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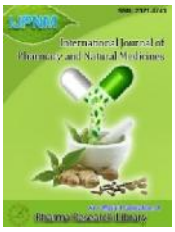

Research Article **Open Access**

Design and Characterization of Controlled Release Tablets of Emtricitabine by Compression Coating Technology

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A B S T R A C T

Extending or controlling the release of highly water soluble drugs from matrix tablets is always a challenge. The research attempt was aimed to explore the compression coating technology for the development of controlled release (CR) tablets of highly water soluble drug i.e., emtricitabine. Emtricitabine controlled release tablets were developed to prolong drug release time and prepared by compression coating technique by employing ethyl cellulose, hydroxy ethyl cellulose and ethyl cellulose with lactose in different ratios as drug release-retarding (coating) polymers. Emtricitabine granules for core tablet and polymer granules for coating were prepared and evaluated for the flow properties like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. All types of granules showed good flow properties. The compression-coated tablets were evaluated for the hardness, uniformity of weight, friability, tensile strength, swelling index, wetting time, drug content and in-vitro dissolution studies. All the formulations were in compliance with pharmacopoeial standards. Through FTIR & DSC studies, it was confirmed that there was no interaction between drug, polymer and other excipients. Among all the formulations ECT14, showed prolong release when compare to the other formulations. The drug release kinetics followed zero order. The diffusion exponent (n) values are found to be more than 0.9 (n>0.9) which indicated that the drug release was predominantly controlled by super case II transport system.

Keywords: Controlled Release, Tablets, Emtricitabine, Compression coating technique, Ethyl cellulose.

A R T I C L E I N F O

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1. Introduction

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. Controlled drug delivery technology is fast growing because of its many potential advantages like minimum fluctuations in plasma drug concentration and a reduced frequency of dosing when compared to the conventional dosage forms. Many newer technologies are also emerging for designing controlling drug delivery systems with improved efficiency and compression coating technology [2] is one such technique.

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of HIV infection in adults and children. Emtricitabine is an analogue of cytidine. The drug works by inhibiting reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA. By interfering with this process, which is central to the replication of HIV. Emtricitabine can help to lower the amount of HIV, or "viral load", in a patient's body and can indirectly increase the number of immune system cells [3].

Extensive research was published on Emtricitabine ER formulations, some of them are, sustained release nanoparticles of emtricitabine by using PLGA [4,5], delayed release tablets of emtricitabine [6]; sustained release microparticles loaded with emtricitabine using ionotropic gelation method by using HPMC and sodium alginate [7]. The main objective of the present research work was to develop CR tablets of emtricitabine for once–a–day dosing using hydrophobic polymers by compression coating technology.

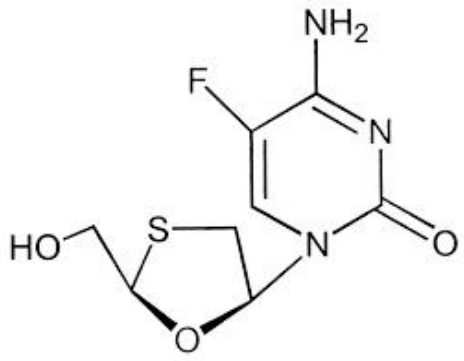

Figure 1: Chemical structure of emtricitabine

2. Materials and method

Materials: Emtricitabine was a gift sample from Hetero Drugs Pvt. Ltd., Hyderabad. Ethyl cellulose (Loba Chemie Pvt. Ltd., Mumbai), Hydroxy ethyl cellulose (Moly Chem, Mumbai), Lactose, Talc and Magnesium stearate were purchased from Merck Specialities Pvt. Ltd., Mumbai, India.

Methods:

Drug-Excipients Compatibility

Fourier transforms infrared spectroscopy (FT-IR)

The physicochemical compatibility between emtricitabine and polymers (EC, HEC and Lactose) used in the research was carried out by subjecting to IR spectral studies using Bruker Fourier Transform infrared Spectrophotometer, USA. The samples were prepared by mixing the 100 mg of the drug with the 100 mg of polymers (1:1 ratio). These samples were scanned under diffuse reflectance mold and plotted the graph by the KBr pellet method and spectra were recorded in the wavelength region between 4000 cm-1to 400 cm-1. The spectra obtained for the pure drug was compared with that of the physical mixtures of the drug with polymers.

Differential scanning calorimetry (DSC)

The thermal behavior of the drug alone (emtricitabine) and with polymers (EC and HEC) was analyzed by using DSC instrument. The drug and its physical mixture with polymers were weighed, crimped in aluminum pans and analyzed at a scanning temperature range from 50 to 400 ^{o}C at the heating rate of 10 ^{o}C/min in nitrogen atmosphere.

Design and Development of Controlled Release Compression Coated Tablets of Emtricitabine [8-11]

The emtricitabine was formulated into compression coated tablets for the controlled release. The tablets were prepared with varying amount of coating granules so as to obtain the tablets of varied thickness of coating layer to study the effect of coating thickness on release rate of the drug. The compression coated tablets were prepared in three successive steps:

Step 1: Preparation of core tablets

Core tablets of 250 mg weight were prepared by wet granulation method. The drug and other excipients were screened (through #80) before processing and weighed according to formulae as shown in the table-1 initially, the drug EMT and lactose were transferred into a clean mortar and mixed thoroughly. The powder mixture was made into wet mass by adding 2% PVP K30 solution as granulation fluid (binder) and triturated with pestle. Then the wet mass was passed through sieve #16 and the obtained granules were subjected to drying in hot air oven at 60 °C. Then dried granules were passed through mesh #20. The granules thus obtained were subjected to lubrication. The lubricated granules were further subjected to compression. The lubricated granules were compressed into tablets weighing 250 mg each using 10 stage rotary tablet press equipped with 8 mm round, flat punches. The obtained tablets were stored properly until further use.

Step 2: Preparation of coating granules

Three types of granules were prepared by using two different polymers i.e. Ethyl cellulose, hydroxy ethyl cellulose and ethyl cellulose with lactose (at different ratios as 1:1, 1:2 & 1:3). Granules were formed by simple mixing

of polymer with 2% w/v aqueous solution of PVP K30 to form dough mass. The formed dough mass was passed through #16, dried and again sieved through #20. Finally, obtained granules were mixed with talc and magnesium stearate.

Step 3: Compression coating of core tablet

The amount of coating granules were taken in two different portions, as shown in the table-1, for the formation of bottom layer and top layer along with side walls. The compression in this step was performed with 10 mm punch die set. First portion of coating granules were placed in the die cavity, the core tablet was placed in the centre of the die cavity and the second portion of the coating granules were filled in the cavity; and compressed to obtain the compression coated tablets.

C) Evaluation of Emtricitabine Cr Tablets [8-11]

i) Flow Properties for pre compressed granules:

Bulk density:

A 10g of the test sample (M) was weighed and passed through a #18 screen to break up agglomerates that were formed during storage, and was transferred to a dry 100-ml cylinder and filled carefully. The powder/granules were leveled without compacting and the unsettled apparent volume (Vo) was noted. The bulk density, in g/mL, was calculated using the formula:

$$°_b = M/V_o$$

Tapped density:

The 10g of test sample was weighed accurately and introduced into a dry 100 mL measuring cylinder. The cylinder containing the sample was tapped mechanically by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester at a nominal rate of 300 drops/min. The cylinder was tapped for 500 times and the tapped volume (Va) was measured. The operation was repeated for an additional 750 tappings and again the tapped volume as (Vb) was measured.

If the difference obtained between Va and Vb is <2%, Vb was the final tapped volume (Vt). If the difference was higher, the tapings were repeated for an additional 1,250 times and then the tapped density was calculated using the following formula

$$°_t = M/V_t$$

Compressibility index:

The compressibility index of powder/granules was determined using Carr's compressibility index, and it was calculated by the following formula:

$$I = (V_0 - V_t)/V_0 \times 100$$

Where, V_0 - bulk volume & V_t - tapped volume.

Haussner's ratio:

The Haussner's ratio is an indirect index of ease of powder flow. It was calculated by using the formula:

$$\text{Haussner's ratio} = °_t/°_b$$

Where, ρ_t= tapped density & ρ_b= bulk density

Angle of Repose:

It was determined by allowing a powder to flow through a funnel and fall freely onto a surface. Further addition of powder was stopped as soon as the pile touches the tip of the funnel. A circle was drawn around the pile without disturbing it. The height and diameter of the resulting cone were measured. The same procedure was repeated three times and the average value was taken. Angle of repose was calculated by using the following equation:

$$\Theta = \text{Tan}^{-}[h/r]$$

Where, h is the height and r is the radius of pile

Disintegration Test for core tablets:

The process of the breakdown of the tablet into smaller particles or granules is known as disintegration. This test was carried out by using USP disintegration apparatus. One tablet was introduced into each tube and a disc was added to each tube. The assembly was suspended in the beaker containing the distilled water and the apparatus was operated for a specified period of time.

Thickness:

The crown thickness and diameter of individual tablets was measured with Vernier caliper scale. Six tablets from each batch were evaluated to determine the average thickness. The tablet thickness should be controlled within a ±5% variation of a standard value. The results were given in table-4.

Hardness:

The hardness of the tablets was determined by using a Monsanto tablet hardness tester. Six tablets from each batch were evaluated to determine the average hardness. The results were given in table-4.

Tensile strength:

The measurement of tensile strengths provides a more fundamental measure of the mechanical strength of the compacted material and takes into account the geometry of the tablet. If tablets fail in tension, the breaking force can be used to calculate the tensile strength. Tensile strength of tablets was calculated using the following formula:

$$T = 2F_c/\pi d\, t$$

Where, F_c - Crushing strength/Hardness, d - Diameter & t - Thickness of tablet.

Friability

Ten tablets were carefully weighed and loaded into the drum of a friabilator and operated for 4 min at 25 rpm. Then tablets were collected, dedusted between tissue towels and reweighed. Percentage friability was calculated and given in table-4.

$$\%\ \text{Friability} = \frac{\text{Initial Wt.} - \text{Final Wt.}}{\text{Final Wt.}} \times 100$$

Weight Variation

Twenty tablets from each batch at random were taken and weighed. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight that was already calculated. The deviation if any in the weight of individual tablets from the average weight was checked. If any weight variation is there, that should be within the I.P limits. The test was considered correct if not more than two tablets fall outside the I.P limits out of twenty tablets taken for the test. Results were given in the table-4.

$$\%\ \text{Weight Variation} = \frac{\text{Avg. Wt.} - \text{Individual Wt.}}{\text{Avg. Wt.}} \times 100$$

Uniformity of Drug Content:

5 tablets were taken and grinded to powder. 100 mg of the drug equivalent tablet powder was taken and dissolved in 10 mL of methanol and the volume was made up to 100 mL with distilled water in a 100 mL volumetric flask. Then the solution was filtered to remove any insoluble matter and the filtrate was taken, made suitable dilutions. Then drug content was estimated by using the developed UV spectroscopic method and the drug content was calculated by using the standard calibration curve. The results were given in table-4.

***In-Vitro* Dissolution Studies**

Dissolution studies on each formulation were performed by using USP type II apparatus, employing 900 ml of 0.1N HCl for first 2 hrs and followed by phosphate buffer 6.8 pH as a dissolution medium. The paddles were operated at a 50 rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 18 hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by 'thermo scientific' double beam UV – VIS spectrophotometer at 280 nm.

Evaluation of Kinetics: Various dissolution parameters such as zero order rate constant, first order rate constant, Higuchi constant and Peppas constant were calculated from the dissolution data obtained from various formulations. The results were given in table-3.

3. Results and Discussion

The spectrophotometric method used for the estimation of emtricitabine in the dissolution medium (0.1N HCl & Phosphate buffer pH 6.8) were found to be linear and reproducible. The standard calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range of 2-16 µg/mL in 0.1N HCl & 5-25 µg/mL in Phosphate buffer pH 6.8. Reproducibility of the method was tested by analyzing 6 separately weighed samples of drug emtricitabine. The results were shown in figure-2. Thus, the method was found to be suitable for the estimation of emtricitabine in dissolution medium.

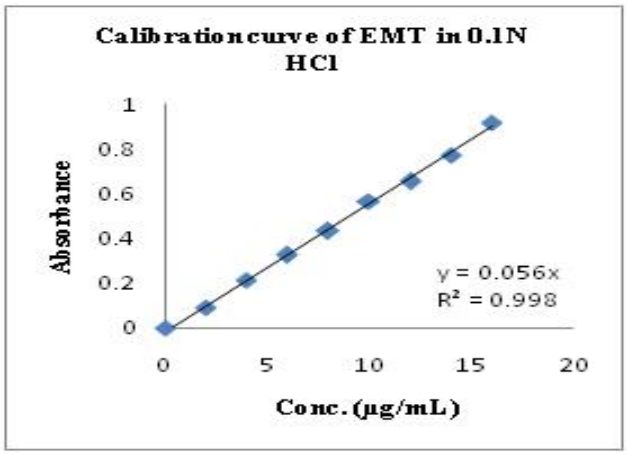

Figure 2A: Calibration curves of emtricitabine

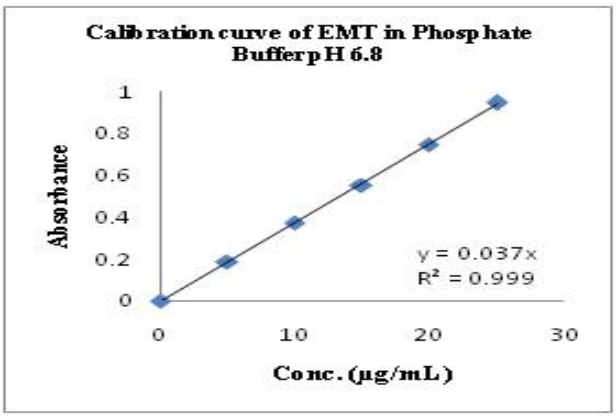

Figure 2B: Calibration curves of emtricitabine

Drug – Excipient compatibility studies:

The pre-formulation studies performed on emtricitabine alone and along with excipient admixtures were found to be stable with no physical changes in the color and nature.

FTIR Studies:

FTIR studies of emtricitabine alone and admixtures with excipients were carried out to study the interaction between the drug and excipients used. The results were shown in figure 3a–3e. C=O stretching (1690.43), O-H stretching (3415.95), N-H stretching (3207.24), Asymmetrical C-O-C stretching (1167.26) and C-F stretching (1218.60) of pure emtricitabine and the admixtures were almost in the same region of wave number ranging from 3415.95 cm^{-1} to 1160.39 cm^{-1}. It showed that IR spectrum of emtricitabine and admixtures were having similar fundamental peaks and pattern. This indicated that there were no drug excipients interactions in the formulations.

Differential Scanning Calorimetry:

DSC studies of emtricitabine and admixture with excipients were carried out to study the interaction between the drug and excipients used and the results of the study were shown in figures 4a – 4c. The DSC Thermogram of emtricitabine showed sharp endothermic peak at 154.95^0C. The DSC Thermograms of drug excipient admixtures showed sharp endothermic peaks for emtricitabine with ethyl cellulose and hydroxy ethyl cellulose at the temperatures 154.46^0C and 153.61^0C respectively. This indicated that there were no drug excipients interactions in the formulations. Based upon these studies suitable excipients were selected and emtricitabine controlled release tablets were formulated.

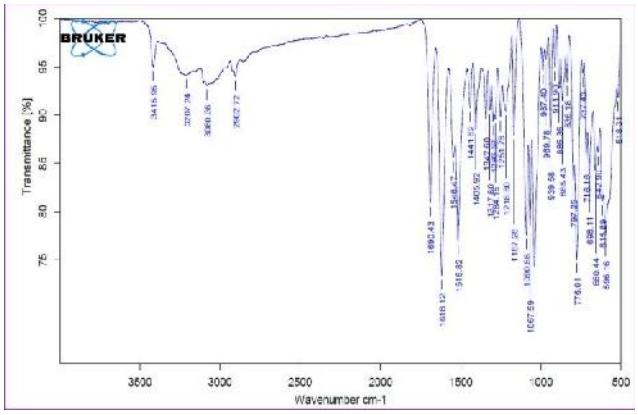

Figure 3a: FTIR Spectrum of Emtricitabine

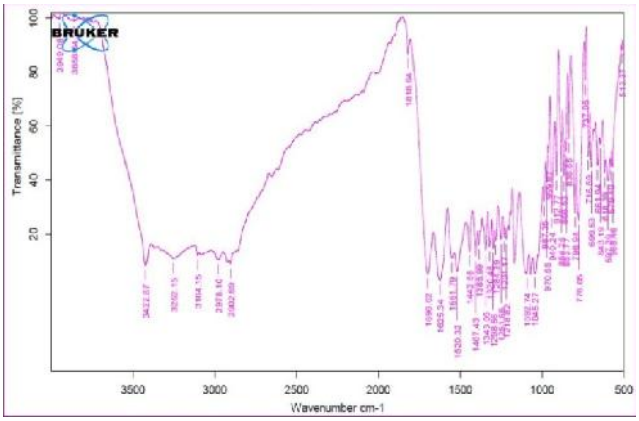

Figure 3b: FTIR Spectrum of EMT with EC

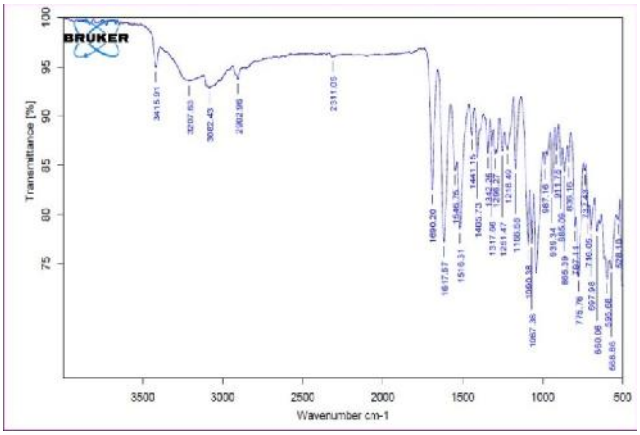

Figure 3c: FTIR Spectrum of EMT with HEC

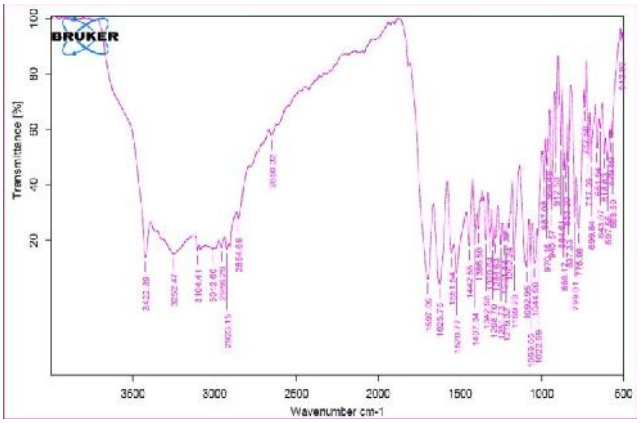

Figure 3d: FTIR Spectrum of EMT with LACTOSE

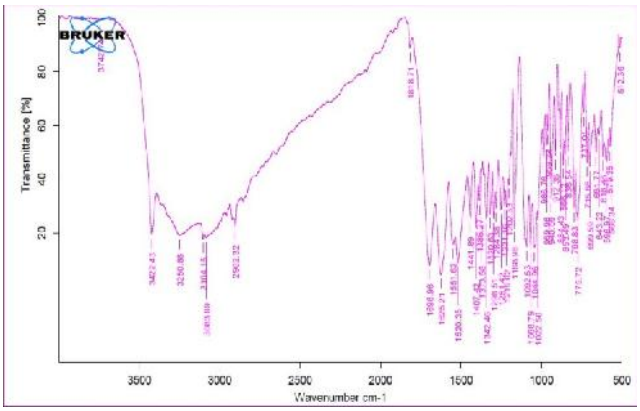

Figure 3e: FTIR Spectrum of EMT with PVP K30

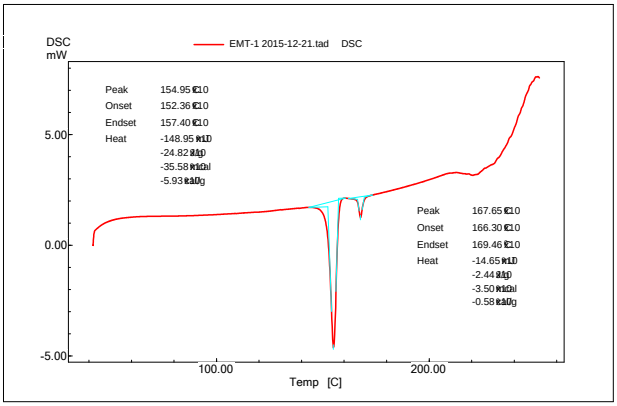

Figure 4a: DSC Thermogram of Emtricitabine

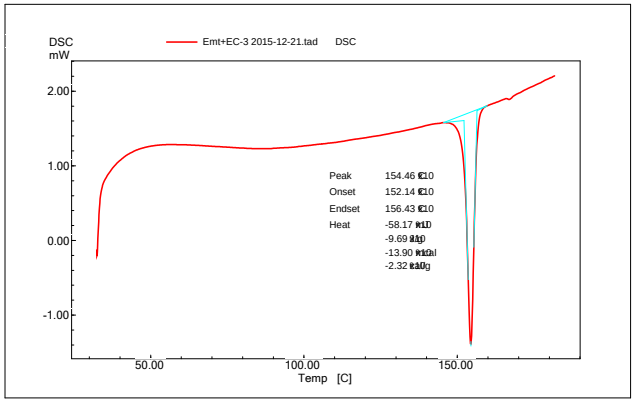

Figure 4b: DSC Thermogram of EMT + EC

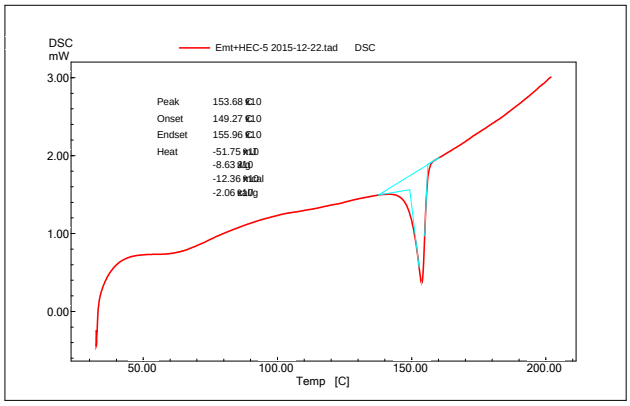

Figure 4c: DSC Thermogram of EMT + HEC

Evaluation parameters:

Initially the core tablet of emtricitabine was formulated and evaluated for physical parameters, disintegration time and drug content. The thickness of the compression coated tablets was found to be in between 2.92–3.27 mm and the hardness was found to be in between 3.22–4.92 kg/cm^2. The tensile strength of the tablets was found to be in between 6.889*10^5– 9.441*10^5 N/m^2. The tablets satisfied friability requirement, as the % friability values were less than 1% (0.26–0.47). The drug content estimations showed values in the range of 97.56% – 102.23%, which reflects good uniformity in drug content among all formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ± 5% of

the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation, which indicate that the prepared tablets are of standard quality. These values were shown in table-4. The results of the in vitro drug release studies for formulations were shown in figure-5. Among all the formulations, ECT13 formulation showed the prolonged drug release up to 20 hrs and the ECT14 formulation showed the prolonged drug release up to 18 hrs. The controlled drug release may be due to increased proportion of polymer. As the concentration of ethyl cellulose as the rate retarding polymer increased the drug release from the tablets was found to be increased in case of all the formulations. The formulations made of HEC were failed to produce controlled release.

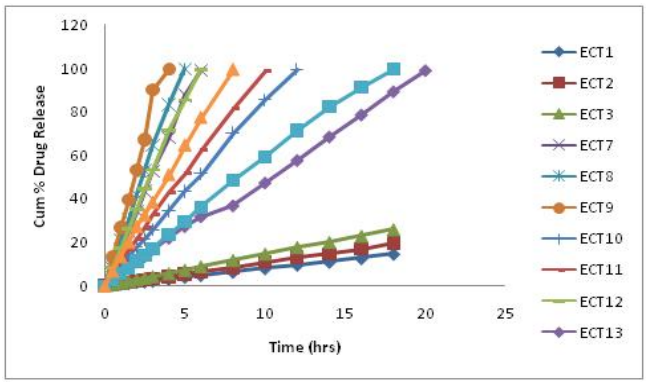

Figure 5: Drug release profiles of emtricitabine CR tablets of all formulations

Dissolution parameters such as zero order rate constant, first order rate constant, Higuchi constant and Peppas constant were calculated from the dissolution data and the results were given in table 3. The 1st order plots for the formulations were not linear when compared to the zero order. All the formulations were found to be linear with zero order release rate with R^2 values in the range of 0.982 – 0.999. Thus, the rate of drug release from all the formulations was concentration independent and was linear with zero order release rate constant.

The Higuchi plots i.e., the amount of drug released vs square root time plots were found to be linear with R^2 values in the range of 0.832 – 0.861. The drug release from the matrix tablet formulations was not by fickian diffusion process. The release exponent (n values) for all the matrix tablet formulations were in the range of n>0.9 which are obtained from peppas plot indicated that the drug release was by super case II transport system.

4. Conclusion

The results of the drug release studies on the prepared tablets revealed that the compression coating technique was more effective for the efficient incorporation of drug in the polymer coating for the preparation of CR formulations to get the desired control release. Therefore, it can be concluded that even for the high water soluble drugs like emtricitabine, extended or controlled release tablets can be effectively prepared by the compression coating technique.

Table 2: Flow properties of granules

Formulation Code	Results (Avg. ± SD; n=6)				
	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (^{0})
Core Tablet granules	0.918 ± 0.013	1.031 ± 0.011	10.918 ± 0.861	1.126 ± 0.014	22.31 ± 0.741
EC granules	0.918 ± 0.009	1.042 ± 0.018	11.911 ± 0.342	1.132 ± 0.018	24.23 ± 0.543
HEC granules	0.927 ± 0.014	1.039 ± 0.012	10.723 ± 0.367	1.121 ± 0.015	22.55 ± 1.072
EC : Lactose -1:1 granules	0.932 ± 0.012	1.035 ± 0.011	09.854 ± 0.546	1.114 ± 0.017	20.34 ± 0.971
EC : Lactose -2:1 granules	0.921 ± 0.008	1.025 ± 0.017	10.210 ± 0.576	1.108 ± 0.012	21.32 ± 0.823
EC : Lactose -3:1 granules	0.916 ± 0.013	1.031 ± 0.015	11.145 ± 0.781	1.128 ± 0.023	22.12 ± 0.654

Table 3: Dissolution kinetics of emtricitabine CR tablets of all formulations

Formulation	Regression coefficient (R^2) value			Dissolution rate constant (%dose/hr)	Peppas 'n' value
	Zero – order	First – order	Higuchi		
ECT1	0.999	0.998	0.832	0.793	- 0.150
ECT2	0.999	0.997	0.839	1.068	0.053
ECT3	0.999	0.998	0.845	1.454	0.154
ECT7	0.998	0.713	0.851	17.03	1.230
ECT8	0.997	0.597	0.860	20.65	1.303
ECT9	0.982	0.716	0.864	26.69	1.430
ECT10	0.998	0.664	0.838	8.53	0.938
ECT11	0.997	0.716	0.850	10.21	1.039
ECT12	0.997	0.664	0.861	17.17	1.240
ECT13	0.997	0.708	0.854	4.925	0.747
ECT14	0.997	0.698	0.850	5.778	0.757
ECT15	0.998	0.635	0.848	12.76	1.133

Table 4: Formulae of controlled release compression coated tablets of Emtricitabine

Formulation Code / Ingredients (in mg)	ECT 1	ECT 2	ECT 3	ECT 4	ECT 5	ECT 6	ECT 7	ECT 8	ECT 9	ECT 10	ECT 11	ECT 12	ECT 13	ECT 14	ECT 15
	EC			HEC			EC : Lactose – 1:1			EC : Lactose – 2:1			EC : Lactose – 3:1		
Core Tablet															
Emtricitabine	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Lactose	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
PVP K-30 (as 2% aq. solution)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total Wt	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
Coat Material															
Ethyl Cellulose	100	75	50	-	-	-	50	37.5	25	66.7	50	33.3	75	56.25	37.5
HEC	-	-	-	100	75	50	-	-	-	-	-	-	-	-	-
Lactose	-	-	-	-	-	-	50	37.5	25	33.3	25	16.7	25	18.75	12.5
Portions of coating granules (L/U)	40/60	30/45	20/30	40/60	30/45	20/30	40/60	30/45	20/30	40/60	30/45	20/30	40/60	30/45	20/30
Total Wt	350	325	300	350	325	300	350	325	300	350	325	300	350	325	300

Table 5: Results of various evaluation parameters of emtricitabine CR tablets

Formulation Code	Results (Avg. ± S.D.; n=6)					
	Thickness (mm)	Hardness (Kg/cm^2)	Tensile Strength (N/m^2)	Average Weight (mg)	Friability (%)	Assay (%)
Core 8 mm	3.46 ± 0.005	4.22 ± 0.52	$9.513*10^5 \pm 0.034$	249.33 ± 0.84	0.35 ± 0.029	99.82 ± 0.22
Core 10 mm	2.26 ± 0.008	3.21 ± 0.14	$8.897*10^5 \pm 0.031$	248.98 ± 0.76	0.43 ± 0.023	98.12 ± 0.33
ECT1	3.25 ± 0.065	4.92 ± 0.36	$9.441*10^5 \pm 0.041$	349.36 ± 0.72	0.36 ± 0.015	100.34 ± 0.15
ECT2	3.03 ± 0.010	4.35 ± 0.21	$8.907*10^5 \pm 0.044$	324.66 ± 0.73	0.31 ± 0.028	98.42 ± 0.39
ECT3	2.93 ± 0.015	3.87 ± 0.42	$8.226*10^5 \pm 0.037$	299.33 ± 0.86	0.38 ± 0.030	101.68 ± 0.08
ECT4	3.27 ± 0.048	3.91 ± 0.12	$7.472*10^5 \pm 0.033$	349.28 ± 0.87	0.47 ± 0.025	99.12 ± 0.12
ECT5	3.02 ± 0.010	3.62 ± 0.28	$7.445*10^5 \pm 0.041$	324.33 ± 0.73	0.42 ± 0.027	98.88 ± 0.28
ECT6	2.94 ± 0.016	3.22 ± 0.22	$6.889*10^5 \pm 0.044$	300.11 ± 0.82	0.31 ± 0.033	102.22 ± 0.13
ECT7	3.26 ±0.015	3.82 ± 0.14	$7.314*10^5 \pm 0.043$	350.33 ± 0.86	0.40 ± 0.032	99.34 ± 0.11
ECT8	3.03 ± 0.023	3.71 ± 0.23	$7.659*10^5 \pm 0.034$	325.66 ± 0.78	0.26 ± 0.025	98.78 ± 0.32
ECT9	2.93 ±0.014	3.62 ± 0.27	$7.774*10^5 \pm 0.049$	298.93 ± 0.88	0.37 ± 0.032	97.56 ± 0.16
ECT10	3.24 ± 0.032	4.62 ± 0.47	$8.913*10^5 \pm 0.051$	349.67 ± 0.86	0.24 ± 0.018	101.72 ± 0. 21
ECT11	3.02 ± 0.024	3.98 ± 0.58	$8.281*10^5 \pm 0.042$	324.45 ± 0.82	0.42 ± 0.035	98.64 ± 0.34
ECT12	2.92 ±0.056	3.31 ± 0.19	$7.004*10^5 \pm 0.044$	300.42 ± 0.78	0.40 ± 0.039	99.35 ± 0.16
ECT13	3.23 ±0.012	4.81 ± 0.51	$9.292*10^5 \pm 0.038$	350.66 ± 0.86	0.37 ± 0.024	98.89 ± 0.38
ECT14	3.01 ±0.021	4.26 ± 0.42	$8.868*10^5 \pm 0.033$	324.33 ± 0.78	0.33 ± 0.029	102.23 ± 0.15
ECT15	2.92 ±0.018	3.71 ± 0.24	$7.995*10^5 \pm 0.041$	299.43 ± 0.88	0.36 ± 0.023	99.77 ± 0.09

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