to get the final powder formulation which was used in this study. Each formulation was appropriately labeled and stored in an airtight container for further studies.

Various drug to polymer ratios were used (1:1 to 1:5 for Eudragit S100 and L100); (1:1 to 1:3 for ethyl cellulose).

Equilibrium solubility studies were performed with all the batches to find out the maximum and minimum levels of polymers which can be further utilized for optimization. The composition of various preliminary batches with their solubility data is given in Table 1.

Table 1: Composition of preliminary batches of solid dispersions and solubility data

Drug : Polymer Ratio	Polymer	Solubility (µg/ml) (mean value ±S.D.) n=3
1:1		174.5 ± 1.125
1:2		157.8 ± 1.115
1:3	Eudragit L 100	147.4 ± 1.245
1:4		127.9 ± 1.354
1:5		110.9 ± 1.654
1:1		170.3 ± 1.254
1:2		157.8 ± 2.111
1:3	Eudragit S 100	143.3 ± 1.358
1:4		123.0 ± 1.124
1:5		73.5 ± 0.985
1:1		165.4 ± 1.678
1:2	Ethyl Cellulose	146.9 ± 1.264
1:3		119.9 ± 1.111

2.2.2 Statistical design for optimization

Box Behnken design was constructed to determine the effect of concentration of polymers on cumulative drug release. Based upon this three factors were selected with three levels (-1, 0, +1). These are X_1- Eudragit S100, X_2- Eudragit L100 and X_3- Ethyl cellulose. 13 formulation batches (F1-F13) were prepared accordingly. The composition and percent cumulative drug release (%CDR) data of all solid dispersion batches is shown in Table 2.

	Coded level	-1	0	+1
X_1	Amount of Eudragit S100 (mg)	400	1200	2000
X_2	Amount of Eudragit L100 (mg)	400	1200	2000
X_3	Amount of Ethyl Cellulose (mg)	400	800	1200

Table 2: Composition of design batches and cumulative drug release data

Formulation code	X_1	X_2	X_3	% CDR (24 h) (mean value ±S.D.) n=3
F1	-1	+1	0	71.24±2.15
F2	+1	-1	0	74.81±2.164
F3	+1	+1	0	72.72±2.211
F4	-1	-1	0	71.3±2.222
F5	0	-1	+1	65.46±2.211
F6	0	+1	-1	66.82±2.156
F7	0	+1	+1	67.4±1.246
F8	0	-1	-1	77.16±2.225
F9	-1	0	+1	72.01±2.222
F10	+1	0	-1	77.38±2.229
F11	+1	0	+1	67.89±2.223
F12	-1	0	-1	77.99±2.265
F13	0	0	0	74.07±2.215
X-coefficient	0.0325	-1.659	-2.984	72.77±2.287

Translation of coded levels in actual units

2.2.3 Characterization and Evaluation of Solid Dispersions

Differential Scanning Calorimetry (DSC)

Thermal properties of pure pentoxifylline, polymeric carriers and solid dispersion batches (F1-F13) were analyzed by differential scanning calorimetry (Mettler Toledo, DSC 821^e). Samples were sealed in aluminium pans and scanned from 50 to 300^{o}C at a heating rate of 10^{o}C/min in nitrogen atmosphere.

Fourier Transform Infrared (FTIR) Spectroscopy: Infrared absorption spectra of pure drug pentoxyfylline, polymeric carriers and solid dispersion batches were obtained using potassium bromide disks, under static air using FTIR spectrophotometer (Perkin Elmer Spectrum 400).

Content Uniformity: Precisely weighed amount of solid dispersion batches (F1-F13) (equivalent to 5 mg) were dissolved in 10 ml of ethanol taken in volumetric flask (100 ml) and the volume was made upto mark with phosphate buffer (pH 7.4). The solution was filtered and content uniformity was analyzed at 273 nm by UV spectrophotometer (Systronics, AU-2701).

***In vitro* Dissolution Studies:** The dissolution studies of pure drug pentoxyfylline and solid dispersion batches(F1-F13) (equivalent to 100 mg of drug) were carried out using USP dissolution apparatus type II in 900 ml phosphate buffer (pH 7.4) at 37 ± 0.5°C at a speed of 100 rpm. Aliquots were withdrawn at regular intervals for 24 h. The withdrawn samples volumes were replenished with equal volumes of phosphate buffer. The samples were analyzed for drug concentration at 273 nm UV spectrophotometer.

X-Ray Diffraction: Powder X-Ray diffraction patterns were traced employing X-ray Diffractometer (XPERT-PRO,PW3050/60 Goniometer) for the samples, using Ni filtered Cu radiation at a voltage of 45 Kv, using a current of 40 mA. The sample analysis was done over 2θ range of 0-50° with scan step size of 0.017° and scan step time 25 sec.

Scanning Electron Microscopy: The samples of drug and the solid dispersions batches (F5, F6) were mounted onto the stubs using double sided adhesive tape and coated with gold palladium alloy using fine coat ion sputter (JEOL, JFC-1100). The samples were then analyzed under the scanning electron microscope (JSM-6100 SEM) for external morphology.

3. RESULTS AND DISCUSSION

3.1 Differential Scanning Calorimetry (DSC)

The results of DSC studies are shown in Figure 1(a) to 1(f). The DSC thermogram of Pentoxyfylline (Figure 1a) showed an endothermic peak at 105.2°C with an enthalpy of 7.977 J/g corresponding to its melting point, which indicates its crystalline nature. DSC thermogram of Eudragit L 100 exhibited an endothermic peak at 70°C with an enthalpy of 27.85J/g (Figure 1b). DSC thermogram of Eudragit S 100 exhibited an endothermic peak at 76°C with an enthalpy of 29.85J/g (Figure 1c). No sharp peaks in DSC thermogram of ethyl cellulose suggested amorphous nature of the polymer (Figure 1d).DSC thermograms of optimized solid dispersion batches F5-F6(Figure 1e - Figure 1f) showed minor changes in characteristic peak of drug such as slight shift or peak of reduced intensity. This suggests minor changes in crystalline habit of the drug during mixing with polymeric carriers. Additional peaks due to polymers were also observed in solid dispersions.

3.2 Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR of the pure drug pentoxyfylline exhibited peaks at 1696.72 cm^{-1}, 1654.26 cm^{-1}, 1546.09 cm^{-1}, 752.92 cm^{-1} which is similar to standard FTIR

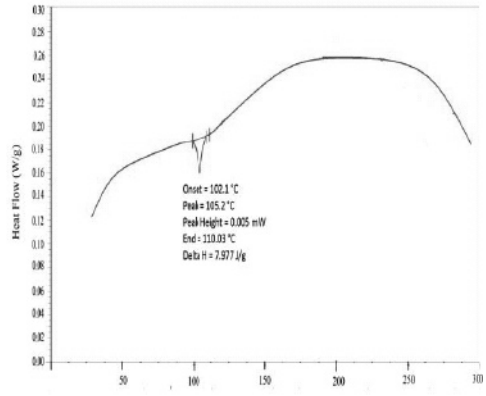


Figure 1(a): DSC thermogram of pure drug Pentoxyfylline

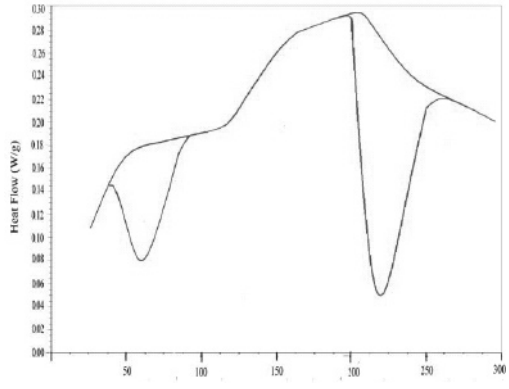


Figure 1(b): DSC thermogram of Eudragit L100

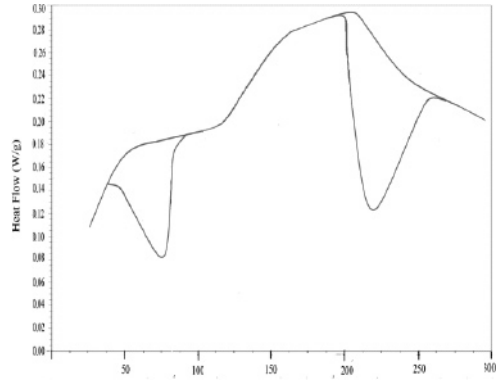


Figure 1(c): FTIR spectrum of Eudragit S100

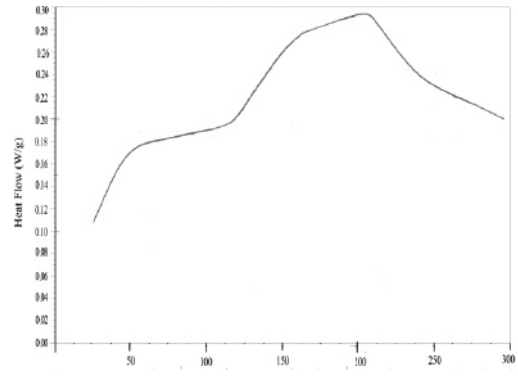


Figure 1 (d): DSC thermogram of Ethyl Cellulose

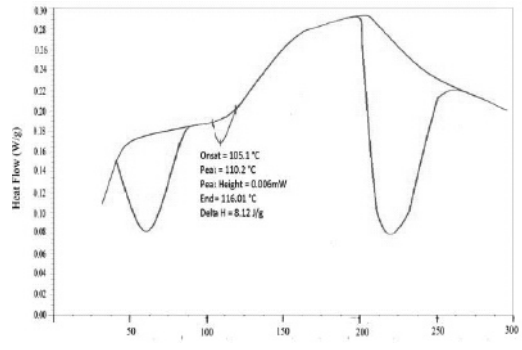


Figure 1 (e): DSC thermogram of batch F5

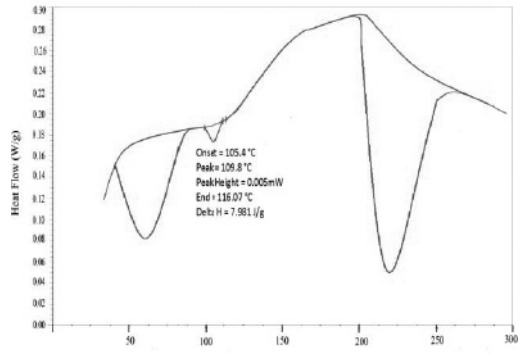


Figure 1 (f): DSC thermogram of batch F6

spectrum of the drug. The FTIR spectrum of Eudragit L100 showed peak at 1155.94 cm^{-1}due to ester vibrations and at 2950.67 cm^{-1} for O-H stretching and at 1255 cm^{-1} due to C-O stretch and Eudragit S100 exhibited peaks at 1153.15 cm^{-1} and 1248.73 cm^{-1} due to ester vibrations and C-O stretch and at 2951.21 cm^{-1} due to O-H stretch. FTIR spectrum of ethyl cellulose showed –C-O-C- stretch at 1051.32 $cm^{-1}$and C-H stretch at 1395.56 cm^{-1}. FTIR spectrum of optimized solid dispersion batches F5-F6exhibited peaks as the additive effect of the drug and the polymers. The characteristic peaks of drug appeared in FTIR of solid dispersions which indicated that there is no any interaction between drug and the polymers. FTIR spectra of pure drug, polymeric carriers and optimized solid dispersion batches (F5-F6) is shown in Figure 2 (a) to 2 (f).

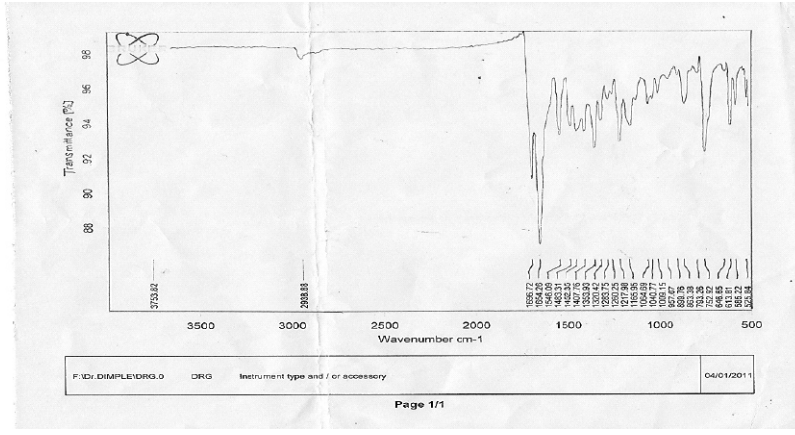


Figure 2 (a): FTIR of pure drug Pentoxifylline

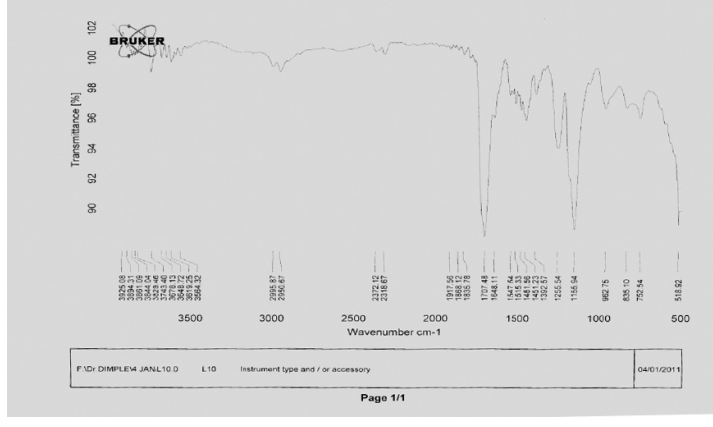


Figure 2 (b): FTIR spectrum of Eudragit L 100

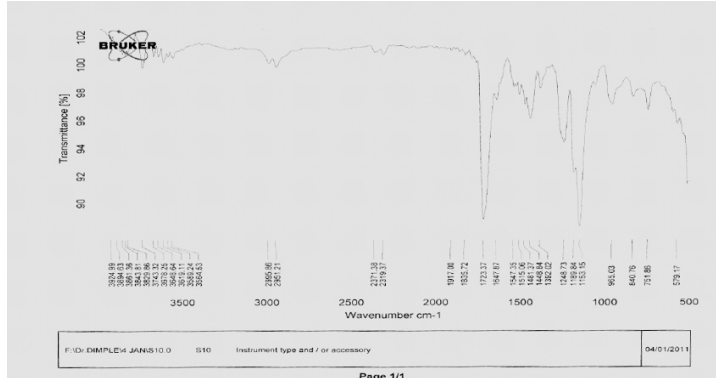


Figure 2(c): FTIR spectrum of Eudragit S100

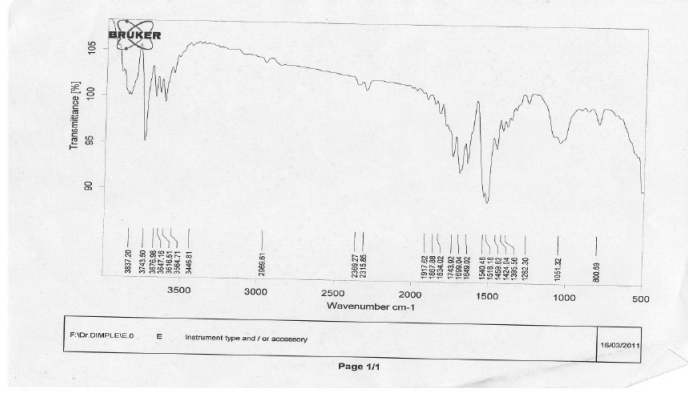


Figure 2 (d): FTIR spectrum of ethyl cellulose

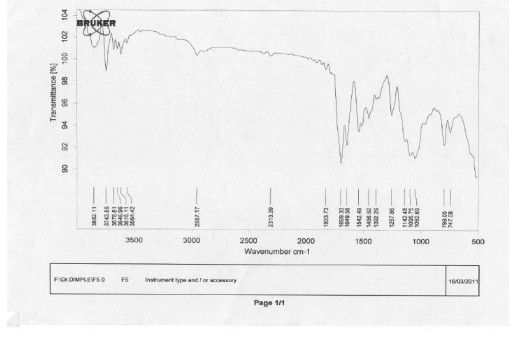


Figure 2(e): FTIR spectrum of Batch F5

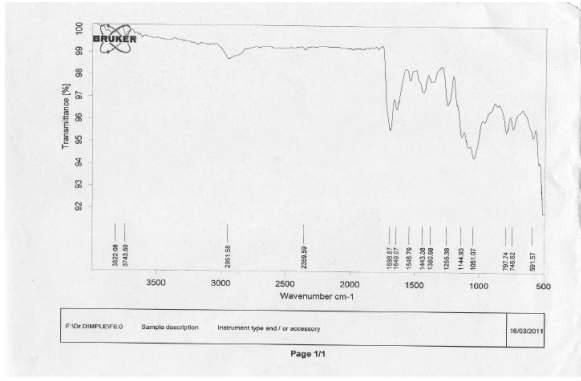


Figure 2 (f): FTIR spectrum of Batch F6

3.3 Content uniformity

The content uniformity of various solid dispersion batches(F1-F13) was found with in USP limit (85-115%). The content uniformity results are depicted in Table 3.

3.4 *In vitro* dissolution studies:

In vitro dissolution of solid dispersion batches (F1-F13) and pure drug is shown in Figure 3. Pure drug pentoxyfylline exhibited almost 100% release in

Table 3: Content uniformity of solid dispersion batches (F1-F13)

Formulation Batches	% Content uniformity (Mean ± SD), n=3
F1	96.8 ± 0.005
F2	99.6 ± 0.011
F3	100.2 ± 0.007
F4	98.4 ± 0.014
F5	100.4 ± 0.009
F6	100.2 ± 0.021
F7	97.8 ± 0.003
F8	94.6 ± 0.007
F9	100.7 ± 0.013
F10	101.2 ± 0.004
F11	100.6 ± 0.012
F12	99.5 ± 0.022
F13	97.4 ± 0.008

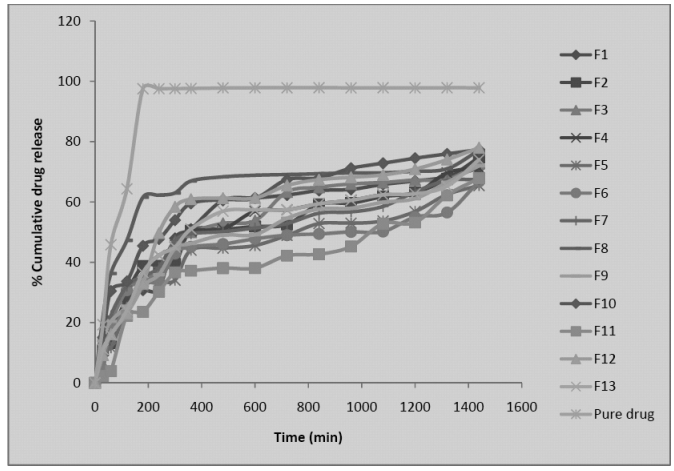


Figure 3: Comparison of dissolution profile of Pentoxyfylline with solid dispersions batches (F1-F13)

3h. Sustained drug release was observed in all solid dispersion batches (65% -77% in 24 h). Batch F5 showed maximum sustained release effect as observed from release data (65.46% in 24 h).A combination of polymers (Eudragit S100, L100 and ethyl cellulose) may lead to better release retarding characteristics as compared to when used alone. Maximum drug release was obtained in F8 and F10 batches which may be attributed to lower concentrations of ethyl cellulose and eudragit L100. Eudragit S100 when present in higher concentrations with other polymers led to higher drug release which is contrary with solubility data of preliminary batches where Eudragit S100 led to more decrease in solubility as compared to Eudragit L100 (Table 1). Therefore, release retarding characteristics depend on synergistic effect of various polymers not the single polymer alone.

3.5 X-Ray Diffraction:

Overlay diagram of X-RD diffraction pattern of pentoxyfylline and best solid dispersion batches (batch F5 and F6) is shown in Figure 4. The presence or absence of crystallanity was determined by comparing some representative peaks in the diffraction of the solid dispersions with that of pure drug(pentoxifylline).X-RD of Pentoxyfylline showed sharp peaks at diffraction angle of 4.50, 13.21, 15.12 with peak intensities of 48.12, 100.00, 26.54 and area 252.46, 385.60, 175.64 respectively. X-ray diffraction patterns of solid dispersion batches F5 and F6 showed presence of characteristic peaks

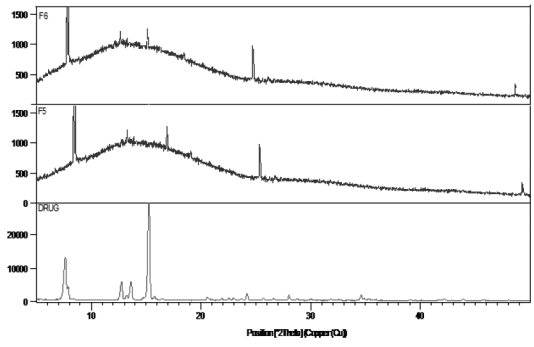


Figure 4: Overlay diagram of X-RD of the pure drug Pentoxyfylline; batch F5 and batch F6

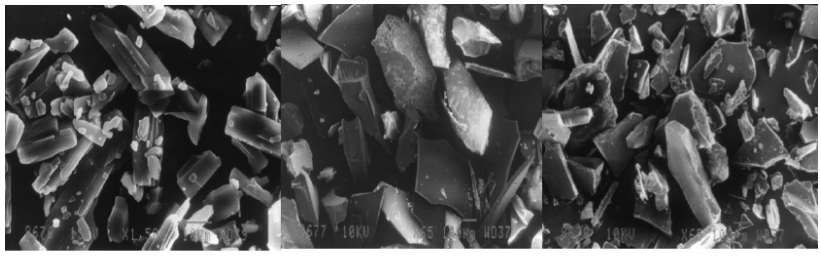
(slight shift) of drug with reduced diffraction intensity, which indicated minor changes in crystallinity.

3.6 Scanning Electron Microscopy

The SEM micrographs of pure drug (Pentoxifylline) (Figure 5a) shows rod shaped crystalline structure. On the other hand, the photomicrograph of solid dispersion batch F5 and F6 (Figure 5b and 5c) showed smooth surfaced rectangular crystalline structure. This suggests change in drug crystalline habit to a new phase in solid dispersion batches.

3.7 Data Analysis

Multiple linear regression analysis was applied to determine the magnitude of contribution of different factors towards dissolution,. Microsoft excel



(a) (b) (c)

Figure 5: SEM micrographs of (a) Pentoxyfylline at 500X, (b) batch F5 at 65X and (c) batch F6 at 65X.

worksheet was used for the execution of multiple linear regression. The real values of the factors were transformed to ease the calculations and to facilitate orthogonality of results. The model developed to estimate cumulative drug release (Y) can be represented mathematically as:

$$Y= 72.77 + 0.0325\ X_1 - 1.659\ X_2 - 2.984\ X_3$$

Where, Y= % Cumulative drug release, X_1= Amount of Eudragit S100, X_2= Amount of Eudragit L100 and X_3= Amount of Ethyl cellulose

To study the fitting and significance of mathematical model, analysis of variance was applied and % cumulative drug release was estimated (Table 4). The obtained F value 2.34 indicates regression to be significant. The estimated model can be used as a response surface for percent cumulative drug release.

Table 4: Analysis of Variance

	Df	SS	MS	F	Significance F
Regression	3	93.24217	31.08073	2.338336	0.141748
Residual	9	119.6263	13.29181		
Total	12	212.8685			

The effect of coefficient on %CDR is shown in Pareto Chart in Figure 6.Pareto chart showed that % CDR increases with increase in the concentration of Eudragit S100 and decreases with increase in concentration of Eudragit L100 and ethyl cellulose.

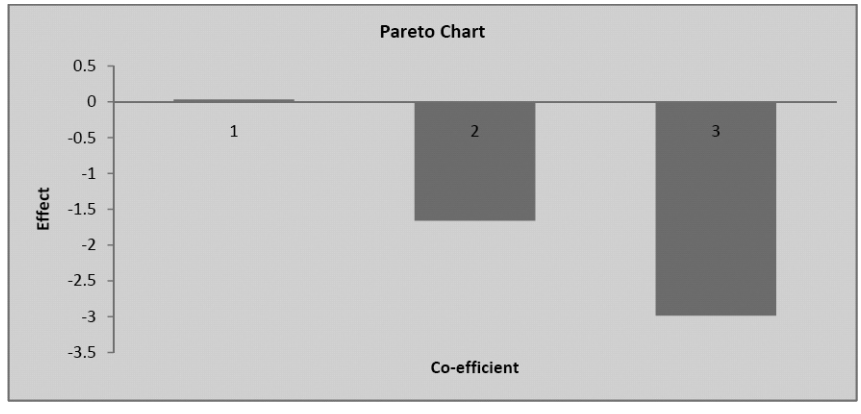


Figure 6: Effect plot of coefficient on % CDR

4. CONCLUSION

A systematically designed study including the preparation and characterization of sustained release solid dispersions of pentoxyfylline was carried out using release retarding polymers (polymethylmethacrylates and ethyl cellulose). Release retardant properties of polymers are found to be concentration dependent in all solid dispersions. An optimized combination of Eudragits (S100 and L100) and ethyl cellulose [i.e. eudragit S 100 at middle level (0), eudragit L100 at low level (-1) and ethyl cellulose at high level (+1)] in (batch F5) leads to maximum release retardant effect. The polynomial equation generated by multiple linear regression also supports the drug release behavior. In retrospect, this model can be successfully used for design of sustained release solid dispersions.

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