Encapsulation of Theophylline into Binary Blend of Ethylcellulose and Eudragit Microparticles: Development, Characterization and Kinetic Release.

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ABSTRACT

The objective of this study was to prepare and evaluate microparticles of Eudragit and Ethyl cellulose binary blend loaded with theophylline for controlled release. Microparticles were prepared by Phase separation method. The method is quite simple, rapid, and economical and does not imply the use of toxic organic solvents. Solid, discrete, reproducible free flowing microparticles were obtained. The yield of the microparticles was up to 92%. More than 85% of the isolated microparticles were of particle size range of 325 to 455 µm. The obtained angle of repose, % carr's index and tapped density values were well within the limits, indicating that prepared microparticles had smooth surface, free flowing and good packing properties. Scanning Electron Microscopy photographs and calculated sphericity factor confirms that the prepared formulations are spherical in nature. Prepared microparticles were sTab. and compatible, as confirmed by DSC and FT-IR studies. The prepared formulations were quantitatively analyzed for the amount of encapsulated drug. It was observed that there is no significant release of the drug at gastric pH. The drug release was controlled more than 12 h. Intestinal drug release from microparticles was studied and compared with the release behavior of commercially available oral formulation Duralyn CR 400. The release kinetics followed different transport mechanisms.

Keywords: Microparticles, Phase Separation, Theophylline, Fickian Release, Eudragit.

INTRODUCTION

The oral drug delivery has its own importance because of its ease of administration and patient compliance. Though the conventional oral drug delivery systems achieve both local and systemic effects, there is no control over drug release from dosage forms that may lead to local or systemic toxicity.

These limitations shifted the focus of pharmaceutical scientists towards the novel drug delivery systems (NDDS), where the required amount of drug is made available at desired time and site of action in the body. These systems maintain plasma concentrations with in the therapeutic range, which minimizes side effects and also reduces frequency of administration. Multiparticulates offer greater advantages over single unit system as they disperse uniformly in GI tract, offer flexibility and less inter and intra individual variability in formulation process. Multiparticulates present several advantages in comparison with single unit forms that they exhibit higher colonic residence time and more predicTab. gastric emptying [1].

One such novel approach is the administration of drug orally in the form of microparticles. A 'microparticle' may be defined as particle with size varying from 1 to 1000µm containing a drug dissolved, dispersed or adsorbed on to the surface of the particle.

Asthma is a chronic obstructive lung disease characterized by airways inflammation and hyperreactivity. In most patients, conditions worsen at night with acute exacerbation being in most common [2]. Clinical and epidemiological studies suggest that asthma is several hundred folds more likely at night than during day with disturbance of sleep. The heightened risk of

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asthma at night coincides with the trough of circadian rhythm. A colonic drug delivery system would be valuable when a delay in absorption of drug is therapeutically desirable in treatment of chronic conditions like nocturnal asthma, which coincides with trough of circadian rhythm [3].

The model drug used in the present study is Theophylline. Theophylline belongs to anti-asthmatic category, lipophilic in nature with narrow therapeutic index and short half life [4], hence a controlled release product is advisable than conventional dosage form.

Conventional dosage forms are to be taken several times a day in divided doses, a controlled release product will definitely reduce the dose requirements and, in turn reduces the patient health care costs and toxic side effects.

Eudragit and ethylcellulose have been used as drug carriers to achieve controlled drug delivery for the past few decades. These polymers have gained a lot of interest owing to their versatile properties. These polymers are bio compatible and gastro-resistant, and due to its non immunogenic properties, they have been employed for many type of biomedical applications. Many researchers had already worked on the suitability of blend of polymers for controlled drug delivery. Huang et al.[5] prepared nifedipine molecular dispersion using binary blends of ammonia methacrylate copolymer and ethylcellulose for controlled drug delivery. Besides, Das et al.,[6] prepared microparticulate dosage form for a highly soluble drug, diltiazem hydrochloride, with Eudragit RS100 and RL100 using a novel dual polymer technique.

The objective of this study was to prepare and evaluate microparticles of Eudragit and Ethyl cellulose binary blend loaded with theophylline for controlled release. Microparticles were prepared by Phase separation method. The method is quite simple, rapid, and economical and does not imply the use of toxic organic solvents. The formulations were prepared using different polymer ratios. The prepared microparticles were characterized by FT-IR analysis, DSC, particle size analysis, micromeritic properties and SEM. They were further evaluated for drug loading, encapsulation efficiency, *in vitro* drug release.

EXPERIMENTAL SECTION

Materials

Theophylline hydrochloride (TH) was a gift sample from French Pharma, Chandigarh, India. Ethylcellulose (EC) was purchased from S. D. Fine-Chem Limited, Mumbai, India. Eudragit RL100 was a gift sample from Cadila, Ahmedabad, India. All other chemicals used were of analytical reagent grade.

Preparation of Theophylline microparticles

Drug-loaded microparticles were prepared by phase separation [7] method as shown in Table 1. Weighed amounts of theophylline were dissolved in 20ml of dimethylformamide, and this solution was added to 30ml acetone solution containing eudragit and ethyl cellulose polymer blend at different EU/EC ratios. Under constant stirring at 600 rpm, a 30ml of non solvent (pH 10.0 Ammonia buffer) was added drop wise to the drug and the polymer solution. In the course of the water addition, the drug and the polymer were co-precipitated out to form microparticles. The resultant microparticle suspension was vacuum filtered with a whatmann # 5 and then vacuum dried at room temperature for 72 hours. The dried microparticles were stored in a desiccator at room temperature until use.

Table 1: Formulation chart of different batches of TH microparticles prepared.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
TH (mg)	400	400	400	400	400	400	400	400	400	400
EU RL100 (mg)	200	133	267	100	300	200	133	267	100	300
EC (mg)	200	267	133	300	100	200	267	133	300	100
DMF (ml)	20	20	20	20	20	-	-	-	-	-
Acetone(ml)	30	30	30	30	30	50	50	50	50	50
Ammonia buffer (pH 10)	30	30	30	30	30	30	30	30	30	30

*TH-Theophylline, EU Rl- Eudragit RL, EC- Ethyl cellulose, DMF- Dimethylformamide

Characterization of Microparticles

The prepared microparticles were characterized by particle size analysis, angle of repose, compressibility, sphericity and compatibility studies by Fourier transform infra red spectroscopic analysis, Differential scanning calorimetric analysis and surface morphology by Scanning electron microscopy. The obtained microparticles formulations were also evaluated for percentage yield, drug loading and encapsulation efficiency, *in vitro* drug release studies.

Particle size analysis

The particle size was measured using a Malvern mastersizer 2000 version 5.1 (Malvern, UK.) The samples of theophylline microparticles were dispersed in 1:20 with methanol and measured at temperature of 37°C [8, 9].

Angle of Repose

Fixed funnel method was employed for determining angle of repose. The angle of repose (θ) for samples was calculated using the formula,

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h / r) \quad (1)$$

Where 'h' is height of heap and 'r' is radius of the heap.

Compressibility

Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro lab tap density tester). Carr's index is calculated using the formula given below:

Carr's index = (tapped density – bulk density) / tapped density

Sphericity of the Microparticles

The sphericity of the prepared microparticles can be determined by using a camera lucida by taking the tracings of the microparticles on a black paper. The tracings help calculate the circulatory factor and confirm the sphericity of microparticles if the obtained values are nearer to 1. The sphericity was determined by tracings of Theophylline microparticles (magnification 45x) which were taken on a black paper using camera lucida, (Model -Prism type, Rolex, India) and circulatory factor (S) was calculated as

$$S = \frac{P^2}{12.56 \times A} \quad (2)$$

Where A is area (cm^2) and P is the perimeter of the circular tracing

Fourier Transform Infrared Spectroscopy (FT-IR)

Drug polymer interactions were studied by FT-IR spectrophotometer (Shimadzu, 8033, USA) by KBr pellet method. The IR spectrum of the pellet from 400 – 4000 cm^{-1} was recorded [10].

Differential Scanning Calorimetry (DSC)

All dynamic DSC studies were carried out on Dupont thermal analyzer with 2010 DSC module. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10ºC/min heating rate of 10ºC/min [11].

Scanning Electron Microscopy (SEM)

SEM photographs were taken for the prepared microparticles with a scanning electron microscope, Joel- LV-5600, USA, at the required magnification in room temperature. The photographs were observed for morphological characteristics. Photographs were taken at the magnifications of 400X, 1500X and 3000X [12, 13].

Percentage Yield

Determining whether the preparation procedure chosen for incorporating a drug into the polymers is efficient and is of prime importance. The raw materials, amount of active compound, Eudragit RL 100, Ethyl cellulose, and other process parameters are deciding factors for the yield of the product during the preparation of microparticles.

The yield was determined by weighing the microparticles and then finding out the percentage yield with respect to the weight of the input materials, i.e., weight of drug and polymers used. The formula for calculation of % yield is as follows;

$$\% \text{ yield} = \frac{\text{wt. of drug + wt. of polymers}}{\text{wt. of microparticles}} \times 100 \quad (3)$$

Drug Loading and Encapsulation Efficiency

100 mg of Theophylline microparticles were weighed and transferred to 100 ml volumetric flask containing pH

7.4 phosphate buffer. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml and absorbance was measured at 270 nm. The drug content was calculated by using the formula

Amount of drug =

$$\frac{\text{Conc. from standard graph X dilution factor}}{1000} \quad (4)$$

Percentage encapsulation efficiency (EE) [14] is found out by calculating the amount of drug present in 100 mg of microparticles. It is further calculated by using formula

$$\% \text{ EE} = \frac{\text{Tot. amt. of drug added - Amt. of drug in supernatant liquid}}{\text{Total amt. of drug added}} \times 100 \quad (5)$$

***In Vitro* Drug Release Studies**

The *in vitro* release of drug from the microparticles was carried out in basket type dissolution tester USP XXIII, TDT-08L, with auto sampler containing 900 ml of pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 10 hrs. The volume of the dissolution media was maintained at 900 ml while constant stirring (100 rpm) and temperature of bath was maintained at 37 ± 0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time points and replaced with fresh media immediately after sampling. The samples are analyzed for drug content by UV visible spectroscopy (Shimadzu UV 1601).The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting for the obtained release profile. Dissolution studies were carried out for all the batches of the prepared formulations and commercial formulation (Duralyn CR 400).

Drug Release Kinetics

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in vitro* dissolution study was analyzed with various kinetic equations. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots. A difference factor (f_1) and similarity factor (f_2**)** were calculated from dissolution data according to the following equations;

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad (6)$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (7)$$

where, f_1 - difference factor, f_2 - similarity factor, n – number of time point, R_t – dissolution value of the reference at time, 't' and T_t - dissolution value of test formulation at time 't'. Difference factor, f_1 was calculated by the percentage difference between the two curves at each time point and measured the relative error between the two curves. The accepTab. range for difference factor, f_1 is 0 -15. The similarity factor, f_2, was logarithmic reciprocal square root transformation of the sum-squared error and is a measure of the similarity in the percentage dissolution between the reference and test products. If dissolution profile to be considered similar, the values for f_2 should be in the range 50 - 100.

RESULTS AND DISCUSSION

Ten formulations were prepared using different polymer blend ratios: 1:1, 1:2, 1:3, 2:1 & 3:1. In the first five formulations (F1 – F5), TP was dissolved in DMF and in the next five formulations TP was dispersed in acetone. The drug: polymer ratio used in all the

formulations was 1:1.

Various formulation and process variables that could affect the preparation and properties of the microparticles were identified and optimized to get small, discrete, uniform, smooth-surfaced, and spherical microparticles as shown in Figure 1.

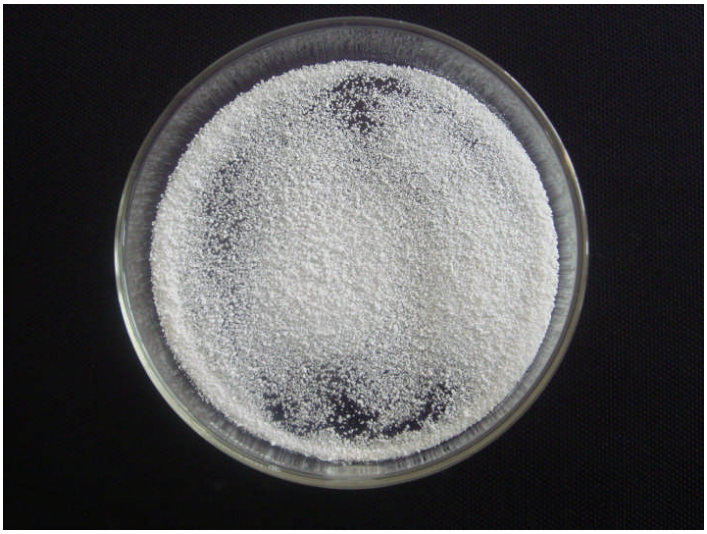

Figure 1: Prepared TP loaded microparticles.

The formulation variables included concentration of the polymer blend and the solvents used. The process variables included the stirring speed & time.

Added volume of Acetone and DMF affects the drug loading. In the first five formulations (F1-F5), the drug was dissolved in 20 ml of DMF, and in the next five formulations (F6-F10), the drug was dispersed in 50ml of acetone.

The important factor that influences the size distribution of microparticles is the optimum stirring speed and time. A stirring speed of 600 rpm and 40 minutes stirring time was used to obtain reproducible microparticles. It was observed that with the increase in the stirring speed from 600-900 rpm; there was a decrease in the average size of the microparticles and recovery yield of the microparticles. It was due to the loss that occurred during successive filtration. When the stirring speed was lower than 600 rpm, larger microparticles were formed. Resulted microparticles were composed of irregular masses, which were not possible to distinguish as individual microparticles as shown in the **Figure 2.**

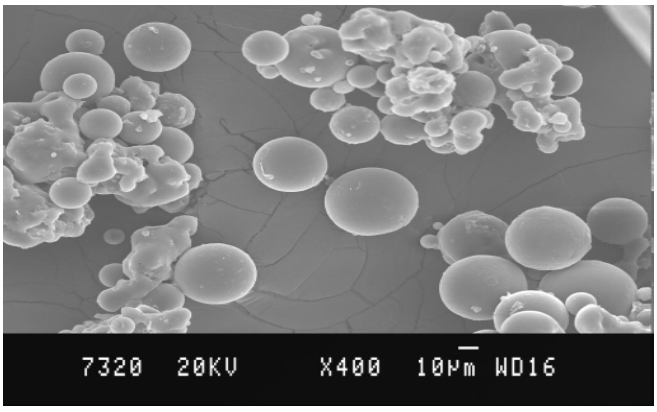

Figure 2: SEM images of prepared TP loaded microparticles showing irregular masses.

When the stirring time was lower than 40 minutes, it was observed that some amount of the dissolved mass adhered to the inner sides of the beaker, resulting in lower percentage yield shown in **Table 2**. Repeat batches treated at an optimized rate proved to produce reproducible sizes showing that stirring speed and stirring time were well controlled.

Table 2: Effect of stirring time on percentage yield of TP loaded Microparticles.

Time in minutes	% yeild
10	55.14
20	65.32
30	81.1
40	92.36
50	90.12
60	75.12
70	67.56

Micromeritic Properties

The flow property of the prepared theophylline microparticles was studied by determining the angle of repose (θ) and % compressibility index (CI). The obtained data along with related parameters are presented in **Table 3**. The values of θ ranged from 26.11 to 29.22, and the Carrs index was found to be between 11.01% to 14.11%. These results indicated that the prepared microparticles exhibited good flow properties.

Table 3: Micromeritic properties and % yield of TP microparticles.

Formulation	θ^0 mean ± SD*	CI% mean ± SD*	Tapped density gm/cm^3 mean ± SD*	% Yield
F1	27.10 ± 0.55	12.35 ± 0.26	0.499 ± 0.04	88.24 ± 1.44
F2	26.45 ± 0.32	11.01 ± 0.56	0.525 ± 0.01	92.36 ± 1.56
F3	28.44 ± 0.30	12.22 ± 0.17	0.492 ± 0.06	90.24 ± 1.24
F4	27.45 ± 0.45	13.33 ± 0.23	0.515 ± 0.02	88.42 ± 1.54
F5	28.44 ± 0.36	14.11 ± 0.67	0.535 ± 0.03	87.56 ± 1.36
F6	26.11 ± 0.26	12.45 ± 0.26	0.535 ± 0.06	87.12 ± 1.72
F7	27.34 ± 0.33	11.22 ± 0.65	0.515 ± 0.02	86.32 ± 1.12
F8	28.12 ± 0.42	12.36 ± 0.44	0.495 ± 0.06	85.33 ± 1.32

Formulation	θ^0 mean ± SD*	CI% mean ± SD*	Tapped density gm/cm^3 mean ± SD*	% Yield
F9	27.28 ± 0.56	13.42 ± 0.32	0.543 ± 0.02	84.43 ± 1.26
F10	29.22 ± 0.33	12.14 ± 0.26	0.549 0.07	82.34 ± 1.46

*Standard deviation, n = 3

The values of tapped density ranged between 0.492 to 0.549 g/cm^3. Density difference between the formulations is negligible, and the density values of formulations were well within the accepTab. limits, indicating that the prepared microparticles were non-aggregated.

Percentage Yield

During the process of microencapsulation, the mechanical variables cause loss of final product and hence process yield may not be 100%. Microparticles were weighed after drying and the percentage yield was calculated. The obtained data is shown in **Table 3.**

Particle Size Determination

The average particle size/volume mean diameter (D[4,3]) and volume median diameters (D[v, 0.5]), (D[v, 0.9]) of the microparticle formulation of theophylline (F5) are given in **Table 4** and the particle size graphs are given in **Figure 3**.

Table 4: Particle size distribution parameters of TP microparticles.

Formulation	Volume mean diameter (D[4,3]) µm	Volume median diameter (D[v,0.50]) µm	Volume median diameter (D[v,0.90]) µm
F5	299.93	234.54	641.59

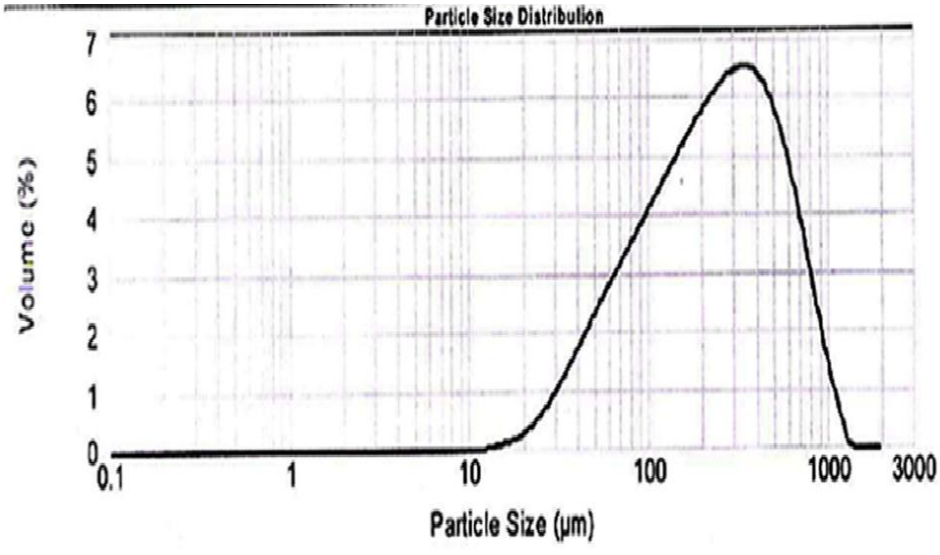

Figure 3: Particle size distribution of TP microparticles (formulation F5).

D[4,3] is the volume mean diameter and the diameter of the sphere having the same volume as that of the microspheres of which size is being determined. D[v,0.50] is the median diameter, and it is the value of particle size that divides the population in to two equal halves, i.e., there is 50% of distribution above this and 50% below this value. D[v,0.90] is the median diameter and it is value for the particle size distribution, which means 90% of the particle size distribution is below the value shown in Table 5.

FT-IR Analysis

Theophylline pure drug and the optimized formulation were subjected for FT-IR spectroscopic analysis for compatibility studies and to ascertain whether there is any interaction between the drug and the polymers used. It was found that there was no any change in their peak position, indicating that there was no chemical interaction between drug and the polymer used as shown in Figure 4.

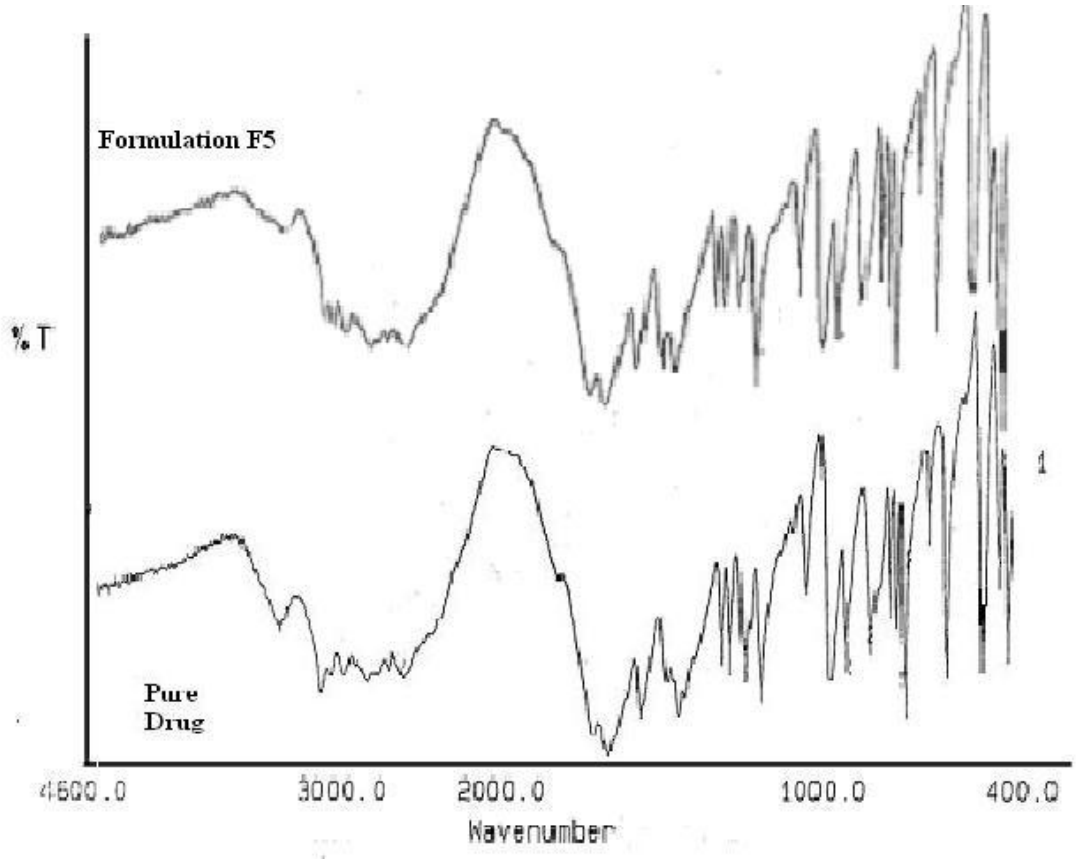

Figure 4. FTIR spectra of Pure drug and Formulation F5.

Differential Scanning Calorimetry (DSC)

In order to investigate the possible interaction between the drug and polymers, differential scanning calorimetry (DSC) studies were carried out. DSC thermogram of the formulation was compared with the DSC thermogram of pure drug sample. About 70 mg of powdered sample was placed in a platinum crucible, and the DSC thermograms were recorded from 0°C to 350°C

at a heating rate of 10°C/min. Theophylline exhibits a sharp endothermic peak at 272.96 as shown in Figure 5 corresponding to its melting point and a similar condition was also observed in the formulation confirming the stability of the drug in the formulation.

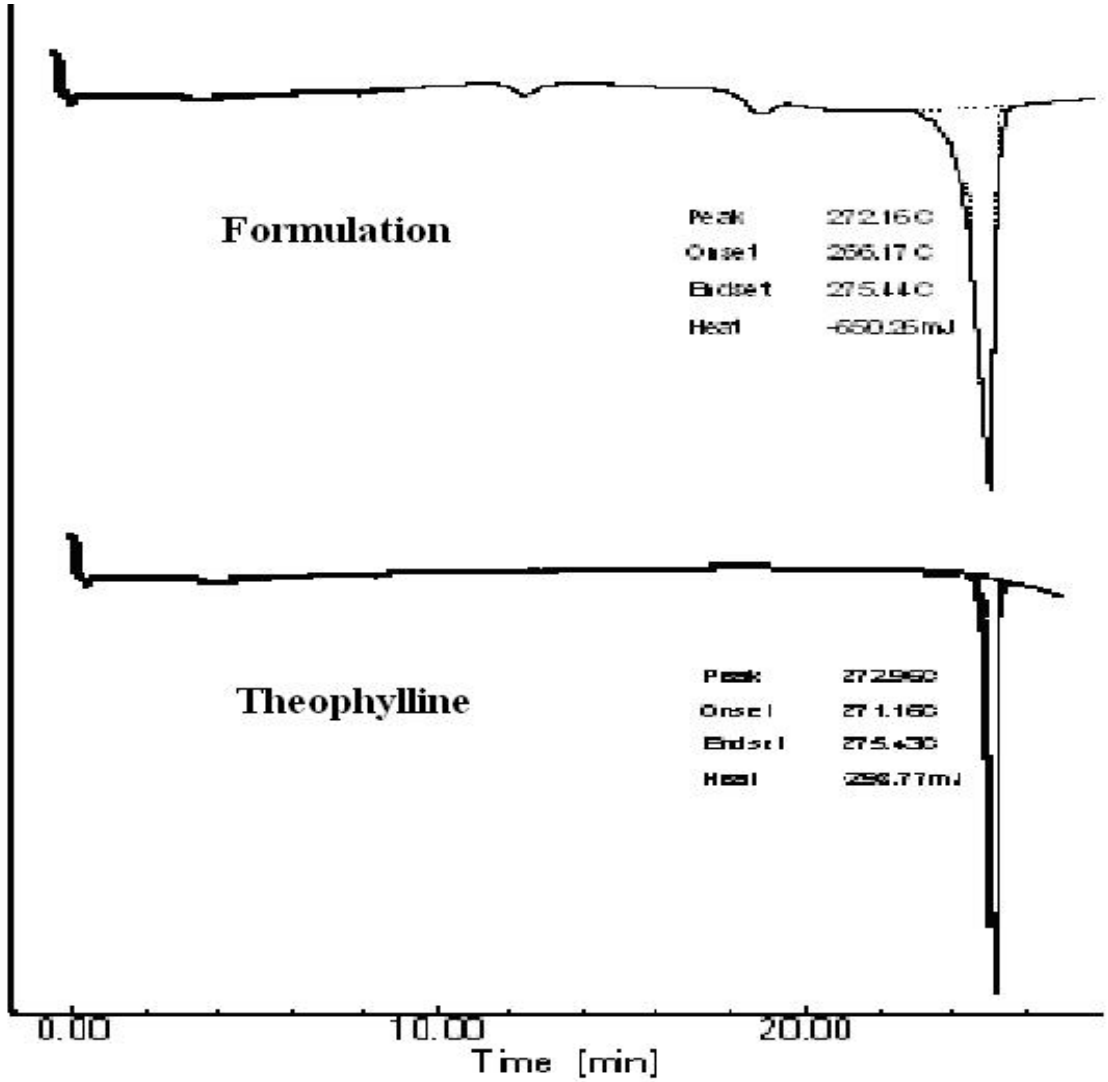

Figure 5: DSC thermograms showing the thermograms of TP pure drug and formulation F5.

SEM and Sphericity

The scanning Electron Microscopy (SEM) studies were done to identify the surface morphology of the prepared TP loaded microparticles, and the obtained microphotographs are presented in **Figure 6**. SEM photographs showed that the Theophylline loaded microparticles were spherical in nature (mean size of around 299.9 µm), having a smooth surface.

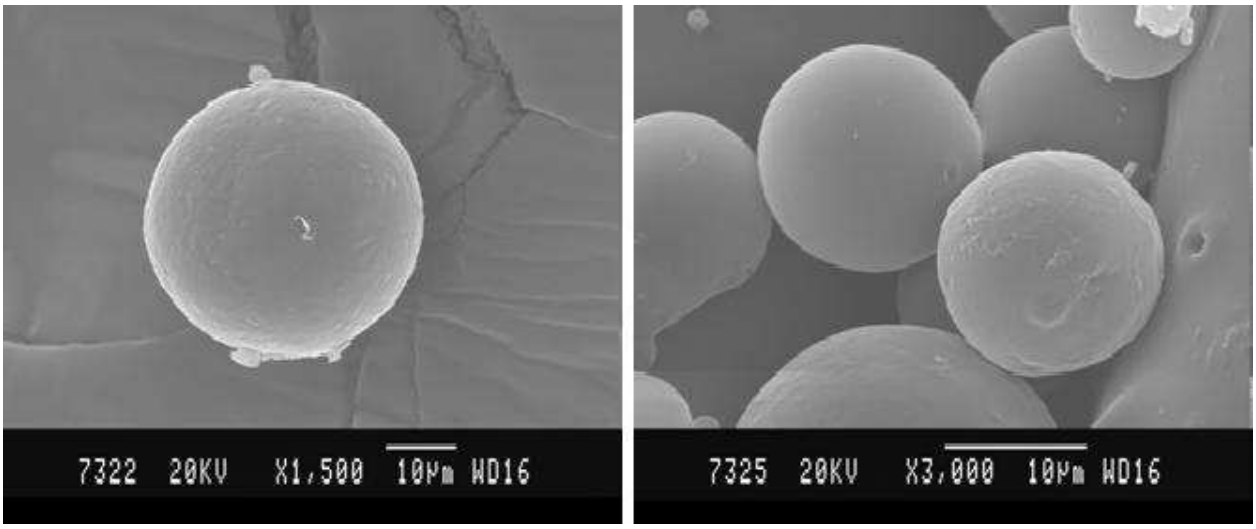

Figure 6: SEM photograph of the prepared formulation F5.

SEM photographs revealed the absence of drug particles on the surface of microparticles indicating the uniform distribution of the drug in the walls of the microparticles. SEM photographs also indicated the presence of minute pores on the surface of the microparticles. It is due to rapid diffusion of the solvent from the walls of the microparticles, and there is a possibility of rupture of microparticle walls. The calculated sphericity factor for the TP loaded microparticles are presented is in Table 6. The sphericity factor was obtained in the range 1.00 to 1.09, indicating that the prepared formulations were spherical in nature.

Drug Loading and Encapsulation Efficiency

The test for drug content was carried out to ascertain that the drug is uniformly loaded in the formulation. The 100 mg of the TP microparticles were taken in 100ml volumetric flask containing 7.4 pH buffer solution and shaken the mixture for 45 min for complete extraction of incorporated drug from microspheres into solution and then filtered through whatmann no.1 filter paper. The amount of TP present in the buffer solution was determined spectrophotometrically at 270 nm. The percent of drug loading in the formulations was found to be in the range of 38.15 % to 47.23 %. The percentage encapsulation efficiency was found to be 69.55 to 90.50 %. The results obtained are given in **Table 5** respectively.

Table 5: Drug loading and encapsulation efficiency of prepared microparticles.

Formulation	Drug loading(mg) mean ± SD*	Encapsulation efficiency (%) mean ± SD*
F1	43.30 ± 0.36	70.50 ±0.26
F2	41.5 ± 0.57	72.52 ± 0.33
F3	44.5 ± 0.56	84.53 ± 1.05

Formulation	Drug loading(mg) mean ± SD*	Encapsulation efficiency (%) mean ± SD*
F4	39.50 ± 0.44	77.55 ± 0.33
F5	47.23 ± 0.36	90.50 ± 0.56
F6	41.11 ± 0.26	69.55 ±0.32
F7	38.15 ± 0.33	71.50 ± 0.44
F8	43.50 ± 0.42	87.50 ± 0.66
F9	38.50 ± 0.38	73.70 ± 0.48
F10	41.20 ± 0.44	82.60 ± 0.67

* Standard deviation, n = 3

***In-Vitro* Drug Release**

The *in vitro* release studies were carried out for all formulations in both acidic media, pH 1.2 for first 2 hr and basic media, pH 7.4 for rest of study. For the formulations F1 – F10, it was noticed that the drug release decreases with increase in Ethyl cellulose concentration as shown in Figure 7. Studies also showed that the drug release increases with increase in Eudragit RL 100 concentration as shown in Figure 7.

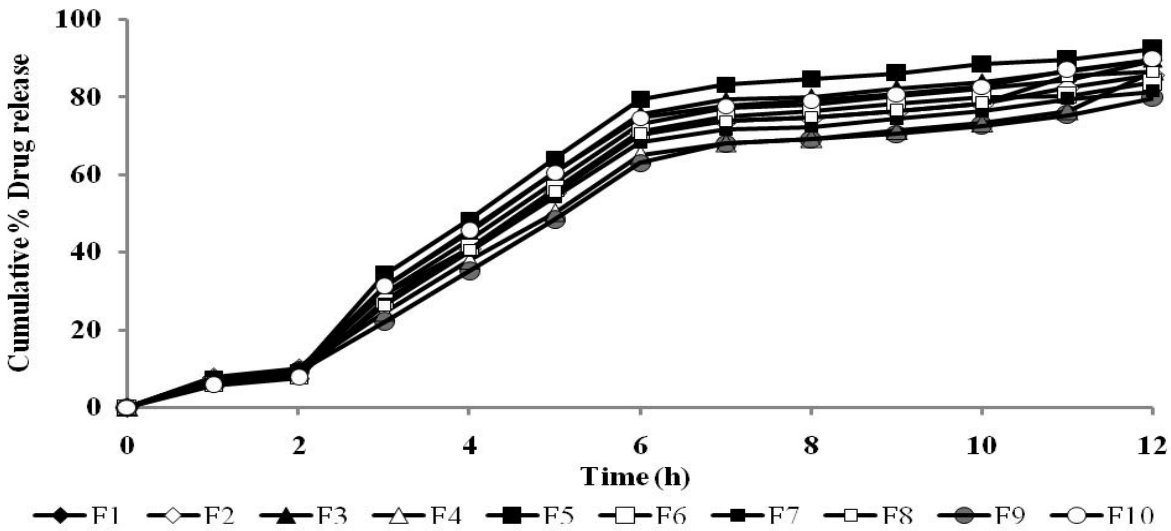

Figure 7: In vitro release profile of prepared TP loaded microparticles.

The *in vitro* release data for the optimized theophylline formulation was compared with the release of marketed product Duralyn CR 400 shown in Figure 8. The overall % release of prepared microparticle formulation and their corresponding marketed product was found to be similar. Among the prepared formulation F5 formulation showed good controlled release effect based on release profile, similarity factor, differential factor, model fitting and release kinetics. The release of drug in acidic pH was less in prepared formulations when compared with marketed formulation.

The *in vitro* release studies data were fitted in to various mathematical models to determine the best-fit model. The results indicated that, the best-fit models were found to be Peppas and Higuchi models. In all the cases the value of intercept, A were found to be less than 0.5. This indicates that the release of drug from all the formulations followed Fickian diffusion. The amount of drug released versus square root of time was plotted. The plot should be linear if the release of drug from the delivery system is diffusion controlled. The plots were linear, and the results inferred that drug release from the microparticle formulation was by diffusion.

The drug release profiles of the optimized formulation F5 was the same that of release profile of oral formulation Duralyn CR 400. The plot of the cumulative percent drug release as a function of time for formulation F5 and Duralyn CR 400 is shown in **Figure 8.** From the figure, it is evident that the prepared microparticle controls the drug release than the commercially available product.

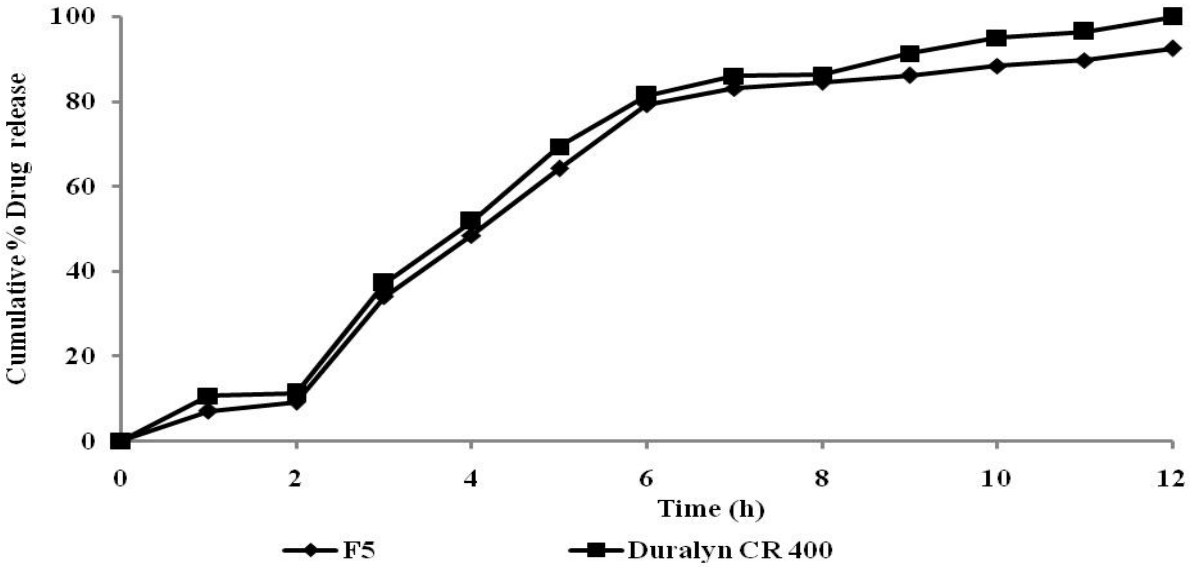

Figure 8: Comparative in vitro release profile of Formulation F5 with marketed product Duralyn CR 400.

Difference factor (f_1) and similarity (f_2) factor was calculated from dissolution profile, and the results were compared with the formulation, F5 and marketed product, Duralyn CR 400. The difference factor (f_1) and similarity factor (f_2) obtained from dissolution profile indicates that the formulation F5 and Duralyn CR 400 were similar.

CONCLUSION

The objective of the study was to prepare and evaluate TP loaded microparticles by the process of phase

separation method for controlled release. Method employed was simple, rapid and economical. The results of micromeritic properties of the microparticles were well within the limits, which indicate good flow potential for the prepared microparticles. Drug loaded microparticles exhibited spherical nature as evidenced by SEM photomicrographs and sphericity studies. From the FTIR and DSC studies, it was observed that there was no chemical interaction between the drug and polymer indicating that drug is in sTab. state. The drug content study revealed uniform distribution of the drug in the microparticles. The drug release rate was found vary among the formulations depending on the compositions of polymer used. The obtained dissolution data indicated that the drug release through the microparticles follows fickian diffusion. Optimized formulation F5 and marketed product Duralyn CR 400 showed similarity in drug release profile. Formulation F5 is an ideal formulation for once daily administration. From the results of the present experimental work, it is stated that Theophylline could be formulated successfully into microparticles as controlled drug release dosage form by Phase separation method.

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تغليف الثيوفيلين في مزيج ثنائي من إيثيل سيللولوز و جسيمات يودراجيت دقيقة: التطوير ، التوصيف وحركية الإطلاق.

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ملخـص

هدفت هذه الدراسة الى تحضير وتقييم جسيمات دقيقة مكونة من مزيج ثنائي يتكون من اليودراجيت و الإثيل سيليلوز ومحملة بالثيوفيلين بهدف التحكم بسرعة إطلاق الثيوفيلين. أعدت الجسيمات الدقيقة باستخدام طريقة الفصل الطوري. تعتبر هذة الطريقة بسيطة جدا ، سريعة ، إقتصادية ، ولا تحتاج الى استخدام مذيبات عضوية سامة. تم الحصول على جسيمات دقيقة ، منفصلة ، صلبة ، متماثلة ، وحرة التدفق. وصل ناتج الجسيمات الدقيقة إلى 92 ٪. أكثر من 85 ٪ من الجسيمات الدقيقة المعزولة لها حجم يتراوح بين 325ـ455 ميكرون. أظهر مسحوق الجزيئات المحضرة قيم زاوية إسترخاء و مؤشر كار المئوي و كثافة نقرية جيدة و ضمن الحدود المقبولة ، والذي بدوره يشير الى أن الجسيمات الدقيقة المجهزة لها سطح أملس ، حرة التدفق و لها خصائص تعبئة جيدة. أكدت صور الميكروسكوب الالكتروني المسحي وعامل الكروية المحسوب أن الجزيئات المعدة كروية الشكل. وكانت الجسيمات الدقيقة المعدة متوافقة ، وهو ما أكدته دراسات الأشعة تحت الحمراء و فرق المسح الحراري . وقد تم تحليل التركيبات المعدة كمياً لمعرفة مقدار الدواء المغلف. ولوحظ أنه لا يوجد اطلاق ذو قيمة إحصائية للدواء على درجة الحموضة المعدية. كما أن الدواء أطلق بشكل متحكم به و ثابت لأكثر من 12 ساعة. وتم فحص اطلاق الدواء من الجسيمات المحضرة في أجواء معوية ومقارنتها مع سلوك الإطلاق لمستحضر Duralyn CR 400الفموي المتوفر تجارياً حيث ظهر أن حركية الاطلاق تتبع آليات نقل مختلفة في الحالتين.

الكلمات الدالة: الجسيمات الدقيقة ، الفصل الطوري ، الثيوفيلين ، اطلاق فيكيان ، يودراجيت.

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