Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2013, 5 (2):284-291
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Development and *in-vitro* evaluation of controlled release multiparticulates of theophylline

Alpana J. Asnani[1]* and Virendra V. Parashar[2]

[1]*J. L. Chaturvedi College of Pharmacy, Nagpur, (MS), India*
[2]*Department of Pharmaceutical Sciences, R. T. M. Nagpur University, Nagpur, (MS), India*

ABSTRACT

A multiparticulate system was developed using the coating pan method with nonpareil seed as the core material for the Theophylline. The drug loaded pellets were prepared by powder layering technique, sprinkling the drug on the nonpareil seeds using PVP K-30 in IPA as binder. The drug loaded pellets were coated by using polymers ethyl cellulose, EUDRAGIT®RS:RL (2:1) and EUDRAGIT® RS:RL (3:1). The fraction of coated pellets were collected on the basis of percentage of coating 5%, 10%, 15% and 20% and evaluated for in-vitro release studied using USP dissolution apparatus. The pellets coated with 15% ethyl cellulose, 15% &20% EUDRAGIT® RS: RL (3:1) shows release profiles as per USP for 12 hours dosing. Product coated with EUDRAGIT®RS: RL (2:1) were unable to retard release of drug in at same percentage of coating on dry basis. Mathematical models like zero-order, first-order, Korsmeyer – Peppas and Higuchi were applied in kinetic studies of theophylline release from the formulated pellets. All the products of theophylline coated pellets are best fitted model for Higuchi and Korsmeyer – Peppas. The mechanism of drug release analyzed by evaluating n-values derived from model fitting, range between 0.5 and 1.0, except SL2:105 and SL3:115, which indicates that drug release is a consequence of anomalous mass transport processes occurring within these dosage forms. This implies that drug release from matrices is both diffusion and swelling controlled which deviates from Ficks 2nd law of diffusion. Scanning electron microscopy study revealed that the microspheres were spherical and porous in nature.

Key words: Eudragit RS100, Eudragit RL100, ethyl cellulose, Theophylline

---

INTRODUCTION

In recent years, considerable attention has been focused on the development of modified release drug delivery system (MRDS). The reason for this paradigm change is the low cost and shorter time required for introducing a MRDS, as compared with a new chemical entity. In the form of an MRDS, an existing drug can get a new lease of life and offer more efficient delivery, thereby increasing its market value, competitiveness and product patent life. Among the various MRDS methods available, the oral controlled release systems play a major role because of their ease of administration and better patient compliance. These products typically provide benefits over immediate release formulations, including greater effectiveness, in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedules [1, 2]. To provide suitable concentrations of drug at the right time means the avoidance of constant plasma levels for drugs that have biorhythm-dependent action profiles, like anti-asthmatic drugs. Multiple unit systems have been developed to guarantee the correct time, correct site and correct rate of specific drug delivery. Various technologies are used for multiple unit drug delivery systems

such as pellets, agglomerates and spherules, and their methods of preparation are termed pelletization, agglomeration and spheronization, respectively. Pelletization is an agglomeration process that converts fine powders or granules of drugs and/ or excipients into small free flowing spherical units called pellets or spheroids. For pharmaceutical purposes, useful agglomerates range from 0.2 to 1.5 mm as they are intended for oral administration [3].

Blythe(1956) described the first pelletization process in a coating pan in 1956[4]. Conventional coating pans are in extensive use because they are less expensive and more versatile in that both pelletization and pellets coating are possible in the same equipment. The typical conventional coating pan installation for pelletization includes a rotating pan air-supply and powder delivery system.

Pelletization in a coating pan generally involves drug layering onto an inert substrate (non-pareil seed) or on dry drug granule or crystals [5].The pellets have certain technological advantages [6, 7] such as good flowability, high physical strength, a smooth surface and the ability to withstand mechanical stress. Spherical granules or spheroids have become more popular in the pharmaceutical industry as a result of increased interest in multiparticulate dosage forms for controlled drug delivery. For controlled drug release, the desired goals can be achieved through the application of a coating to the surface of spheroids/pellets [8].

These also have several therapeutic advantages, such as the dispersion of spherical particles throughout the length of the gastrointestinal tract, reduction in peak plasma levels by adjustment of the release rate, and reducing side effects, compared with single unit dosage forms like tablets or powder-filled capsules [9]. According to the American Thoracic Society, asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by excessive narrowing of the airways and which changes in severity either spontaneously or as a result of therapy. The various therapeutic approaches available and being used to treat asthma aimed at treating symptoms rather than curative. So, patients have to live with their problem throughout their life and, if not managed properly, it can significantly affect their quality of life as well as their productive contributions to society [9].

Theophylline is a naturally occurring 1,3-dimethyl xanthine alkaloid. It competitively inhibits phosphodiesterase, the enzyme that degrades cyclic 3',5'-adenosine mono phosphate (cAMP). Increased concentrations of intracellular cAMP may mediate most of the pharmacological effects of the drug. The drug has a narrow margin of safety and has dose-related side effects (> 20 µg/ml), such as cardiac arrhythmia, ulcers, nausea, epigastric pain and CNS effects. The recommended dose lies in the range 150–850 mg/d with a t1/2 ranging from 3 to 12 h [10]. Moreover, the drug is administered three times a day in a conventional dosage regime, which consumes valuable time as far as the physician, patient and pharmacist are concerned. Dose-related side effects associated with long term administration have limited its use and this has led to the search for a new drug system, which can overcome these side effects by controlling the drug release.

In this study, theophylline pellets were prepared in coating pan in a laboratory-scale by powder drug layering technique using 5% PVPK-30 in IPA as binder solution. The drug loaded pellets were coated by using polymers ethyl cellulose, EUDRAGIT® RS: RL (2:1) and EUDRAGIT® RS:RL (3:1) to produce controlled release drug loaded pellets. The fraction of coated pellets were collected on the basis of percentage of coating 5%, 10%, 15% and 20% and evaluated for *in-vitro* release studied using USP dissolution apparatus. Model independent analyses may be divided into pair wise comparison procedures and ratio tests [11]. The ratio tests determine the relationship between parameters obtained from the analysis of drug release from a reference formulation and from a test formulation at the same time point and include the determination of a simple ratio of percent drug dissolved at a specific time (t x %).

The similarity factor, commonly known as f_2 fit factor, is model independent pair wise comparison of the dissolution profiles, and is currently given in most guidance documents published by regulatory agencies.

In model-dependent analysis application of mathematical modeling using defined equations is useful in the design of new controlled release dosage forms as it can provide information on mass transport release mechanisms which govern the release of a drug from a specific system. In addition, these models can be used to quantitatively predict the kinetics of drug release from specific dosage forms. Mathematical models used to describe drug dissolution curves were zero order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell.

MATERIALS AND METHODS

Methacrylic acid copolymers (Eudragit RS100 and RL100) were supplied by Rohm GmbH Chemische Fabrik, Darmstadt, Germany. Theophylline, ethyl cellulose, RS100 and RL100, polyethylene glycol 6000, dibutyl phthalate, PVPK-30, sugar, lake colours, talc, non-pariel seeds(18/20 mesh),were procured from Zim Laboratories Ltd., Kalmeshwar, Nagpur, isopropyl alcohol, acetone and chloroform were purchased from Loba Chemicals. Commercially available control release TheoSR® was chosen as the reference.

Preparation of drug-loaded pellets

A laboratory-scale coating pan was used for powder drug layering. The drug loaded pellets of theophylline were prepared by powder drug loading technique by using 5.0% polyvinyl pyrrolidone (PVPK-30) in isopropyl alcohol (IPA) as a binder and talc as antisticking agent. The non pareil seed were loaded in coating pan and drug powder was carefully added to the frequently wetted (by binder solution) non-pareil seeds to avoid tackiness and/or dust formation. Air supply and exhaust were cut off during addition of drug to minimize its loss due to blowing away. The entire process of drug layering was performed within 5 to 10 min followed by rolling of the layered pellets for additional 15 min. After completion of the process, the pellets were dried at 60^{o}C for 2 h. The meshed pellets were evaluated for percentage of agglomeration, size distribution, bulk density, percentage friability and repose angle.

Preparation of modified, coated pellets

Ethyl cellulose, Eudragit RS100 and in varying concentrations were used for coating trials on 50 g of pellets containing drug. The different compositions of coating solutions are given in Table 1. The required quantity of polymers was dissolved in IPA and acetone solvent using Dibutyl phthalate (DBP) as a plasticizer. The solutions were filtered through a nylon cloth before coating. Coating of the pellets was carried out in a coating pan at an inlet temperature of 60-65°C, a pan rotation speed of 40 r/min, a spray pressure of 40 psi and a spray rate of 8 ml/min. A pilot type spray gun (Bullows 630) fitted with a 1 mm atomizing nozzle was used to spray the solution. A conventional coating pan and spray gun were used to carry out the coating operation to build up different levels of coating i.e. 5%, 10%, 15%, 20% on a dry weight basis. Fractions of pellets with various coating levels were withdrawn at suitable intervals. The coated pellets of all batches of theophylline were evaluated for Fourier transform infra red (FTIR) spectroscopy, drug content, *in-vitro* drug release and scanning electron microscopy (SEM).

Fourier transforms infra red (FTIR) spectroscopy

In order to evaluate the integrity and compatibility of the drug in the formulations, IR spectra were recorded using an FTIR spectrophotometer (Perkin Elmer-1,000, Japan) using the potassium bromide pellet method over the wave length range 4,000–500 cm-1.

Assay of the drug content

The theophylline content of the pellet formulations were evaluated by accurately weighed 100 mg pellets. After completely powdering pellets in mortar, the complete residue was transferred into a volumetric flask and added up to 100 mL with pH 6.6 phosphate buffer solution. This solution was kept in the ultrasonic bath for 15 minutes and centrifuged for 30 minutes at 5000 rpm. The UV absorbance of the supernatant was measured at λ=271nm. The content uniformity test was evaluated six times for each of the formulations and the results were expressed with the standard deviations and variation coefficients.

In-vitro release studies and comparison with marketed product [12]

In-vitro release of theophylline from pellet formulations and TheoSR® commercial dosage form was investigated by the USP apparatus I (Basket method). The release medium was 1000 mL pH 6.6 phosphate buffer solution at 37±0.5^{o}C and the rotating speed of the apparatus was set to 100 rpm for all formulations (pellets and TheoSR®). At certain time intervals, 5 mL of samples were withdrawn and immediately, same amount of fresh medium (37±0.5^{o}C) was added. For the determination of theophylline amount, the UV absorbance of the samples was measured at λ=271 nm and total amount of theophylline contents were calculated by using standard curve. In vitro release data were analyzed using PCP dissolution and Graph Pad Instat software. The results of model independent and dependent analysis are listed in Tables: 5.3

Scanning electron microscopy (SEM)
A scanning electron microscope, Joel LV-5,600, USA, was employed to study the dimensions of the drug pellets and the morphology of the porous film.

Table 1: Compositions of different coating solution

Compositions	Formulation code		
	EC	SL2:1	SL3:1
Ethyl cellulose(g)	5.0	-	-
Eudragit RS(g)	-	3.35	3.75
Eudragit RL(g)	-	1.65	1.25
Dibutyl phthalate(g)	1.0	1.0	1.0
Talc(g)	0.5	0.5	0.5
Color (lake) (g)	0.5	0.5	0.5
IPA(mL)	100	50	50
Acetone(mL)	-	50	50

All the coated pellets of above drugs have different product code depends upon the type of coating solution used and % w/w of coating on dry basis.

1. Coating solution containing ethyl cellulose
5.0% coating on dry basis: **EC-05**
10.0% coating on dry basis: **EC-10**
15.0% coating on dry basis: **EC-15**
20.0% coating on dry basis: **EC-20**

2. Coating solution containing Eudragit RS: RL (2:1)
5.0% coating on dry basis: **SL2:105**
10.0% coating on dry basis: **SL2:110**
15.0% coating on dry basis: **SL2:115**
20.0% coating on dry basis: **SL2:20**

3. Coating solution containing Eudragit RS: RL (3:1)
5.0% coating on dry basis: **SL3:105**
10.0% coating on dry basis: **SL3:110**
15.0% coating on dry basis: **SL3:115**
20.0% coating on dry basis: **SL3:120**

RESULTS AND DISCUSSION

The obtained values for the physical properties, such as bulk density and sphericity of the drug pellets, were 0.828 g/cm3 and 1.009 respectively. These values are within the expected range.

FT-IR analysis
The obtained IR spectra of theophylline and the drug loaded pellets were found to be identical . The characteristic IR absorption peaks of theophylline at 3,480 (N-H stretch) 1,715 (C=O stretch), 1,565 (C=C stretch), 1,484 (C=N stretch), 1,445 (C-H bend) and 1,187 cm-1 (C-N vibration) were present in all the formulations. The FTIR spectra of the pure drug and coated formulations indicated that no chemical interaction occurred between the drug, theophylline and the carriers used. However, a slight shift in the position of the absorption peaks was noticed. This result showed that a minor physical interaction might have occurred between the drug and polymers used.

Particle size distribution
The measured particle size distribution for the 14/16, 16/18 and 18/20 mesh cuts was 74.9%, 24.5% and 0.6%, respectively. The particle size results revealed that the process used gave a maximum particle size for the 14/16 mesh cut (74.9%). About 24.5% of the pellets were found in the 16/18 mesh cut. The obtained average pellet diameter was in the range 1,235–1,250 μm. Overall, 99% of the pellets obtained were in the desired particle size range proving that the process is very reproducible.

In vitro release studies and Comparison with a marketed product

The *in-vitro* dissolution test were performed to study the release behavior of different formulations to established a correlation between *in-vitro* drug release, type of drug release mechanism and model for the controlled release pellets. The results show that release profiles of EC-15, SL2:120 and SL3:115 pass as per USP for 12 hours dosing. Product coated with ethyl cellulose and eudragit RS and RL 100 in ratio 3:1 are able to retard the release of theophylline up to 15% coating of polymers on dry basis but Eudragit RS and RL100 in ratio 2:1 is unable to retard release of drug in at same percentage of coating on dry basis. The drug release data of formulated products were compared with market sample TheoSR, it was found that product SL3:115 and EC-15 had highest similarity factor i.e., 98.27 and 97.05, respectively. It is evident that the prepared theophylline pellets i.e., SL3:115 and EC-15 have same release profile as market product. The product EC-15, EC-20, SL2:120, SL3:115and SL3:120 show higher R values for all models tested. The above products were coated by high percentage of coating on dry basis, where other products have low percentage of coating. These products are probably best fit to all models due to the fact that these products demonstrated slower rates of drug release as compare to other products. All the products of theophylline coated pellets best fitted model for Higuchi and Korsmeyer – Peppas. The mechanism of drug release analyzed by evaluating n-values derived from model fitting, range between 0.5 and 1.0, except SL2:105 and SL3:115, which indicates that drug release is a consequence of anomalous mass transport processes occurring within these dosage forms. This implies that drug release from matrices is both diffusion and swelling controlled which deviates from Ficks 2nd law of diffusion.

Theophylline pellets coated by ethyl cellulose were examined by SEM for the evaluation of the surface characteristics. The surface of pellets were smooth and spherical and pellets after treatment with dissolution medium shows rough surface and small pores on it as shown in figure 2.

Stability studies

All the selected formulation products were filled in the capsules by calculating the loading dose and maintenance dose alone or in combination, with the other drugs were subjected to accelerated temperature stability studies.

The products were stored in tightly capped dry amber colored bottles at 25^0C for six months, 45^oC for three months and 37^oC 75%RH for three months. The percentage content of the products and *in-vitro* dissolution studies were performed at the end of programmed. All formulations exhibited good chemical stability over the study period.

Table 2: Results of model-independent and model-dependent analysis of Theophylline pellets

Product code	Similarity factor	Zero order	First order	Higuchi	Hixon - Crowell	Korsmeyer - Peppas		
	f_2	R	R	R	R	R	n	k
EC – 05	76.29	0.6873	0.7042	0.9452	0.6987	0.9325	0.5805	2.9308
EC – 10	90.01	0.9493	0.9560	0.9799	0.9539	0.9927	0.7564	1.7450
EC – 15	**97.05**	**0.9858**	**0.9887**	**0.9581**	**0.9878**	**0.9971**	**0.8970**	**1.1841**
EC – 20	**94.94**	**0.9977**	**0.9987**	**0.9389**	**0.9985**	**0.9930**	**1.0709**	**0.6666**
SL2:105	72.69	0.1050	0.2220	0.8928	0.1914	0.9201	0.3491	4.8136
SL2:110	78.82	0.7572	0.7752	0.9722	0.7694	0.9742	0.5045	3.2900
SL2:115	80.88	0.8285	0.8418	0.9775	0.8375	0.9795	0.5822	2.7541
SL2:120	76.37	0.9117	0.9199	0.9765	0.9172	0.9874	0.6913	2.0956
SL3:105	75.05	0.5242	0.5572	0.9398	0.5466	0.9509	0.4151	4.1179
SL3:110	84.61	0.9056	0.9141	0.9770	0.9113	0.9872	0.6872	2.1315
SL3:115	**98.27**	**0.9915**	**0.9938**	**0.9557**	**0.9931**	**0.9988**	**0.8386**	**1.2933**
SL3:120	**91.90**	**0.9996**	**0.9990**	**0.9215**	**0.9992**	**0.9997**	**0.9966**	**0.7225**
Market Sample*	--	0.9870	0.9899	0.9637	0.9890	0.9980	0.8561	1.1399

**Reference sample was marketed product TheoSR*

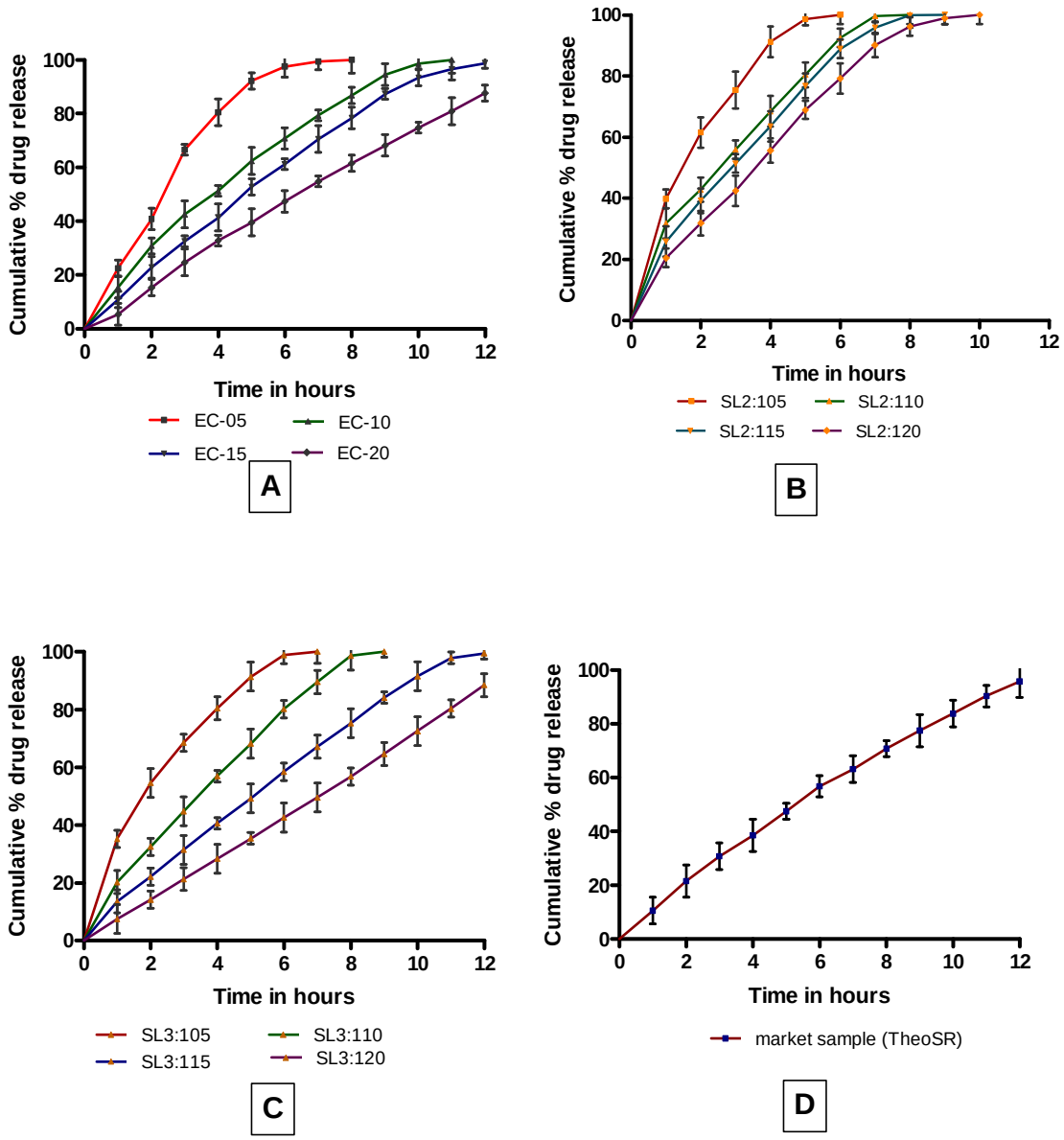

Figure 1: Dissolution profile of Theophylline pellets coated by (A) Ethyl cellulose, (B) RS100 & RL100 (2:1), (C) RS100 & RL100 (3:1), (D) Marketed sample

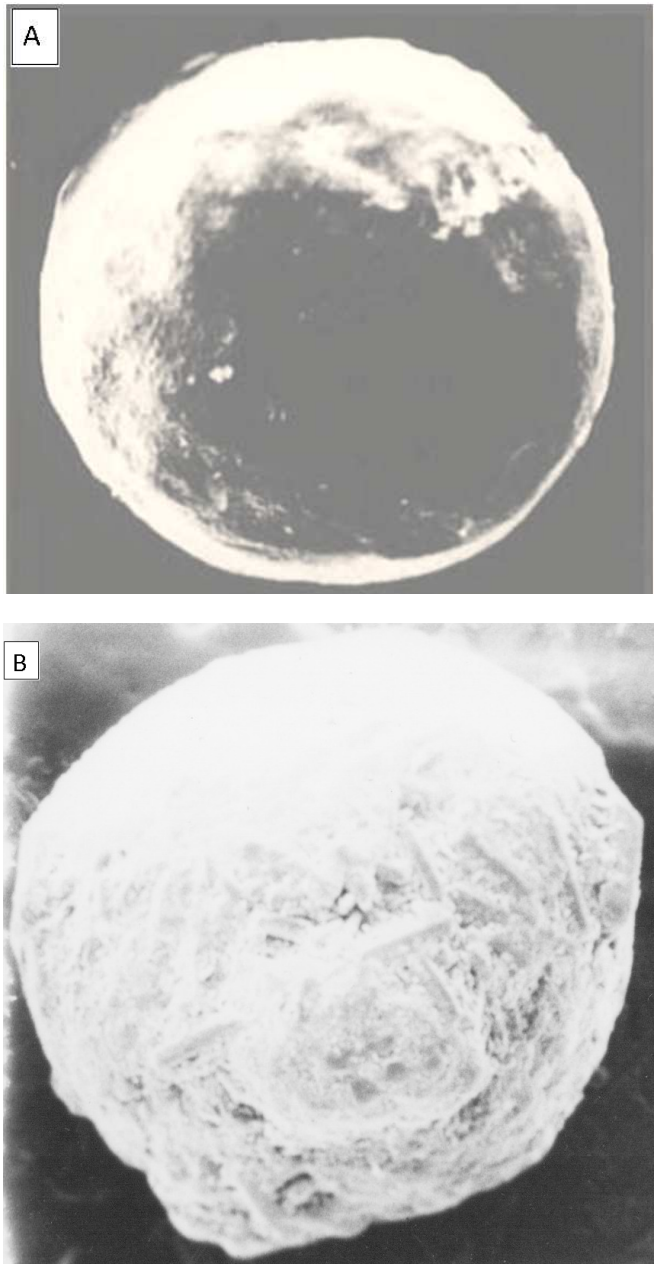

Figure 2: Stereomicrographs of Theophylline pellets coated by ethyl cellulose (A) non treated and (B) treated

CONCLUSION

The objective of this study was to prepare theophylline-loaded pellets by using powder drug layering technique in coating pan. Drug loaded pellets were coated by different ratio of polymers like ethyl cellulose, Eudragit RS100 and Eudragit RL100. The coated pellets were evaluated for total drug content and percentage of drug release for 12 hr. The drug profile was further studies by model independent and dependent analysis and compared with market sample.

From the FTIR studies, it was observed that there was no chemical interaction between the drug and polymers.

In the present study, it showed that drug releases from ethyl cellulose coated pellets were sustained up to 12 hr in range 10-20 % coating on dry basis. Pellets coated by using eudragit RS: RL (2:1) were failed to sustained release of drug up to 12 hr in 20% coating on the dry basis. However eudragit RS: RL (3:1) sustained drug release up to 12 hr in the range of 10-20% coating on the dry basis. Eudragit RS: RL (2:1) was more permeable as compared to the eudragit RS: RL (3:1) and also at high percentage of coating level, it was unable to sustain the release of drugs having higher solubility in dissolution media for 12 hr.

The use of model independent and model dependent analyses proved useful to allow for the comparison of drug release profiles and the elucidation of drug release mechanisms, respectively. These analyses enable researchers to ascertain the closeness of fit of test and reference dissolution profiles, in addition to establishing mechanisms by which the drugs are released from these dosage forms.

The surface morphology of coated pellets and treated pellets were examined by SEM. The surface of pellets was smooth and spherical and treated pellets showed holes on the surface which indicate release of drug from matrices.
All the selected formulations show satisfactory release and excellent stability, they can be tried further for in-vivo studies and clinical trials for their commercial application.

Acknowledgement
We are thankful to Head of Department, Department of Pharmaceutical Sciences, R.T.M. Nagpur University, Nagpur for providing Laboratory facilities, equipments & their valuable guidance time to time.

REFERENCES

[1] Vyas S. P., Khar K. R., Controlled Drug Delivery Concepts and Advances, 1st Ed., CBS Publishers, New Delhi, **2002**, 1-51.
[2] Chopra J. R., Alderborn G., Podczeck F. et al. *Int. J. Pharm*., **2005**, 39, 171.
[3] Ghebre-Sellassie. Pellets: A general view. In Pharmaceutical Pelletization Technology. Ghebre-Sellassie, 1st Ed., Marcel Dekker Inc., New York (NY), **1989**, 1-13.
[4] Varvaet C., Baert L., Remon J. P., *Int. J. Pharm*., **1995**, 116, 131-146.
[5] Tapia C., Buckton G., Newton J. M., *Int. J. Pharm.*, **1993**, 92, 211-218.
[6] Tunon A., Graasjoe J., Alderborn G., *Eur. J. Pharm. Sci*., **2003**, 19, 333.
[7] Bechgard H., Nielson G. H., *Drug Dev. Ind. Pharm*., **1978**, 4, 53.
[8] Goodman, Gilman. The Pharmacological basis of therapeutics, 7th Ed., McGraw Hill, New York, **1985**, 1463-1464.
[9] Chambliss W., Conventional and specialized coating pan, in Pharmaceutical Pelletization Technology, (Ghebre-Sellassie, ed.), Marcel Dekker Inc., New York, **1989**, 15-38.
[10] Deasy P., Pan coating in Microencapsulation and Related Drug Processes, Marcel Dekker Inc., New York, **1984**, 147-160.
[11] Olsen K., Fluid-bed equipment, in Pharmaceutical Pelletization Technology, (Ghebre-Sellassie, ed.), Marcel Dekker Inc., New York, **1989**, 39-69.
[12] United State Pharmacopeia 24, Published by: United State Pharmacopiel Convention.Inc. 393, 574, 936, 1183, 1441, 2107