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DESIGN, DEVELOPMENT AND EVALUATION OF PRESS COATED TABLETS OF AN EPROSARTAN MESYLATE

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ABSTRACT

The chronopharmacotherapy drug delivery system is widely used for treatment of diseases occurs due to circadian changes in the body the body. This system is aims to release drugs at a programmed pattern i.e.at appropriate time and/or at appropriate site of action. In this research, formulation developed for the chronotherapy of cardiovascular diseases to treat high blood pressure early in the morning. In the present study, an attempt was made to design and evaluate a press coated tablet of Eprosartan Mesylate, in Order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. The tablets, each consisting of a core and a coat, were prepared using compression coating technique. The coat layer consists of HPMC K100M, Sodium alginate and Ethyl cellulose in different ratio. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies; XRD analysis, FTIR spectrum, TLC analysis and UV overlay spectra. All the formulations showed marked improvement in the solubility behavior and improved drug release.

KEYWORDS: Pulsatile drug delivery system, Eprosartan Mesylate, HPMC K4M, Ethyl cellulose, Compression coating.

INTRODUCTION

Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. These systems are designed for chronopharmacotherapy which is based on the circadian rhythm of the body. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or Pulsatile drug delivery system[1, 2].

An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problems greater attention has been focused on sustained release drug delivery system[3, 4]. Press-coated formulation can be used to protect hygroscopic, light-sensitive, oxygenable or acid-liable drugs, to separate incompatible drugs from each other or to achieve sustained release. Compression coating can

involve direct compression of both the core and the coat, obviating needs for separate coating progress and use of coating solutions. Material such as hydrophilic cellulose derivates can be used. Most such formulations release drug after a lag phase, followed by a rapid dissolution of a core. A press-coated device in which the inner core contains the drug and the outer coat is made of different types of polymers[1, 5].

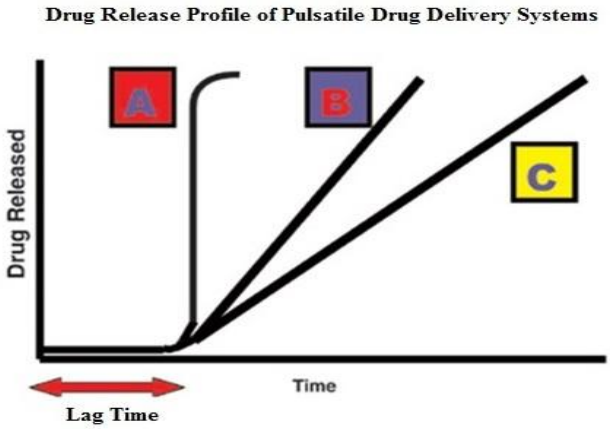

Fig. 1: Drug release profile of Pulsatile Drug Delivery System

(Where (A) sigmoidal release after lag time. (B) Delayed release after lag time. (C) Sustained release after lag time.)

Cardiovascular diseases: Hypertension or Congestive Heart Failure mostly will Comes after midnight or early in mornings. So it is important to control the blood pressure at that particular time, if not control may lead to increase in blood pressure and finally heart failure which may causes death also. This can be done by using antihypertensive drugs, which can lowers the blood pressure at that time. Eprosartan Mesylate is an antihypertensive drug which is the angiotensin II receptor blockers. It can blocks the angiotensin II receptor in vascular smooth muscles and adrenal gland, producing decrease in blood pressure and avoids vasoconstriction and aldosterone secretion. The effect of drug is essential after some lag time, thus it can be achieved by using the time and pH dependent polymer coating [6, 7, 8].

Eprosartan Mesylate (EM) (Figure 2), mono-methane sulfonate salt of (E)-2-butyl-1-(p-carboxybenzyl)-α-2-thienylmethylimid-azole-5-acrylic acid, is a non-biphenyl non-tetrazole angiotensin II receptor (AT1) antagonist[9,10,11].

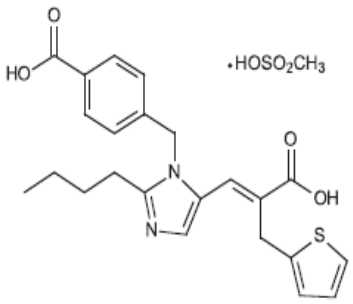

Fig. 2: Chemical structure of Eprosartan Mesylate

MATERIALS: Eprosartan Mesylate was obtained as gift sample from Life Care Laboratories Pvt. Ltd. Hyderabad; HPMC K4M from Healthcaps India Ltd. Chandigarh, Ethyl Cellulose & cellulose acetate propionate was obtained from SD Fine Limited, Mumbai. All other solvents and reagents used were of analytical grade.

METHODS:

1. **Preformulation Study[12]:**

A. **Drug Characterization:** Characterization of drug was done to check whether the obtained sample is in pure form or not. Eprosartan Mesylate sample was subjected for various tests like solubility, melting point, UV, FTIR analysis.

B. **Polymer Characterization:** Characterization of polymers were done to check whether the obtained sample is in pure form or not. All polymer samples were subjected for various tests like solubility, melting point, UV, FTIR analysis.

C. **Compatibility Study:** The compatibility study was carried out at 55^{0C} and for 12 days with moisture and without moisture in hermetically sealed glass container of individual drug and Drug: Excipient was taken [Table]. Individual IR graph were taken before placing the ingredient and drug into the glass vials and these vials were kept for 12days for 55^{0C} in duration of 12 days all the vials were observed for any color change, gas formation, caking and liquefaction and lastly after 12 days its IR was studied.

Differential Scanning Calorimetry study[22]: Thermographs of pure drug, polymers and their physical mixers were recorded. An empty aluminium pan was used as reference. DSC measurement was performed at a heating rate of 100C /min from 400 to 3000C using aluminium sealed pan. During the measurement, the sample size was 1-4 mg for each measurement and sample cell was purged with nitrogen gas.

Infrared spectra analysis[13]: IR spectroscopy was also used to determine the molecular interaction between polymer and drug. All physical mixtures and drug sample were mixed with dried KBR in ratio 1.100. Then small fraction of mixture was compressed on automatic IR press at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellet was taken on FTIR spectrophotometer.

2. Preparation of Eprosartan Mesylate Compression Coated Tablet:

I. **Preparation of Core Tablet:** The inner core tablets were prepared by using direct compression method. Powder mixture of Eprosartan Mesylate, sodium starch glycolate, microcrystalline cellulose and lactose ingredients were dry blended for 20 mins. Followed by addition of magnesium stearate. The mixture was then further blended for 10 mins; 100 mg of resultant powder blend was manually compressed with 6 mm punch and die to obtain the core tablet. (Rimek Mini Press-I)

II. **Preparation of Core-In-Cup Pulsatile Tablets by Direct Compression Method:** As given in the table no-, an impermeable coating cup consisting of cellulose acetate propionate was applied under the bottom and around the core tablet. The cellulose acetate propionate powder (100 mg) was filled into a die of 10 mm diameter and then gently compacted to make a powder bed with a flat surface. The core tablet was carefully placed in the center of the powder bed; the die was filled with the remaining quantity of coating powder (60 mg) so that the surrounding surfaces of the core tablet were fully covered. On the top, hydrophilic polymer was added and the bed was compressed directly by using 10mm flat punch. (Rimek Mini Press-I), to produce the desired core-in-cup system. The above procedure was repeated by using different hydrophilic sweallable polymer (SA, HPMC K4M, SCMC) in different concentrations as given in Table.

Table: Formulation of Core -In-Cup Pulsatile Tablets

INGREDIENS (mg)	**ESA -1**	**ESA -2**	**ESA -3**	**ESA - 4**	**EHP -1**	**EHP -2**	**EHP -3**	**EHP -4**	**ESCMC -1**	**ESCMC -2**	**ESCMC -3**	**ESCMC -4**
Eprosartan Mesylate	50	50	50	50	50	50	50	50	50	50	50	50
Ethyl Cellulose	160	160	160	160	160	160	160	160	160	160	160	160
Sodium Alginate	30	60	90	120	-	-	-	-	-	-	-	-
HPMC-K4M					30	60	90	120	-	-	-	-
Sodium Carboxy Methyl Cellulose	-	-			-	-	-	-	30	60	90	120
Total	**240**	**270**	**300**	**330**	**240**	**270**	**300**	**330**	**240**	**270**	**300**	**330**

Evaluation of pre compression parameter of powder blend[13, 14]: The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.

Evaluation of Press-Coated Tablet: Tablets from all the formulations were evaluated for various properties like hardness, Friability and weight variation.

1. **Evaluation of Pre compression Parameter for both core and coat material[15]:**

a) **Bulk density:** 250 ml of measuring cylinder was taken and 100 gm of powder of all batches were Weighed and passed through the sieves and filled into the cylinder and their volumes were noted down and bulk density was calculated. The formula used for calculation is as follow.

Bulk density = Mass / volume

b) **Tapped Density:** 250 ml of the measuring cylinder was taken and 100 gm of the powder of all batches were weighed and filled into the cylinder, volume of powder measured and noted then that cylinder was tapped about 300 times and again volume of powder measured and tapped density of powder calculated by following formula.

Tapped density = Mass of powder / tapped volume

c) **Carr's Index:** Carr's index of the powder was determined for determination of flow of the powder, for the calculation of Carr's index it requires tapped density and bulk density. Formula for the calculation of the Carr's index is given below.

Carr's index = [tapped density- bulk density / tapped density] × 100

d) **Hausner's ratio:** Hausner's ratio gives information about flow ability of the powder, for the determination of the Hausner's ratio it requires tapped density and bulk density.

Hausner's ratio = tapped density / bulk density

e) **Angle of repose:** Angle of repose was determined according to USP 2007 method, funnel was taken and it is fixed at 1cm height on the stand. One cotton was placed at the orifice of the funnel and on that cotton a constant powder weight was placed. The cotton was removed and the diameter formed by powder and height formed by the pile of the powder was measured and angle of repose was calculated from the following formula.

$$\tan^{-1}[\theta] = h / r$$

Where h = height formed by the pile of the powder.

R = diameter formed by powder.

2. **Evaluation of core tablet and compression coated tablet of Eprosartan Mesylate:**

a) **Friability testing:** 20 tablets were taken, it is weighed and initial weight was noted then it was placed into the Roche friabilator and test was performed for 4 min by using 25 rpm after that tablets were weighed and friability was calculated by using following formula.

% loss = [Final wt. of tablets - Initial wt. of tablets/Initial wt. of tablets] x100

b) **Weight variation:**

Table: Percentage weight variations allowed under weight variation

Average tablet of the tablet [mg]	Percentage deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 or more	±5

20 tablets were selected randomly and average weight was calculated, not more than 2 tablets from this average weight should not be deviate shown in table. The test was performed According to the Indian Pharmacopoeia 2010 and results were recorded in table 15 and 18. Weight variation was calculated by using following formula.

%weight variation = [Weight of single tablet – Average weight of tablet /Average weight of tablet] x 100

c) **Hardness testing:** The crushing strength kg/cm^2 of prepared tablets was determined for tablets by using Monsanto hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded. Average of three readings was taken and results were tabulated.

d) **Diameter and thickness of core tablet[16]:** The diameter and thickness of core tablet were measured by using Vernier caliper.

e) **Disintegration test for core tablet of Eprosartan Mesylate:** Disintegration test on core tablet of Eprosartan Mesylate was performed by using distilled water as media. 6 core tablets of Eprosartan Mesylate were taken and placed in 6 respective tubes of disintegration apparatus and disintegration time of core tablet was measured.

f) **Dissolution testing of core tablet of Eprosartan Mesylate[11, 17]:** Dissolution testing of core tablet of Eprosartan Mesylate was performed by using pH 6.8 phosphate buffers and 0.35% w/v Tween20 as dissolution medium. Dissolution study was carried out for about 30 min. at 370 C and 50 rpm by using USP type II apparatus. 5ml sample were removed from dissolution medium at every 5 min. and its absorbance was checked by using UV (Systronics India Limited UV-Vis Spectrometer-2203).

g) **In vitro dissolution testing of compression coated tablet of Eprosartan Mesylate in phosphate buffer pH 1.2, 6.8, and 7.4 [18]:** Dissolution testing was carried out by using USP type II dissolution apparatus [Lab India]. Dissolution medium used for the testing were 500ml phosphate buffer pH 1.2, pH 6.8, pH 7.4 each. Compression coated tablet was placed in pH 1.2 phosphate buffer for 2 hrs because gastric emptying time is 2 hrs, then that medium was replaced with pH 6.8 phosphate buffer and testing carried out for 3 hrs because intestinal emptying time is 3 hrs, after that pH 6.8 was replaced by using pH 7.4 phosphate buffer and testing carried out. Samples of 5 ml were withdrawn after every hour, filtered with Whatman's filter paper and replaced with 5 ml of fresh dissolution medium. The Temperature condition used for dissolution testing was 37.5 ±0.50 C. The rotation speed was kept at 50rpm for dissolution testing. Each sample was tested for its absorbance at 233 nm by using UV spectrophotometer.

h) **Assay of the Eprosartan Mesylate compression coated tablet[19]:** Ten tablets were weighed and powdered. An amount of powder equivalent to 8 mg of Eprosartan Mesylate was dissolved in 100 ml of phosphate buffer [pH 6.8]. It was shaken by mechanical means for 1 hr. Then it was filtered through a whatsman filter paper. From this resulted solution 1ml was taken, diluted to 100 ml with phosphate buffer of pH 6.8 and absorbance was measured against blank at 234 nm using UV-Visible spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated using calibration curve. Procedure was repeated by using two or more tablets from the same formulation and the average value of all three tablets were calculated.

i) **Stability study[20, 21]:** Stability of a drug has been defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.

The best formulation was kept for stability study in stability chamber for period of 3 months at temperature 45±20C and RH 75±5%. The changes in physical appearance, % drug release and drug content were observed for an interval of 1 month to 3 months.

RESULT AND DISCUSSION:

1. **Preformulation Study**: Preformulation study of Eprosartan Mesylate drug was carried out by using parameters like solubility, loss on drying, melting point, IR, calibration curve.

Table: Preformulation study of Eprosartan Mesylate

Parameter	Observation	Standard
Solubility Study of Eprosartan Mesylate	Practically insoluble in water, sparingly soluble in methanol	Practically insoluble in water, sparingly soluble in methanol
Loss of Drying	0.3%	NMT 0.5%
λ_{max} of Eprosartan Mesylate	234nm	233nm
Melting point of Eprosartan Mesylate	248-251°C	250°C

λ_{max} of Eprosartan Mesylate drug was performed in three phosphate buffers that were pH 1.2, 6.8, 7.4.The λmax of Eprosartan Mesylate was found to be 234 nm. The standard λmax of Eprosartan Mesylate was 233 nm.

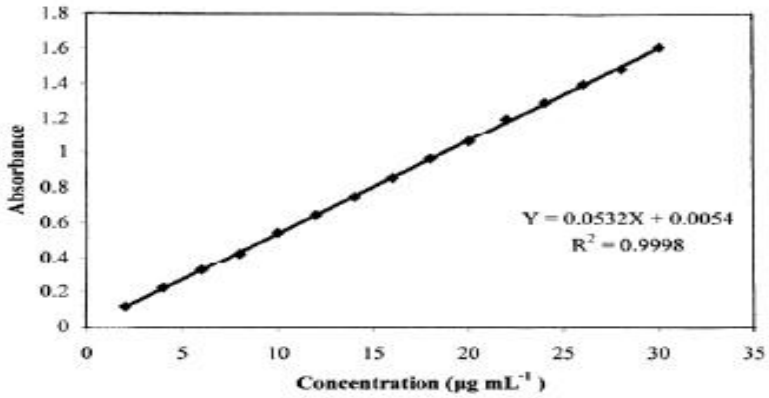

Fig.: Calibration curve of Eprosartan Mesylate 7.4 buffer

IR study of Eprosartan Mesylate bulk drug:

After physical characterization of Eprosartan Mesylate the drug was subjected to FTIR to check the structure and purity of Eprosartan Mesylate. IR study of Eprosartan Mesylate drug was done by using Bruker instrument and it was compared with standard IR of Eprosartan Mesylate of USP35–NF30.

Solubility study of Eprosartan Mesylate in phosphate buffer: Solubility study of Eprosartan Mesylate was carried out in 3 different phosphate buffers i.e.; pH 1.2, 6.8, 7.4. Solubility study of Eprosartan Mesylate is shown in the table**.**

Table: Solubility of Eprosartan Mesylate pure drug

pH	Solubility found (mg/ml)
1.2	0.60
6.8	1.79
7.4	1.72

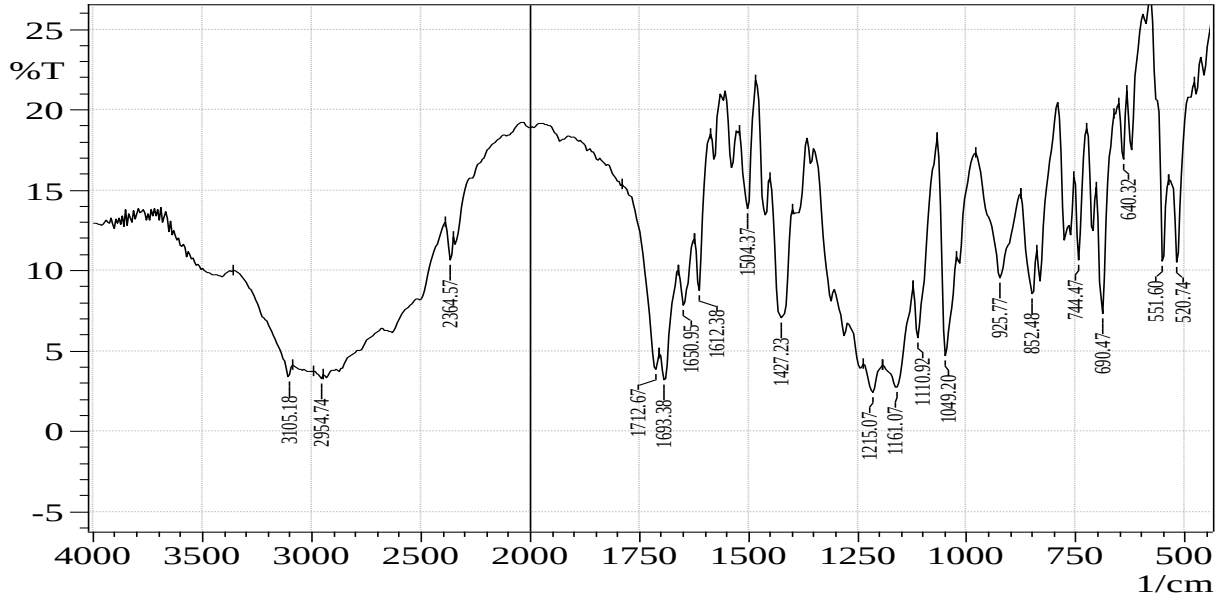

Fig: . IR Spectrum of SD and PM compared with pure drug Eprosartan Mesylate

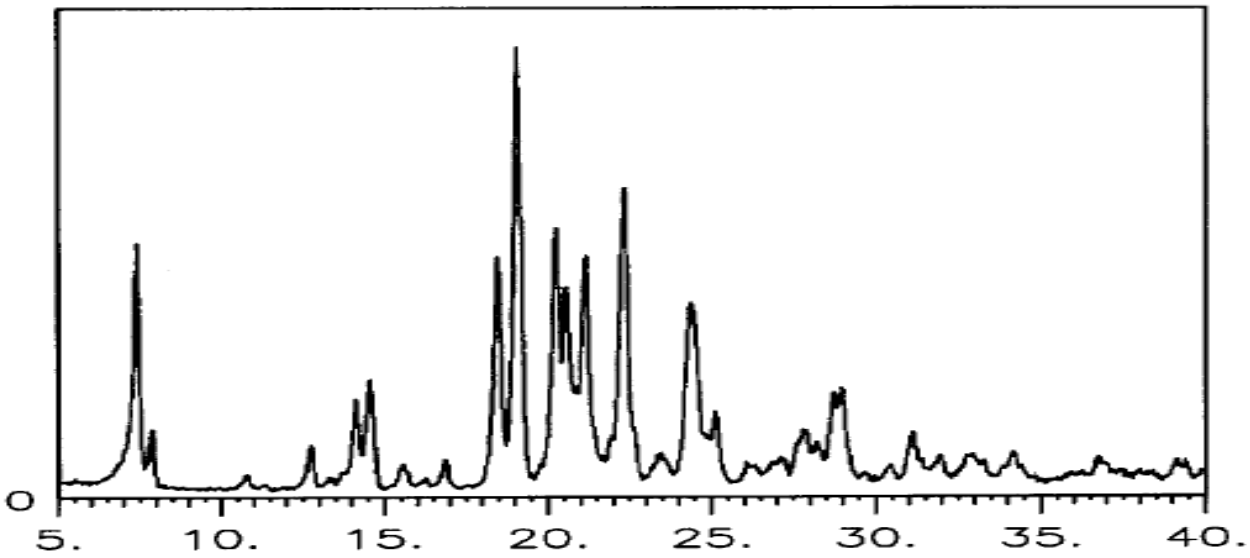

Fig..: IR of Eprosartan Mesylate sample

Polymer characterization: The different parameters for which polymers where characterized. Three polymers where characterized namely

HPMC K4M - Insoluble in Ethanol, LOD of 1.9% (Standard - Insoluble in ethanol, LOD - NMT 5%)

Ethyl Cellulose – Soluble in methanol and acetone, LOD of 2.8%

Cellulose acetate propionate – Soluble in methanol and acetone, LOD of 3.5%

IR study of polymers:

The IR study of HPMC K4M, Cellulose acetate Propionate were performed by Bruker instrument. IR study was performed to check the structure and purity of polymers. IR of and HPMC K4M is shown in fig.

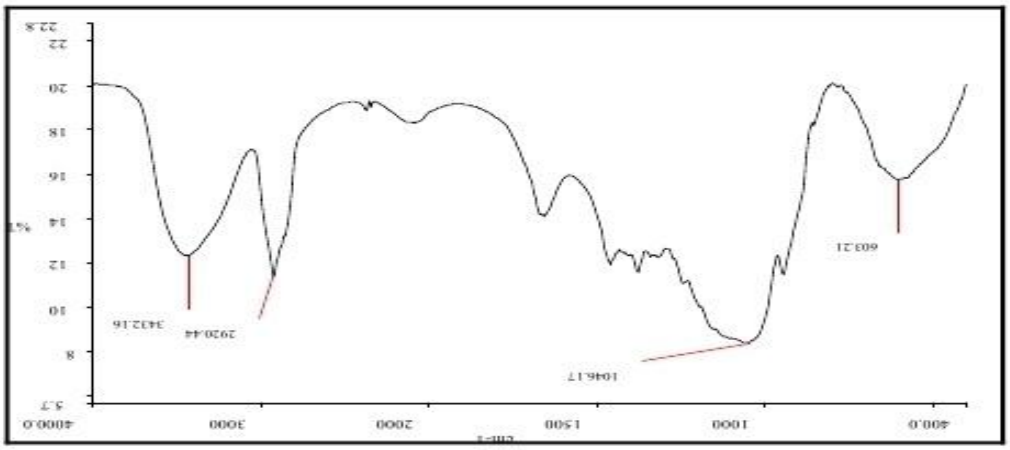

Fig. IR Spectra of HPMC K4M

CONCLUSION

Eprosartan Mesylate was selected for this investigation because less biological half life, to improve bioavailability by retaining the drug in acidic environment as its solubility decreases with increasing pH and to reduce wastage. Step by step studies were carried out to develop and evaluate oral sustain release tablet for Eprosartan Mesylate using hydrophilic polymers. The oral sustain release tablets were prepared by direct compression press coating technique using rate controlling hydrophilic polymers. In the preliminary trials, the effect of various polymers i.e. HPMC K100M, and Ethyl cellulose was studied on their different ratios to produce time release tablet of Eprosartan Mesylate. HPMC K100M, Ethyl cellulose was found to be suitable for press coating. Physical parameters like hardness, weight variation, thickness and friability were within pharmacopoeial limit.

REFERANCES

[1]. Janugade BU, Patil SS, Patil SV and Lade PD: Pulsatile drug delivery system for chronopharmacological disorders: an overview. Journal of pharmacy research 2009; 2(1): 132-143.

[2]. Suresh Rewar et al, Pulsatile Drug Delivery System: An Overview, JGTPS, 2014, Vol. 5(3): 1943 – 1955.

[3]. Chien YW; Novel Drug delivery Systems. Marcel Dekker, Inc., New York, U.S.A., 1992: 139-196.

[4]. Brahmankar DM, Jaiswal BS; Controlled release medication. In Brahmankar DM, Jaiswal BS editors; Text book of biopharmaceutics and pharmacokinetics a treatise, 1st edition. Delhi, Vallabh Prakashan, 1995: 335-340.

[5]. Jain KK; Drug delivery systems – An overview. In Jain KK editor; Drug delivery systems. New Jersey, Humana Press, 2008: 1-50.

[6]. Oates J.A., "Anti-hypertensive agents and the drug therapy of hypertension" chapter-33 in Goodman and Gillman's "The pharmacological basis of therapeutics" 9th edition, McGraw Hill, New York, 1996, p. 780-81.

[7]. Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology: 5th Ed. Edinburgh: Churchill Living Stone; 2003, p.203-14.

[8]. Parfitt K, Sweetman SC, Blane PS, Parsons AV. Martindale: The complete drug reference. 32nd Ed. London: Pharmaceutical Press; 1999.

[9]. Rockville MD. United States Pharmacopoeia: United States Pharmacopoeial Convention Inc, 25th Edn. 2002. p. 2150.

[10]. Palmer A. Hypertension: Eprosartan. In Drugs in Context, Edited by Kassianos G. CSF Medical Communications Ltd. 2006; 2(13): 557-600.

[11]. Kamila M., Mondal N. and Ghosh LK., Spectrophotometric determination of eprosartan mesylate mesylate in raw material and experimental tablets, Indian J Chem Tech. 2008; 15: 194-196.

[12]. Carstensen JT. Preformulation. In: Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed. New York: Marcel Dekker; 1996. p. 213-37. (Drug and the pharmaceutical sciences; vol 72).

[13]. Stuart B; Infrared spectroscopy - Fundamental and application. John Wiley and sons, 2004: 46-63.

[14]. Sinko PJ; Martin's physical pharmacy and pharmaceutical sciences. 5th edition, Noida, BI Publisher, 2006: 550-560.

[15]. Hadkar UB: A Handbook of Practical Physical Pharmacy and Physical Pharmaceutics, Nirali Prakashan, 85-88.

[16]. Niazi SK: Handbook of Preformulation, Informa healthcare, 2007; 241-276.

[17]. Available online from: USFDA dissolution methods www.accessdata.fda.gov/scripts/cder/dissolution/dsp_searchResults_Dissolution.cfm?PrintAll=/ [cited on: 27 Sept. 2014].

[18]. Malik D, Singh I: Formulation and evaluation of press coated tablets of esomeprazole for colonic delivery. Asian Journal of Pharmaceutics 2012; 6(4):252-258. [cited 2014 Sept.] Available from: http://www.asiapharmaceutics.info/text.asp?2012/6/4/252/107560

[19]. USP35–NF30, The United States of Pharmacopoeial Convention, Rockville MD, 2012; 36(6):1506.

[20]. Malik A, Kumar V: World Health Organization's Guidelines for Stability Testing of Pharmaceutical Products. Journal of Chemical and Pharmaceutical Research, 2011; 3(2):892-898.

[21]. Available online from: www.who.in, Design of stability study. [cited on: 27 Sept. 2014].

[22]. Schimdt P; Secondary electron microscopy in pharmaceutical technology. In Swarbrick J, Boylon JC editors; Encyclopedia of Pharmaceutical Technology. 3rd edition, volume 5, Marcel Dekker Inc., New York, 2007: 3217- 325.