# PREPARATION AND CHARACTERIZATION OF ZIDOVUDINE MICROCAPSULES USING EUDRAGIT RL 100 AND EUDRAGIT RS 100

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**Abstract**

The objective of the present study was to prepare and characterize the microcapsules for the controlled release of Zidovudine using Eudragit RL 100 and RS 100. The microcapsules were prepared by solvent evaporation method using acetone and liquid paraffin as a dispersion medium and liquid manufacturing phase respectively. The prepared microcapsules were characterized for the percent drug content, entrapment efficiency, Fourier Transform Infrared Spectroscopy (FTIR), differential scanning calorimetry (DSC), microscopic study and in vitro dissolution studies. The solution state stability of the zidovudine microcapsules was determined in the dissolution medium for 24 hours. Encapsulation efficiency of 69-76 % was observed in the microcapsules prepared with Eudragit RL 100 and that of 72-76 % was observed in the microcapsules prepared with Eudragit RS 100.The release of drug from the microcapsules extended up to 9 to 12 hours and more. FTIR and Differential scanning calorimetry thermographs shows the stable character of Zidovudine in the microcapsules. Microscopic study revealed that the prepared microcapsules were spherical.

**Keywords**: Zidovudine, Eudragits, microcapsules, controlled release, DSC, FTIR.

## INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. AIDS is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). HIV infects human cells and uses the energy and nutrients provided by those cells to grow and reproduce, so it is necessary to take lot of medicines for longer periods of time. This can lead to an increase in non compliance of drugs. This problem is very serious in case of drugs having shorter biological half life which then requires frequent administration of doses. It is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment[1, 2]. One method is to solve such problems is by releasing the drug for a longer period of time.

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido (-N3) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP), by the sequential action of the cellular enzymes[3]. Zidovudine is rapidly absorbed and extensively distribute; the extent of Zidovudine absorption (AUC) was similar when a single dose of Zidovudine was administered with food.

The peak serum concentration of Zidovudine (Cmax) was 41.8 ± 7.7 µg/mL. The mean elimination half-life (t½) ranged from 0.5 to 3 hours thus necessitating frequent administration to maintain constant therapeutic drug levels.[4] Thus the object of the present investigation is to provide a long-acting pharmaceutical composition containing Zidovudine in a modified release matrix formulation, which is designed such that the resulting composition maintains the blood levels of the active ingredient for a prolonged period of time.

The drug is freely soluble at any pH and the absorption is rapid, judicious selection of release retarding excipients is necessary for achieving constant in vivo release. A limited study has been done so far for preparing the Zidovudine extended release[5]. In the present study an attempt was made to prepare the extended-release microcapsules of zidovudine.

## MATERIALS AND METHODS

### Materials

Zidovudine was obtained as a gift sample from Alkem laboratories Ltd (Mumbai, India). Eudragit RL 100 and Eudragit RL 100 was obtained from Degussa, Germany. All other chemicals and reagents used in the study were of analytical grade.

### Methods

### Preparation of microcapsules

Zidovudine microcapsules were prepared with Eudragit RL 100 and Eudragit RS 100 by using solvent evaporation method where the drug and polymer was dissolved in the organic volatile solvent. The organic volatile solvent used in this study was acetone. The drug and polymer at different ratios such as 1:1, 1:2 and 1:3 were dissolved or dispersed in the organic solvent and added to the liquid manufacturing vehicle which was under stirring condition. The liquid manufacturing vehicle used in the study was heavy liquid paraffin. The prepared microcapsules were recovered by treating with n-hexane

### Characterization of micro capsules

### Encapsulation efficiency (EE) [7]

Drug loaded micro capsules (100 mg) were powdered and suspended in water and then sonicated (Power sonic 505, HWASHIN technology co) for about 20 minutes. It was shaken for another (ORBITEX, Scigenics biotech) for about 20 minutes for the complete extraction of drug from the microcapsules. The resultant solution was filtered through 0.45 µm membrane filter (MILLIPORE). Drug content was determined by UV-visible spectrophotometer (Schimadzu, UV-1700 E 23) at 266 nm. The percent entrapment was calculated by using the following formula.

$$\textit{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

### Particle size distribution

Particle size analysis[8] of the microcapsules was done by sieving method using Indian Standard Sieves # 16, #20, #30, #40, #60 and #80. The results of particle size distribution were given in the Table-1.

### Fourier Transforms Infrared Radiation measurement (FT-IR) [9]

The FT-IR spectra acquired were taken from dried samples. A FT-IR (Thermo Nicolet 670) spectrometer was used for the analysis in the frequency range between 4000 and 400 cm-1, and 4 cm-1 resolution. The results were the means of 16 determinations. A

quantity equivalent to 2 mg of pure drug and drug loaded micro capsules were selected separately.

**Differential scanning calorimetry (DSC) study**

Differential scanning calorimetry (DSC) study of drug loaded microcapsules was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug excepient compatibility study. The analysis was performed at a rate 5 $^{0}$ C min $^{-1}$ from 50$^{0}$ C to 200$^{0}$ C temperature range under nitrogen flow of 25 ml min $^{-1}$.

**Morphological characterization**

Morphological characterization of the microcapsules was done by using microscope. (QUASMO ANISO 9001-2000) microscope equipped with Digital camera DCE2.

**In Vitro Drug Release Studies**

The in vitro dissolution studies were performed using USP type I dissolution apparatus (LABINDIA, DISSO-2000, Mumbai, India) at 100 rpm. The micro capsules were weighed and filled in the empty capsule shells and placed in the basket. The dissolution medium (900ml) consisted of phosphate buffer pH 6.8. the temperature was maintained at 37°C ± 5°C. An aliquot (5 mL) was withdrawn at specific time intervals and replenished with an equivalent volume of dissolution fluid. Drug content was determined by UV- visible spectrophotometer (Shimadzu, UV-1700 E 23) at 266 nm. The release studies were conducted in triplicate and the results are showed in Table 2.

**Solution state stability of zidovudine**

Dissolution is the most important step in the formulation development. The ultimate goal of the formulation scientist is to provide the drug concentration at right time to the site of absorption. In case of the dissolution of extended-release formulations the release was extended up to 24 hours and more. In such situation the formulation will remain in the dissolution medium for 24 hours. So, solution state stability is important parameter in the extended-release formulations. In the present study 200 mg of the pure zidovudine was placed in the 900 ml dissolution medium and allowed for 24 hours at 37°C ± 5°C. The samples were scanned for maximum absorbance at initial and 24 hours.

**Results and discussion**

**Encapsulation efficiency (EE)**

Entrapment efficiency was increased with the increasing in the polymer proportion in the formulation. Encapsulation efficiency of 69-76 % was observed in the microcapsules prepared with Eudragit RL 100 and that of 72-76 % was observed in the

microcapsules prepared with Eudragit RS 100. (Table 1) However the encapsulation efficiency depends on the polymer proportion and stirring rpm and batch size.

**Particle size distribution**

Particle size analysis[12] of the microcapsules was done by sieving method using Indian Standard Sieves #10, #20, #30, #40, #60 and #80. Highest particle size was observed in the range of 445 µ (Table 1) in both the microcapsules prepared with Eudragit RL 100 and RS 100. The percent of microcapsules obtained varies with the polymer proportion in the formulation. 70-80 % of the particles were obtained in the range of 445 µ. How ever the particle size may change with the polymer proportion and stirring rpm because of the droplet formation in the emulsification process.

Table 1 Physical and chemical properties of Zidovudine microcapsules

| | **DRUG: RL 100** | | | **DRUG: RS 100** | | |
|---|---|---|---|---|---|---|
| | **1:1** | **1:2** | **1:3** | **1:1** | **1:2** | **1:3** |
| **10/20 (1242 µ)** | 5 | 7 | 12 | 1 | 7 | 12 |
| **20/30 (666.5 µ)** | 15 | 10 | 10 | 9 | 10 | 10 |
| **30/40 (445 µ)** | 70 | 78 | 69 | 82 | 76 | 70 |
| **60/80 (225 µ)** | 10 | 5 | 9 | 8 | 7 | 8 |
| | | | | | | |
| **Drug content (%)** | | | | | | |
| **Theoretical (%)** | 50 | 33.3 | 25 | 50 | 33.3 | 25 |
| **Estimated (%)** | 34.56 | 25.33 | 19.16 | 36.11 | 24.32 | 19.17 |
| **Entrapment efficiency (%)** | 69.12 | 76.06 | 76.64 | 72.22 | 73.03 | 76.68 |

**Fourier Transforms Infrared Radiation measurement (FT-IR)**

FTIR studies were conducted on the prepared microcapsules. Absorption peaks of carbonyl group at 1685.72 and azido group at 2083.03 for Zidovudine microcapsules prepared with Eudragit RL 100 and carbonyl group at 1685.06 and azido group at 2082.77 for Zidovudine microcapsules prepared with Eudragit RS 100 clearly indicates the stable nature with these polymers. Fig-1 shows the spectrum peaks points of zidovudine microcapsules during FTIR.

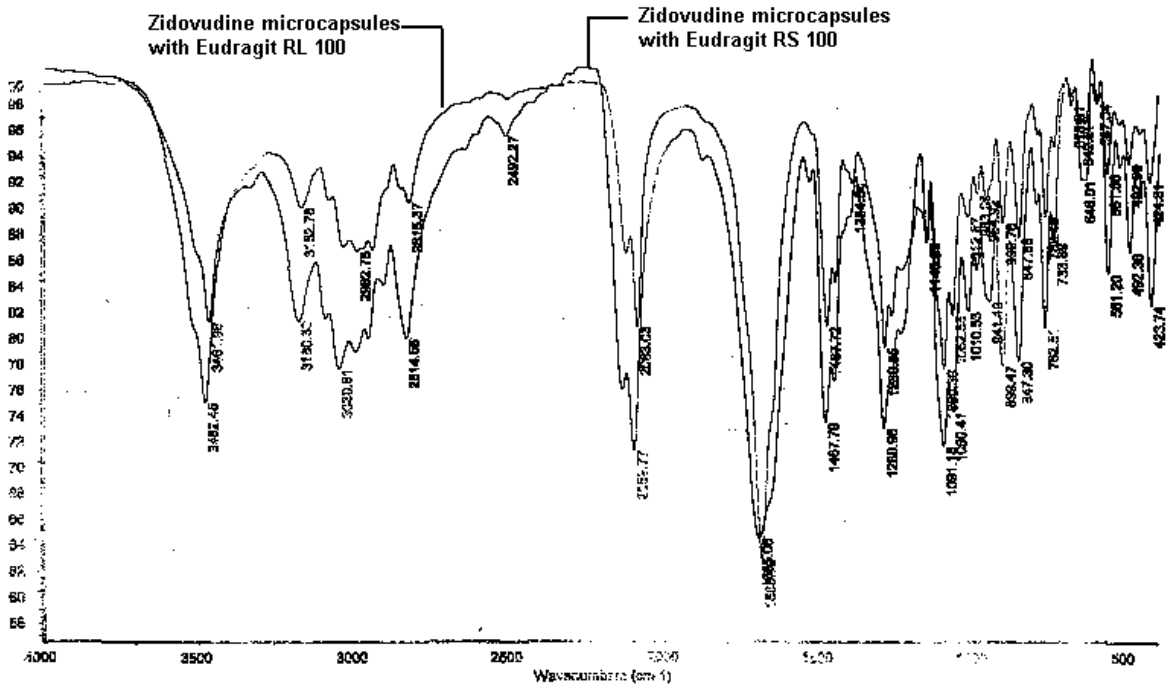


Figure 1 FTIR spectrum peak points of Zidovudine microcapsules with Eudragit RL 100 and Eudragit RS 100

**Differential scanning calorimetry (DSC) study**

Differential scanning calorimetric (DSC) study of drug loaded microcapsules was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug excepients compatibility study. DSC thermo grams shows sharp endothermic peaks at 121°C and 122°C which corresponds to the Zidovudine microcapsules prepared with Eudragit RL 100 and RS 100 clearly indicates the stable nature of the drug. (Fig-2)

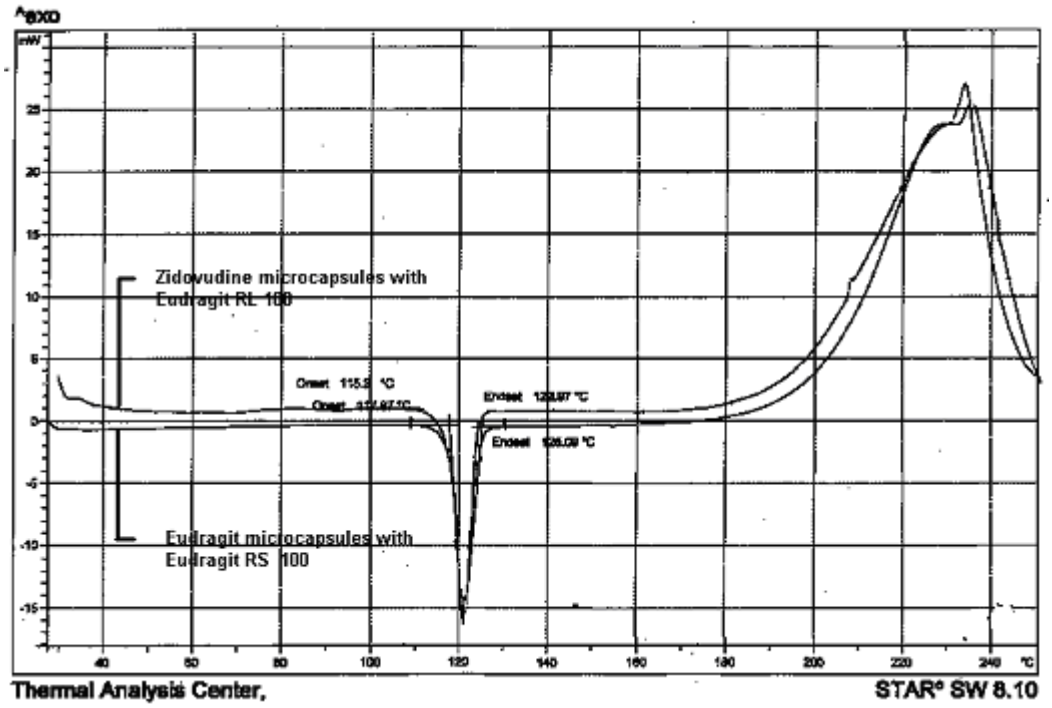


Figure 2 DSC thermo grams showing melting process of Zidovudine microcapsules with Eudragit RL 100 and Eudragit RS 100.

**Morphological study of Zidovudine microcapsules**

Morphological characterization of the microcapsules was done by using microscope. The microcapsules prepared both the Eudragit RL 100 and RS 100 are free flowing. Spherical microcapsules were formed with Eudragit RL 100 where as irregular shaped ie spherical, oval; rectangular straight elongated microcapsule was formed with Eudragit RS 100 (Fig-3).

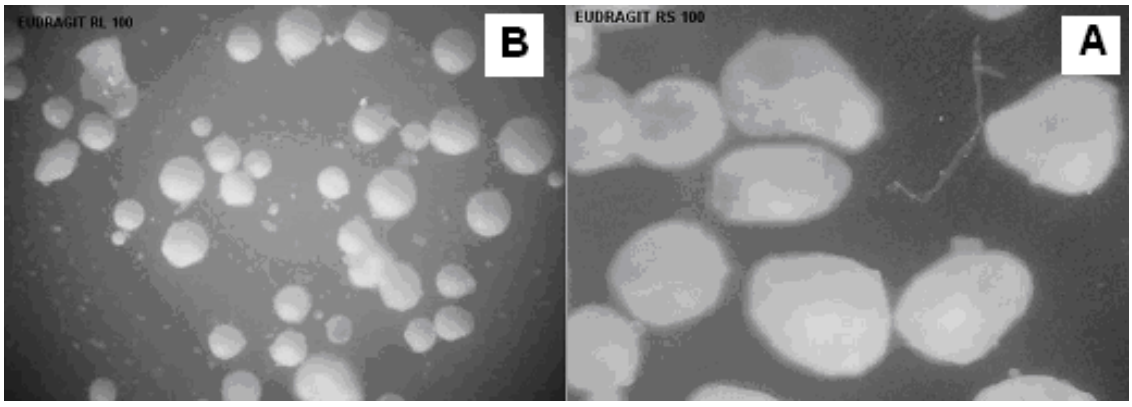


Figure 3 Microscopic photograph showing (A) Zidovudine microcapsules with Eudragit RL 100 (B) Zidovudine microcapsules with Eudragit RS 100

**In Vitro Drug Release Studies**

**Microcapsules prepared with Eudragit RL 100**

Cumulative percent drug release varies with the polymer proportion. As the polymer proportion increases the drug release rate decreases. Drug release of around 96 % was found in 1:3 ratios in 12 hours in the microcapsules prepared with Eudragit RL 100. The release kinetics shows that the drug release followed zero order (Fig 4). Higuchi correlation indicates the drug release mechanism to be diffusion controlled Elimination half life was found around 6.23 hours (Table 2) for the microcapsules prepared at 1:3 ratios. Increase in the elimination half life with increase in polymer proportion and decrease in release rate constant clearly indicates the prolonged release of the drug.

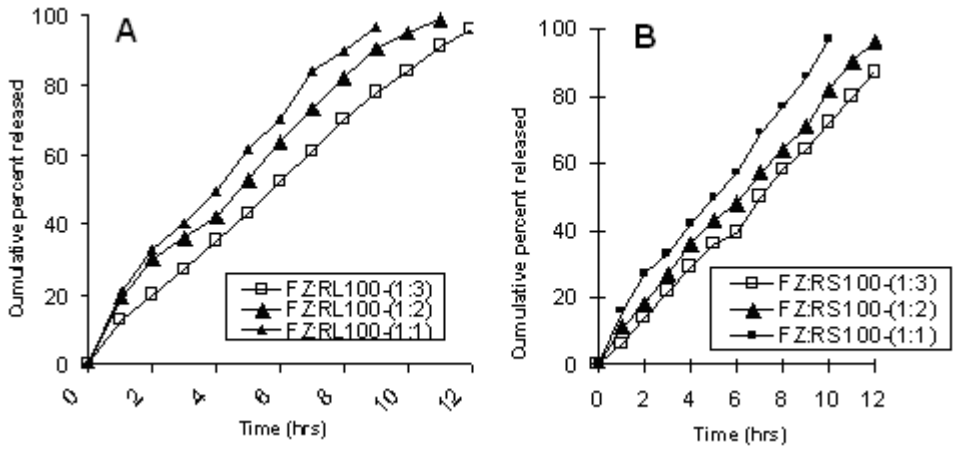


Figure 4 Cumulative Percent release vs time plot of (A) Zidovudine Eudragit RL 100 microcapsules (B) Zidovudine Eudragit RS 100 microcapsules

Table 2 Release kinetics of Zidovudine microcapsules with Eudragit RL 100 and Eudragit RS 100

| Kinetics | Zero order | | | First order | | | Higuchi | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1:1 | 1:2 | 1:3 | 1:1 | 1:2 | 1:3 | 1:1 | 1:2 | 1:3 |
| | Micro capsules with Eudragit RL 100 | | | | | | | | |
| $r^2$ | 0.9861 | 0.985 | 0.9964 | 0.752 | 0.828 | 0.8843 | 0.991 | 0.9896 | 0.9849 |
| K | 10.36 | 8.83 | 8.03 | 0.336 | 0.269 | 0.233 | 44.5 | 40.89 | 37.44 |
| t-50 | 4.83 | 5.66 | 6.23 | 2.06 | 2.87 | 2.98 | 1.25 | 1.49 | 1.8 |
| | Micro capsules with Eudragit RS 100 | | | | | | | | |
| $r^2$ | 0.9942 | 0.998 | 0.998 | 0.934 | 0.842 | 0.919 | 0.982 | 0.9792 | 0.9704 |
| K | 9.1 | 7.85 | 7.26 | 0.216 | 0.18 | 0.154 | 40.27 | 36.04 | 32.96 |
| t-50 | 5.49 | 6.37 | 6.89 | 3.2 | 3.56 | 4.49 | 1.53 | 2.75 | 2 |

**Microcapsules prepared with Eudragit RS 100**

97 % of the drug release in 10 hours, 96 % in 12 hours and 87 % in 12 hours was observed in 1:1, 1:2 and 1:3 drugs to polymer ratio respectively. However the release depends upon the polymer proportion and type of polymer. The drug release of Eudragit RS 100 is slower than Eudragit RL 100 Drug release followed Zero order kinetics (Fig-4). Higuchi correlation indicates that the drug release mechanism is diffusion controlled. Elimination half life found around 6.89 hours (Table 2) for 1:3 drug to polymer ratio. Increase in the elimination half life with increase in polymer proportion and decrease in release rate constant clearly indicates the prolonged release of the drug

**Solution state stability of zidovudine**

A standard concentration of Zidovudine was analyzed at initial and 24 hours. The UV spectra of Zidovudine show similar absorption maxima at initial and 24 hours shows almost similar absorbance. Similar absorption spectra with similar lambda maximum indicate the stable nature of the drug. (Fig-5)

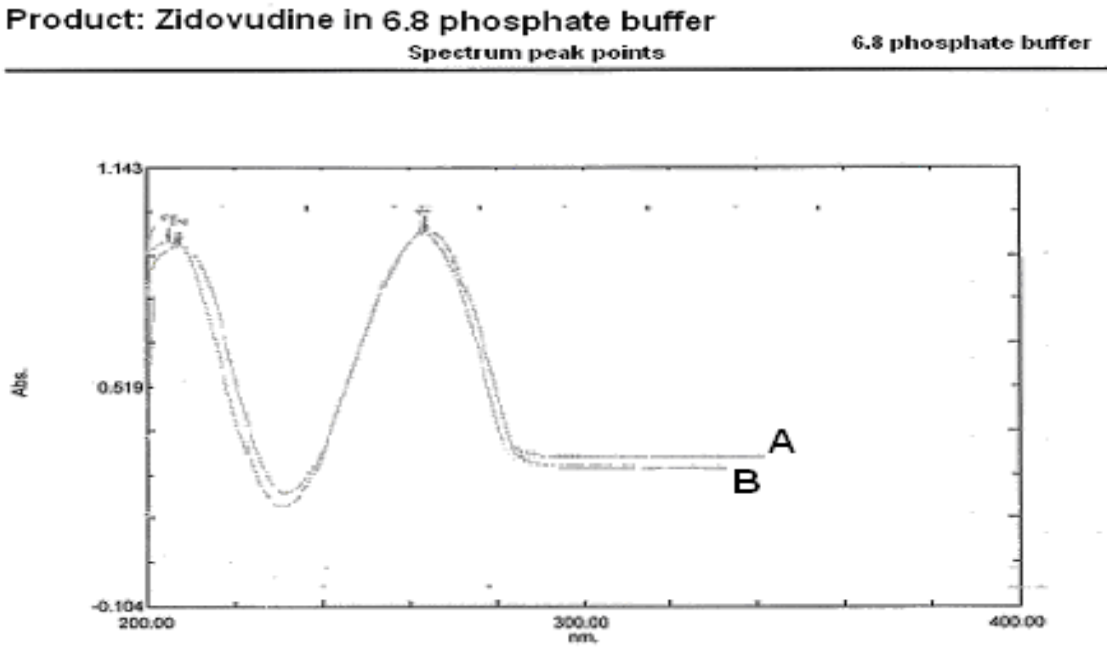


Figure 5 UV absorption spectrum of the Zidovudine (A) at initial and (B) at 24 hours in 6.8 phosphate buffer.

**Conclusions**

Results of the present study demonstrated that the prepared microcapsules were prolonging the drug release form 9 to 12 hours. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional Zidovudine tablets. The in-vitro dissolution of microcapsules showed that the drug release was mainly depends on the

polymer proportion in the formulation. The FTIR and DSC study of the present study clearly indicated that there is no drug and polymer interaction. Microscopic study of the microcapsules showed the spherical and irregular shaped microcapsules. Solution state stability of the pure zidovudine clearly indicates the stability of the zidovudine in solution state for 24 hours.

**Acknowledgements**

The authors are greatly acknowledging the Alchem Laboratories, Mumbai, India, for supply of Zidovudine as gift sample. The authors are grateful to Indian Institute of chemical technology, Hyderabad, India for help in performing the characterization studies.

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