Effect of Channeling Agents on Release Kinetics of Stavudine from Methocel K100 LVCR and Ethocel 20 cps Based Matrix Tablets

Nazia Tajrin, Md. Elias-Al-Mamun, Md. Habibur Rahman[¶] and Md. Selim Reza

Department of Pharmaceutical Technology, Faculty of Pharmacy
University of Dhaka, Dhaka-1000, Bangladesh

Received: November 19, 2014; Accepted: June 01, 2015; Published (web): June 15, 2015

ABSTRACT: The study was performed to investigate the effect of channeling agent on the release profile of Stavudine from Methocel K100 LVCR and Ethocel 20 cps based matrix systems. Stavudine, a nucleoside analog drug, is used in the treatment of acquired immune deficiency syndrome (AIDS). Stavudine matrix tablet was prepared using Methocel K100 LVCR and Ethocel 20 cps as polymer and also using PEG 3350 and PEG 6000 as channeling agents. The drug release mechanisms from different matrix tablets were explored and explained by zero order, first order, Higuchi, Korsmeyer and Hixson-Crowell equations. The release rate, extent and mechanisms were found to be governed by polymer type used and the content of the channeling agent. It was found that the release of drug from the matrix tablet was increased with the increasing concentration of channeling agent. However, PEG 6000 enhanced the release of drug greater than PEG 3350 from the matrix. On the other hand, Stavudine matrix containing Ethocel 20 cps showed a strong tendency to retard the drug release to 51-56% after 8 hours of dissolution, whereas the release was found to be increased for the Methocel containing matrix to 90-100%. Kinetic modeling of dissolution profiles revealed drug release mechanism ranged from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was mainly dependent on the presence of relative amount of channeling agent and type of polymer. These studies indicate that the proper balance between a matrix forming agent and a channeling agent can produce optimum drug dissolution kinetics from Stavudine matrix tablet. The mechanism was also revealed by Scanning Electron Microscope (SEM) pictures taken at various intervals of dissolution which showed that the extent of pore formation in the matrix increases with the increasing amount of channeling agent and also the hydrophilic nature of the polymer used in the formulation.

Key words: Stavudine, Methocel K100 LVCR, Ethocel 20 cps, release profile, SEM

INTRODUCTION

HIV/AIDS is a global pandemic.[1] As of 2012, approximately 35.3 million people are living with HIV globally.[2] Of these, approximately 17.2 million are men, 16.8 million are women and 3.4 million are less than 15 years old. There were about 1.8 million deaths from AIDS in 2010, down from 2.2 million in 2005.

The annual number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient-compliant antiretroviral medications are available at affordable prices. The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance, and their huge cost.

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 alike. 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.[3] Sustained-released oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side

Correspondence to: Md. Selim Reza
Tel: +880-2-9672733 Ext.-8175; Fax: 880-2-8615583
E-mail: selim.du@gmail.com
[¶]Deceased

effects.[4] Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target sites. Realistic drug candidates exhibit high permeability across the GI epithelium (Class I & Class II drugs according to Biopharmaceutics classification system) such that their absorption rate is controlled exclusively by the rate of release from the dosage form. It is only under these conditions that in vitro dissolution rate can possibly used to predict in vivo absorption rates and guide formulation development. Matrix type drug delivery systems are an interesting and promising option when developing an oral controlled release system.

Stavudine has been chosen as the experimental drug. Stavudine is a nucleoside analog reverse transcriptase inhibitor (NARTI) active against HIV. Stavudine, lamivudine and Zidovudine belong to the same genre of drug. They can be used alone or in combination. In the market Stavudine is available as capsule or liquid dosage form, 40 mg BID and its half-life is 0.8 to 1.5 hours. If it is given as tablet 100 mg BID, theoretically it should not produce any cumulative toxic effect to the patient. On the other hand, both lamivudine and zidovudine are available as capsule, tablet and liquid dosage form and zidovudine is reported to undergo first pass metabolic effect. As its absorption following oral administration is over 80% and it is not yet available in extended release tablet form, it is the relatively more ideal drug candidate among these three HIV drugs to work with. Also, Stavudine is unavailable in Bangladesh in any dosage form. So, for the reasons articulated above, Stavudine has been chosen for this research study.

The purpose of the present study is to develop a controlled release dosage form of Stavudine using a hydrophilic and a hydrophobic matrix material to examine *in-vitro* release characteristics of Stavudine from formulated tablets.[5-7] PEG 3350 and PEG 6000 will be incorporated as channeling agent. As water comes in contact with channeling agent, they dissolve in medium and several channels are formed which causes the rapid release of drug from the tablet. Investigations to be performed were whether there was any effect of channeling agent (type and amount) on the release kinetics of Stavudine from matrix tablets. The impact of different polymeric matrix materials such as Methocel K100 LVCR and Ethocel 20 cps, on the release kinetics of Stavudine was also investigated.

MATERIALS AND METHODS

Materials used in the formulations obtained from different suppliers are Stavudine (Asterix laboratories ltd, India), Ethocel 20 cps (Colorcon, India), METOCEL K100 LVCR (Colorcon, India), PEG 3350 (BASF, Germany), PEG 6000 (BASF, Germany), Ludipress (BASF, Germany), Aerosil (Degussa, Germany), and magnesium stearate (Wilfrid Smith Ltd, UK).

Preparation of matrix tablets of Stavudine. For tablet preparation, method of dry blending of the active ingredients with polymers, filler, lubricant and flow promoter followed by direct compression was followed. At first PEG 6000 and PEG 3350 was crushed using multimill. The active ingredient and other excipients were accurately weighted for matrix tablets according to the formulations (Table 1 and 2). Properly weighed methocel or ethocel 20 cps, ludipress, and Stavudine were passed through 40 mesh then taken in a container and blended in a laboratory designed small drum blender machine for about 30 minutes. Then aerosil and magnesium stearate was passed through 40 mesh size, and then they were added to the blended material and were further blended for another 3 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were then compressed using a “Clit” tablet compression machine equipped with 11.7 mm faced punch and die set. The tablet pressure was in between 120 N to 150 N. All the preparations were stored in airtight containers at room temperature for further study.

Measurement of organoleptic properties of the pepared matrix tablets. All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods .The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics, Mumbai, India) for 4 minutes at 25 rpm.

Preparation of standard curve of Stavudine. 20 mg of Stavudine was taken in 100 ml of voluemetric flask and dissolved in 30 ml of water. Then the final volume was made upto the mark with the same solvent. Then 2.5 ml, 3.0 ml, 4.0 ml, 5 ml, 6 ml and 7.5 ml of this solution were taken in seven different 50 ml voluemetric flask respectively and diluted to 50 ml with water. Then absorbance was measured using Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan) at 266 nm & calibration curve was created using Microsoft Excel.

***In vitro* release studies of Stavudine from the prepared matrix tablets.** The release rate of Stavudine from matrix tablets was determined by using Tablet Dissolution Tester USP XXIII. The dissolution test was performed using 900 ml distilled water at 37 °C ± 0.5 °C and 100 rpm. At 1, 2, 4, 6 and 8 hour time intervals, samples of 10 ml were withdrawn from the dissolution medium and that amount was replaced with distilled water to maintain the volume constant. The samples were filtered through a Whitman filter paper and diluted to a suitable concentration with distilled water. The absorbance of the solutions was measured at 266 nm for drug Stavudine. Percentage of drug release was calculated using an equation obtained from the standard curve. The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the *in vivo* condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. This drug release profiles were fitted into several mathematical models to get an idea of the release mechanism of Stavudine from the matrix tablets. The % dissolution was calculated by using the following equation:

$$\% \text{ Dissolution} = \frac{As \times P \times 100}{Ast}$$

where, As = absorbance of the sample solution

Ast = absorbance of the standard solution

P = potency of standard Stavudine

The average % release of six tablets of each proposed formulation was calculated. The average percent release of drug was then plotted against time.

Determination of release mechanism observing morphology of matrix tablets by using SEM technology. The tablets were then investigated after 2^{nd}, 4^{th}, 6^{th} hour during dissolution by SEM (scanning electron microscope). The objective was to find the change of the surface of the tablet to predict the drug release mechanism. The tablets were mounted on the SEM sample stab (aluminum stabs) which were coated with a double sided sticking tape, sealed and finally coated with gold (200 A^{o}) under reduced pressure (0.001 torr) for 15 minutes using ion sputtering device. The SEM was operated at 15 KV. The condenser lens position was maintained at constant level. Gold coated samples were scanned using scanning electron microscope (S-3400N, Hitachi, Japan) under different magnification ranging from 20x to 100x.

RESULTS AND DISCUSSION

Analysis of organoleptic properties. To evaluate the organoleptic properties of the prepared matrix tablets, we have determined the average weight, diameter, thickness, hardness and percent of friability of the methocel K100LVCR and ethocel 20 cps containing matrix tablets of Stavudine (Table 3). The results from weight variation of the matrix tablets were evaluated as per USP. According to USP tablet weighing more than 250 mg, the % RSD of weight variation should not be more than ± 5%. Here, the theoretical tablet weight was 405 mg. And the average weight of the experimented tablet was found 416.90 mg. It is well within the ± 5% range of the theoretical tablet weight. So, the uniformity of weight complies as per USP. Hardness & Friability test is a

non-official test. Usually the limit of hardness is between 5-20 kg/square cm[8], whereas the limit for friability is less than 1.0%. Here the average hardness and friability of the tablets were found 5.05 kg/cm^2 and 0.29% respectively. So, we observed that the prepared matrix tablets followed and meet all the criteria specified in the monograph accordingly (Table 3).

***In vitro* release kinetics of Stavudine from the prepared matrix tablets.** Dissolution studies were performed at 100 rpm, by paddle method in which distilled water was used as medium and the medium temperature was maintained at 37 °C (± 0.5 °C). Six tablets from each formulation were used in each dissolution study and the release profile of Stavudine was monitored up to 8 hours.

Table 1. Formulation of matrix tablet of Stavudine using Methocel K100 LVCR.

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Drug	50	50	50	50	50	50	50
Ludipress	250	200	150	100	200	150	100
Methocel K 100LVCR	100	100	100	100	100	100	100
PEG 6000	-	50	100	150	-	-	-
PEG 3350	-	-	-	-	50	100	150
Aerosil 200	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2
Total Wt. (mg)	405.00	405.00	405.00	405.00	405.00	405.00	405.00

Table 2. Formulation of matrix tablet of Stavudine using Ethocel 20 cps.

Ingredients (mg)	F-8	F-9	F-10	F-11	F-12	F-13	F-14
Drug	50	50	50	50	50	50	50
Ludipress	250	200	150	100	200	150	100
Ethocel 20 cps	100	100	100	100	100	100	100
PEG 6000	-	50	100	150	-	-	-
PEG 3350	-	-	-	-	50	100	150
Aerosil 200	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2
Total Wt. (mg)	405.00	405.00	405.00	405.00	405.00	405.00	405.00

Table 3. Measurement of organoleptic properties of prepared matrix tablets.

Formulation	Weight	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F-1	412.69 ± 1.54	11.702 ± 0.0023	4.70 ± 0.0023	5.0 ± 0.0003	0.22 ± 0.0014
F-2	413.77 ± 1.97	11.703 ± 0.0025	4.60 ± 0.0029	5.6 ± 0.0008	0.24 ± 0.0015
F-3	407.63 ± 0.56	11.702 ± 0.0025	4.60 ± 0.0018	5.2 ± 0.0007	0.24 ± 0.0021
F-4	411.25 ± 2.78	11.705 ± 0.0008	4.50 ± 0.0003	4.8 ± 0.0009	0.25 ± 0.0023
F-5	416.89 ± 1.78	11.705 ± 0.0023	4.50 ± 0.0013	5.0 ± 0.0005	0.23 ± 0.0016
F-6	418.30 ± 1.24	11.704 ± 0.0018	4.36 ± 0.0017	5.1 ± 0.0006	0.25 ± 0.0022
F-7	416.72 ± 1.96	11.704 ± 0.0016	4.50 ± 0.0021	5.6 ± 0.0008	0.48 ± 0.0012
F-8	420.75 ± 2.01	11.703 ± 0.0020	4.60 ± 0.0026	4.4 ± 0.0002	0.24 ± 0.0025
F-9	415.94 ± 2.17	11.703 ± 0.0020	4.50 ± 0.0015	4.9 ± 0.0008	0.25 ± 0.0026
F-10	417.89 ± 2.45	11.704 ± 0.0016	4.75 ± 0.0020	5.1 ± 0.0006	0.25 ± 0.0012
F-11	418.56 ± 1.78	11.704 ± 0.0018	4.80 ± 0.0009	5.1 ± 0.0005	0.24 ± 0.0013
F-12	419.88 ± 1.27	11.704 ± 0.0018	4.55 ± 0.0011	4.8 ± 0.0010	0.25 ± 0.0015
F-13	423.67 ± 1.78	11.703 ± 0.0016	4.60 ± 0.0022	4.9 ± 0.0011	0.24 ± 0.0017
F-14	422.65 ± 1.89	11.704 ± 0.0019	4.45 ± 0.0023	5.2 ± 0.0003	0.25 ± 0.0019

Release profile of Stavudine from Methocel K100 LVCR based matrix tablet preparation. The formulations from F1 to F7 are methocel K100LVCR based formulations, where F1 is the control formulae. Formulations F2, F3, and F4 contain increasing amount of PEG 6000 as channeling agents (Table 1). Formulations F5, F6 & F7 contain increasing amount of PEG 3350 as channeling agents (Table 1). By this, we can understand the effect of increasing amount of channeling agents & difference between the release profiles of two types of channeling agents.

From the zero order release profile, it is observed that the total percent release of Stavudine from formulations F-1, F-2, F-3, and F-4 were 84.01%, 92.56%, 96.05% and 100.27% respectively at the end of 8 hour (Figure 1).

Table 4. Release rate constants and R-squared values for different release kinetics of four formulations of Methocel K100 LVCR based matrix tablets of Stavudine containing PEG 6000 as channeling agent.

Formulation	Zero order		Highuchi		First order		Korsmeyer		Hixson Crowell	
	K_o	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-1	9.95	0.9549	30.11	0.983	-0.097	0.9853	0.577	0.9779	-0.258	0.9886
F-2	10.92	0.9392	33.51	0.9942	-0.136	0.9819	0.566	0.9972	-0.3267	0.9938
F-3	11.26	0.9393	34.58	0.9954	-0.185	0.9565	0.558	0.9976	-0.366	0.9918
F-4	11.83	0.9347	36.40	0.9959	-0.242	0.8944	0.560	0.9983	-0.591	0.9030

Table 5. Release rate constants and R-squared values for different release kinetics of four formulations of Methocel K100 LVCR based matrix tablets of Stavudine containing PEG 3350.

Formulation	Zero order		Highuchi		First order		Korsmeyer		Hixson Crowell	
	K_o	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-1	9.95	0.9549	30.11	0.983	-0.097	0.9853	0.577	0.9779	-0.258	0.9886
F-5	10.47	0.9417	32.88	0.9932	-0.125	0.9879	0.579	0.9972	-0.308	0.993
F-6	11.09	0.9373	34.02	0.9918	-0.142	0.9833	0.577	0.9955	-0.336	0.9921
F-7	11.42	0.9352	35.07	0.9913	-0.166	0.9733	0.575	0.9948	-0.371	0.9915

Table 6. Release rate constants and R-squared values for different release kinetics of four formulations of Ethocel 20 cps based matrix tablets of Stavudine containing PEG 6000.

Formulation	Zero order		Higuchi		First order		Korsmeyer		Hixson Crowell	
	K_o	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-8	4.09	0.5455	15.20	0.7612	-0.025	0.4877	0.1081	0.9712	-0.258	0.9886
F-9	4.56	0.5205	16.72	0.7858	-0.029	0.5992	0.1225	0.9622	-0.094	0.5716
F-10	4.66	0.522	17.67	0.7857	-0.0305	0.6048	0.1213	0.9528	-0.094	0.5757
F-11	4.97	0.547	18.02	0.6422	-0.033	0.6422	0.1375	0.9779	-0.102	0.6089

Table 7. Release rate constants and R-squared values for different release kinetics of four formulations of Ethocel based matrix tablets of Stavudine containing PEG 3350.

Formulation	Zero order		Highuchi		First order		Korsmeyer		Hixson Crowell	
	K_o	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-8	4.091	0.5455	15.2	0.7612	-0.025	0.4877	0.1081	0.9712	-0.258	0.9886
F-12	4.45	0.5118	16.37	0.7793	-0.0284	0.5859	0.1174	0.9812	-0.088	0.5598
F-13	4.59	0.5202	16.84	0.7844	-0.0298	0.6007	0.1203	0.9556	-0.092	0.5724
F-14	4.86	0.5391	17.67	0.8014	-0.032	0.6293	0.133	0.9795	-0.099	0.5979

F-1 best fits with Hixson Crowell (R^2 = 0.9886) and first order (R^2 = 0.9853) kinetic models to same extent and then with Korsmeyer (R^2 = 0.9779) model. The value of release exponent obtained from Korsmeyer model is 0.577 which indicates that the release pattern of Stavudine from F-1 followed anomalous transport mechanism, which appears to indicate a coupling of the diffusion and erosion mechanism.[4] Whereas F-2 follows Korsmeyer model (R^2 = 0.9972) and then Hixson Crowell (R^2 = 0.9938)

release patterns. The value of n for Korsmeyer release is 0.566 (Table 4). This value indicates that the drug was released by anomalous transport. F-3 also follows Korsmeyer model (R^2 = 0.9976) and then Hixson Crowell (R^2 = 0.9918) release patterns. On the other hand F-4 primarily follows Korsmeyer release pattern (R^2 = 0.9983) and secondarily follows Higuchian[9] release pattern (R^2 = 0.9959). The values of release exponent of Korsmeyer model for F-3 and F-4 are 0.558 and 0.560 respectively. The values of the release exponent indicate that the drug was released from F-3 and F-4 by more than one process, called anomalous diffusion.[10]

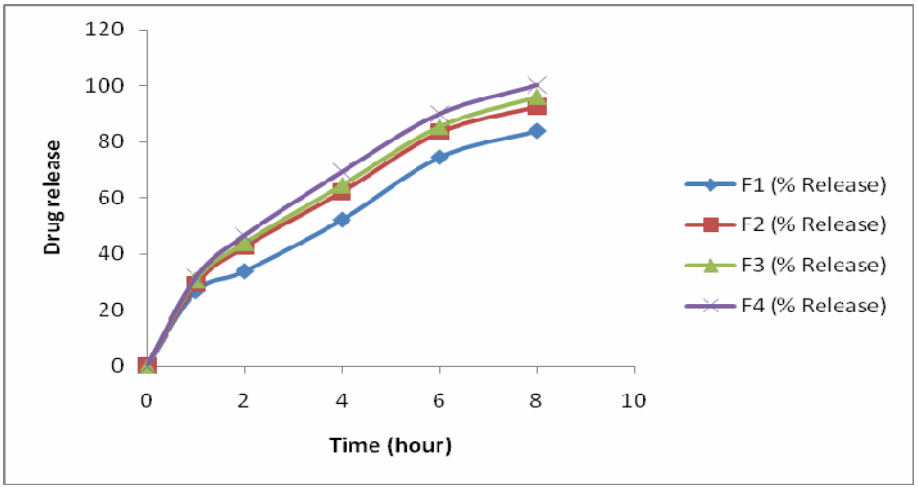

Figure 1. Zero order release profile of Methocel K100 LVCR based formulations containing PEG 6000.

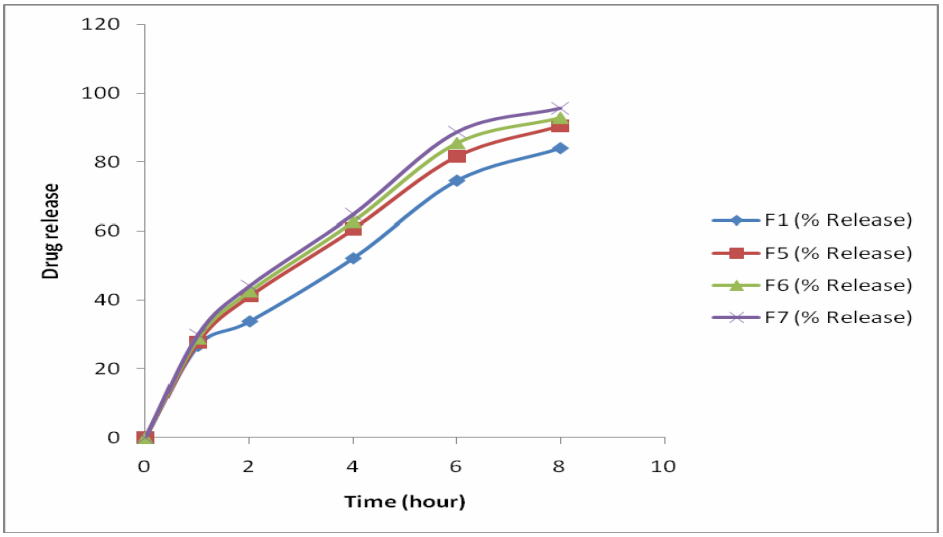

Figure 2. Zero order release profile of Methocel K100 LVCR based formulations containing PEG 3350.

From the zero order release profile it is observed that the total percent release of Stavudine from F-1, F-5, F-6, and F-7 were 84.01%, 90.48%, 92.91% and 95.55% respectively at the end of 8 hour (Figure 2).

F-1 best fits with Hixson-croswell (R^2 = 0.9886) and first order (R^2 = 0.9853) kinetic models to same extent and then with Higuchi (R^2 = 0.983) model. Whereas F-5 follows Korsmeyer model (R^2 = 0.9972) and then Higuchi (R^2 = 0.9932) release patterns. F-6 also follows Korsmeyer model (R^2 = 0.9955) and then Higuchi (R^2 = 0.9918) release patterns. On the other hand F-7 primarily follows Korsmeyer release

pattern (R^2 = 0.9948) and secondarily follows Hixson release pattern (R^2 = 0.9915). The release can be poorly explained by zero order release profile which is supported by the R squared value (0.9352) of F-7 (Table 5).

From the above data it is observed that the drug release from the formulation F-1 was comparatively slow due to absence of channeling agent. This effect was due to the characteristic property of Methocel to form gels *in situ*. This type of polymers forms a gel like layer around the matrix system. However, from the other formulations containing channeling agent, we observed that the rate and extent of Stavudine release increases from the matrices with increasing the amount of channeling agents.

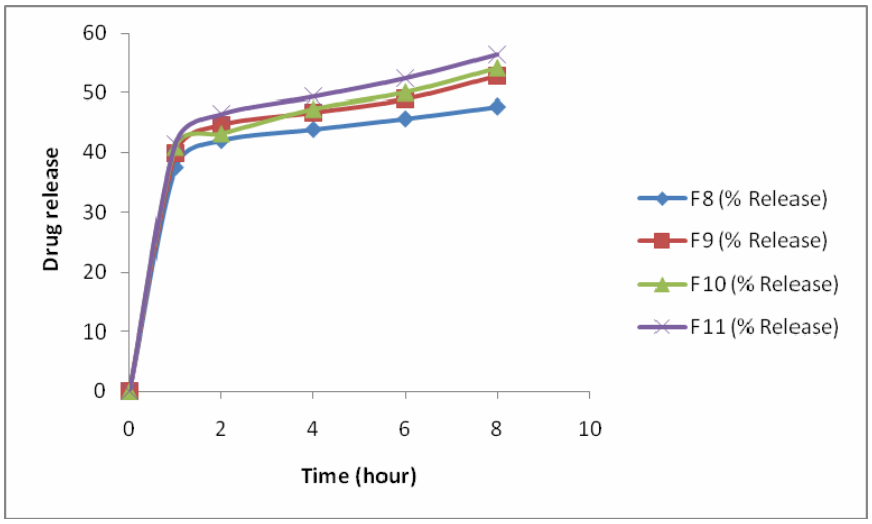

Figure 3. Zero order release profile of Ethocel 20 cps based formulations containing PEG 6000.

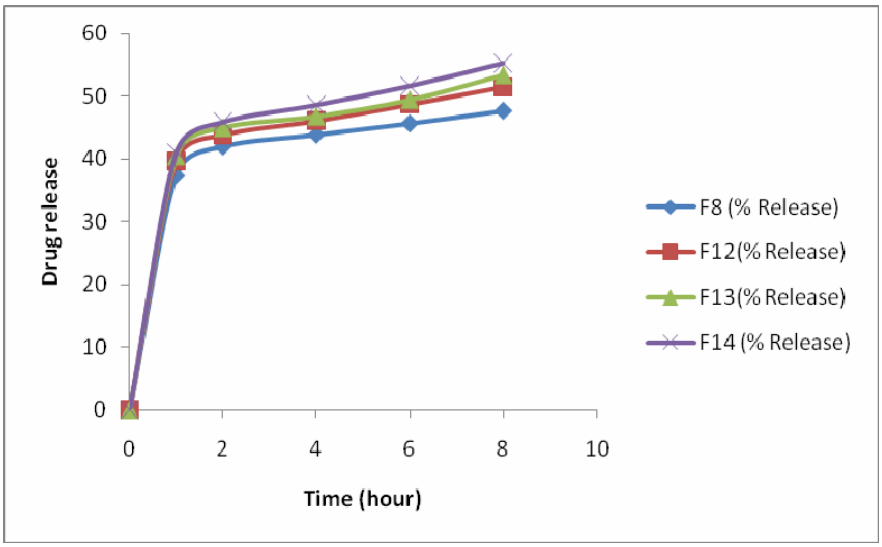

Figure 4. Zero order release profile of Ethocel 20 cps based formulations containing PEG 3350.

Release profiles of Stavudine from Ethocel 20 cps based matrix tablet preparation. The formulations from F8 to F14 are Ethocel 20 cps based formulations, where F8 is the control formulae. Formulations F9, F10, and F11 contain increasing amount of PEG 6000 as channeling agents (Table 2) and formulations F12, F13 & F14 contain increasing amount of PEG 3350 as channeling agents (Table 2).

By this, we can understand the effect of increasing amount of channeling agents & difference between the release profiles of two types of channeling agents.

From the zero order release profile it is observed that the total percent release of Stavudine from F-8, F-9, F-10, and F-12 were 47.74%, 52.82%, 54.10% and 56.40% respectively at the end of 8 hour (Figure 3).

F-8 best fits with Hixson-crowell (R^2 = 0.9886) and Korsmeyer release pattern (R^2 = 0.9712) kinetic models whereas F-9 follows Korsmeyer model (R^2 = 0.9622). F-10 also follows Korsmeyer model (R^2 = 0.9528). On the other hand, F-11 primarily follows Korsmeyer release pattern (R^2 = 0.9779). The release can be poorly explained by zero order release profile which is supported by the R squared value (0.5455) of F-8.

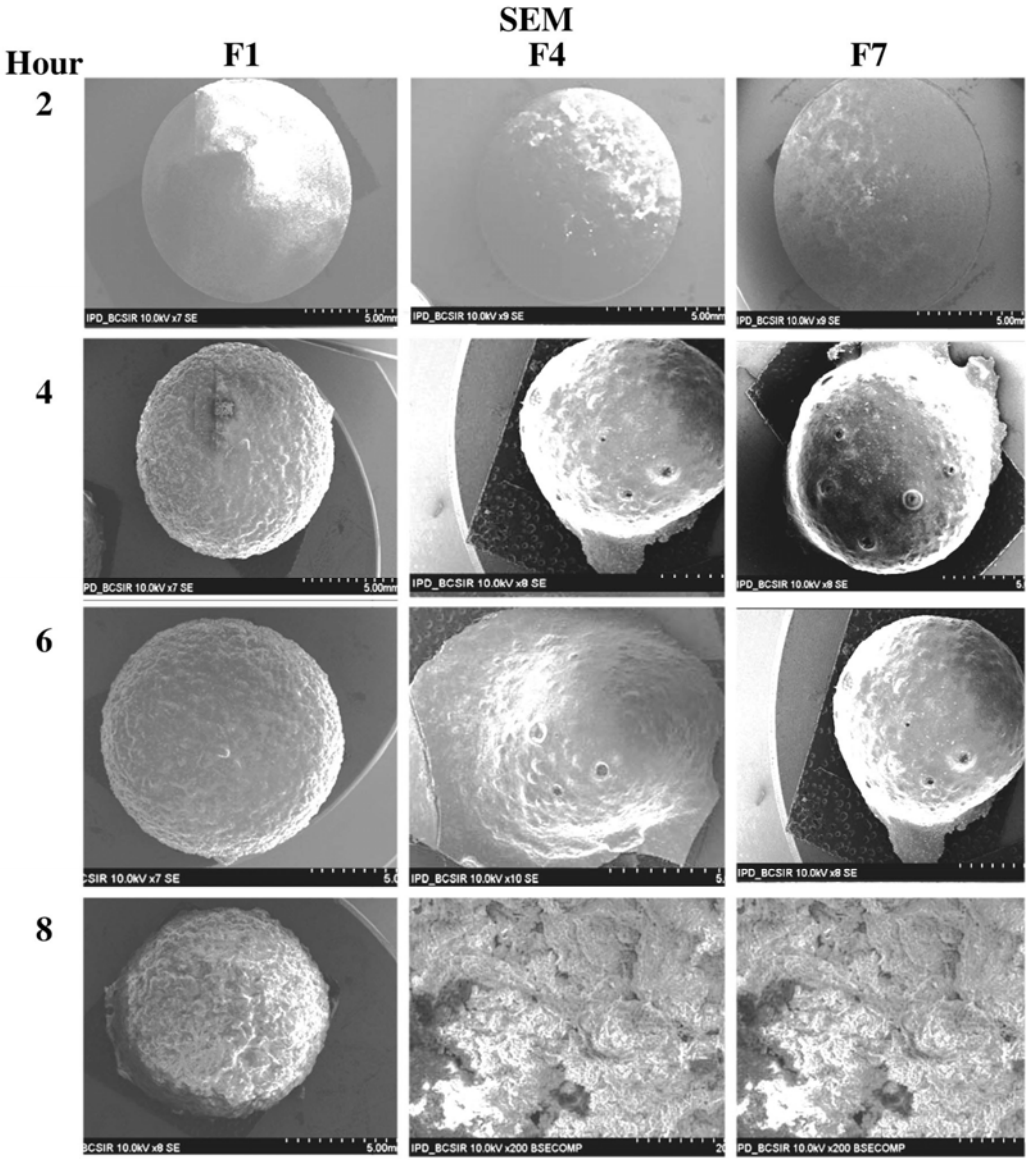

Figure 5. Photomicrographs of Methocel K100 LVCR based formulations by using SEM.

From the above data it is observed that the drug release from the formulation F-8 was comparatively slow due to the absence of PEG 6000. This effect was also due to the characteristic hydrophobic property of Ethocel. However, in other formulations containing channeling agent PEG 6000, the rate and extent of

Stavudine release increases from the matrices with increasing the amount of PEG 6000 as in F-9 and F-10. The addition of PEG 6000 deviates the formulations to follow zero order kinetic model. The release profile of Stavudine from the four formulations fits only Korsmeyer release profile (Table 6). From the abovementioned discussion and data, we also observe that the drug release from ethocel based matrix tablet is very slow comparative to methocel based matrix tablet.

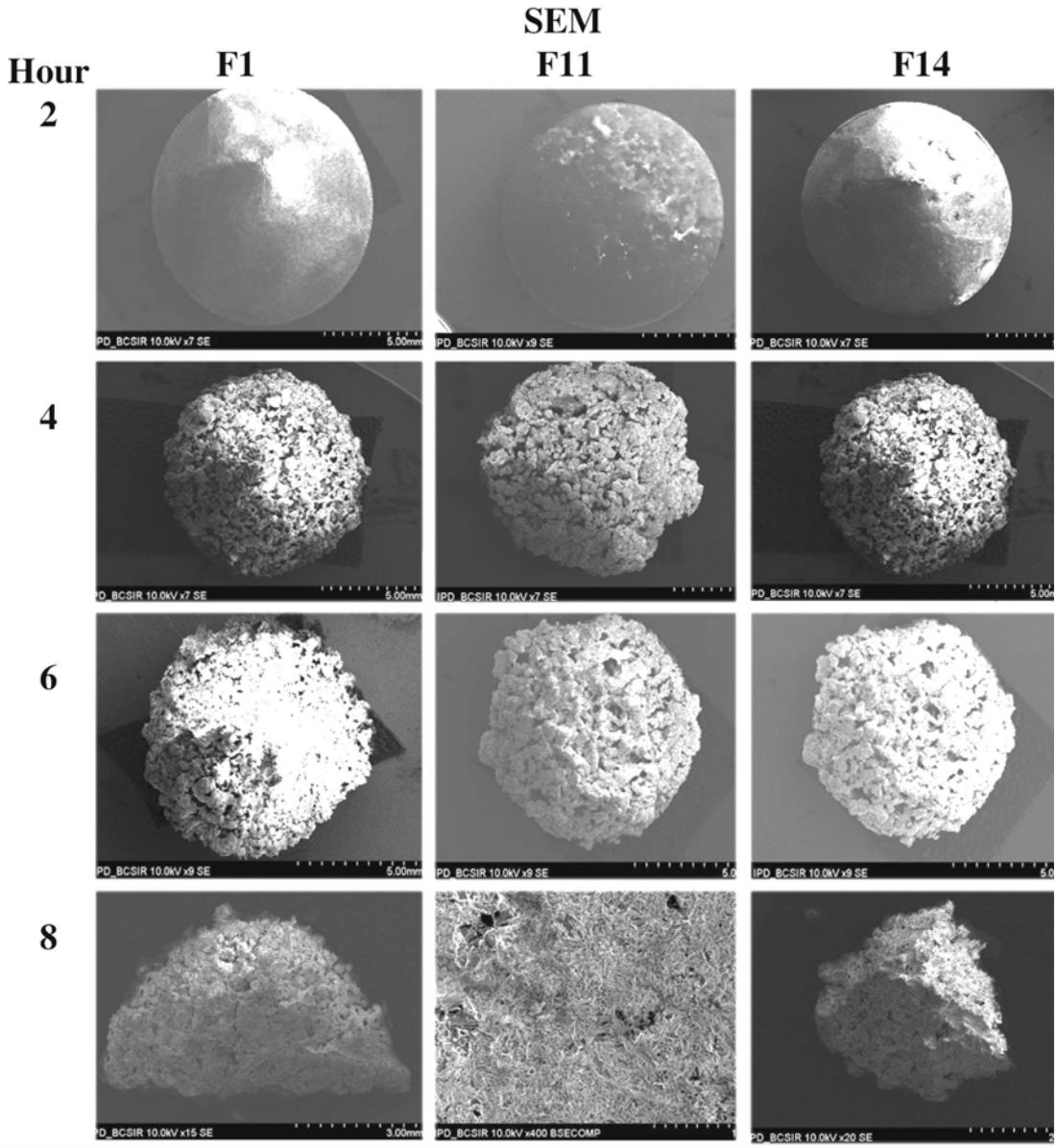

Figure 6. Photomicrographs of Ethocel 20 cps based formulations by using SEM.

From the zero order release profile it is observed that the total percent release of Stavudine from F-8, F-12, F-13, and F-14 were 47.74%, 51.45%, 53.33% and 55.35% respectively at the end of 8 hour (Figure 4).

F-8 best fits with Hixson-croswell (R^2 = 0.9886) and Korsmeyer release pattern (R^2 = 0.9712) kinetic models whereas F-12 follows Korsmeyer model (R^2 = 0.9812). F-13 primarily follows Korsmeyer release pattern (R^2 = 0.9556). F-14 primarily follows

Korsmeyer release pattern (R^2 = 0.9795). The release can be poorly explained by zero order release profile which is supported by the R squared value (0.5455) of F-8.

From the above data it is also observed that the drug release from the formulation F-8 was comparatively slow due to the absence of channeling agent. This effect was due to the characteristic hydrophobic property of ethocel. We also observed like the previous release pattern in other formulations containing channeling agent that the rate and extent of Stavudine release increases from the matrices with increasing the amount of PEG 3350 as in F-12, F-13 and F-14. The addition of PEG 3350 also deviates the formulations to follow zero order kinetic model. The release profile of Stavudine from the four formulations fits only the Krosmeyer release profile.[10]

Determination of release mechanism observing morphology of matrix tablets by using SEM technology. After 2nd, 4th, 6th & 8th hours of dissolution, the matrix tablets were collected from dissolution medium, dried & SEM photographs were taken. The release profiles of the experimented tablets were explained by the SEM.

SEM of formulations F-1, F- 4, F-7, F-8, F-11 and F-14 were taken at different intervals of their dissolution. SEM pictures of formulation F-1 (containing only Methocel K100 LVCR), formulation F-4 (containing Methocel K100 LVCR and PEG 6000) and formulation F-7 (containing Methocel K100 LVCR and PEG 3350) were compared to see the effects of channeling agents. In the same way, the SEM pictures of formulation F-8 (containing only Ethocel 20 cps), formulation F-11 (containing Ethocel 20 cps and PEG 6000) and formulation F-14 (containing Ethocel 20 cps and PEG 3350) were compared to see the effects of channeling agents. Some representative pictures were shown here (Figure 5).

SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the matrix tablet. SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was ruptured in some places and pores had formed throughout the matrix (Figure 5 & 6). SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time. SEM photomicrograph of the surface of intact tablet did not show any pores. Photomicrographs at 2, 4, and 6 hours revealed pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of matrix tablets Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Stavudine from prepared matrix tablets.

From the SEM photomicrograph, it can be seen that there is pore formation in F-11 with time. F-11 contains Ethocel 20 cps as matrix former and PEG 6000 as channeling agents. As Ethocel is a hydrophobic polymer, so the rupture and erosion of matrix is very negligible. Only the pore, which is formed due to PEG 6000 increases the release of drug slightly from the matrix.

SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the matrix tablet. SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix, though pore formation was very little when compared to that of Methocel.

So, it can be said that PEG 6000 and PEG 3350 can be used as channeling agents which increase the drug release by pore formation in the matrix.

From the above comparison, we can see that the Methocel matrix is ruptured in places with time and the pore is seen being formed which may be due to the reason of adding channeling agents in the formulation.

Stavudine matrices were prepared successfully utilizing hydrophilic matrix, Methocel K100 LVCR & hydrophobic matrix, Ethocel 20 cps as carrier and PEG 6000 & PEG 3350 as channeling agents. From the technological point of view, the direct compression process enables the preparation of these

matrices. After performing dissolution study, Stavudine release profiles were analyzed on the basis of various mathematical models such as zero order kinetic model, first order kinetic model, Higuchi release pattern, Korsmeyer release pattern and Hixson-Crowell release pattern.

The overall experiment has revealed the effect of channeling agents (PEG 6000 and PEG 3350) on the release kinetics of Stavudine from different polymers based matrix tablets. The following features are quite notable from the above study:

(1) Increase the amount of channeling agent always displayed a common phenomenon that the drug release rate and extent were increased in all cases. The load of channeling agent, polymer type and polymer concentration affect the release profile of Stavudine from matrix significantly.

(2) Maximum formulations displayed highest fitting with Korsmeyer release pattern and in all cases lowest fitting with Zero order kinetic model of drug release.

(3) With the increase of amount of channeling agent, maximum formulations deviates to follow zero order release kinetics. But interestingly it has been observed that at higher channeling agent content, maximum formulations showed better fitting with Korsmeyer mathematical model of release kinetics. In cases of Methocel K100 LVCR, the increase of the channeling agent content causes a lowering of the magnitude of release exponent (n) obtained from Korsmeyer release pattern which indicates the shifting of release mechanism from non-Fickian to Fickian direction (Table 4 and 5). However, in cases of Eethocel 20 cps, the n values indicated Fickian diffusion. Though the increase of the channeling agent content causes increasing of the magnitude of release exponent (n) obtained from Korsmeyer mathematical model, this is not prominent enough that the release would shift from Fickian to non-Fickian direction (Table 6 and 7).

(4) An important conclusion can be drawn that the increase of PEG 6000 and PEG 3350 content causes the increase of rate and extent of Stavudine release from both Methocel K100 LVCR & Ethocel 20 cps based matrix tablet.

CONCLUSION

Finally, we can say that there is a release rate difference between Methocel K100 LVCR & Ethocel 20 cps based matrix tablet system. In both the systems, channeling agents facilitate dissolution by creating pores or channels. So, it can be proclaimed that PEG 6000 is more effective channeling agent than PEG 3350.

REFERENCES

1. Cohen, M.S., Hellmann, N., Levy, J.A., DeCock, K. and Lange, J. 2008. The spread, treatment, and prevention of *HIV-1*: evolution of a global pandemic. *J. Clin. Invest.* **118**, 1244-1254.
2. "Fact Sheet". UNAIDS.org. 2013. Retrieved December 4, 2013. UNAIDS 2011, p. 1.
3. Ford, J.L., Rubinstein, M.H. and Hogan, J.E. 1991. Study on controlled drug release kinetics from hydrophilic matrices. *Int. J. Pharm.* **24**, 327-338.
4. Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E. and Edgar, P.J. 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxyl propyl methylcellulose matrices. *Int. J. Pharm.* **40**, 223-234.
5. Marina, L., Bernard, J. and Hudis, C. 2004. The influence of excipients on drug release from HPMC matrices. *J. Pharm. Sci.* **93**, 2746-2753.
6. Lipidus, H. and Lordi, N.G. 1968. Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.* **57**, 1292-1301.
7. Kuksal, A., Tiwary, A.K., Jain, N.K. and Jain, S. 2006. Formulation and *in vitro*, *in vivo* evaluation of extended release matrix tablet of *Zidovudine*: Influence of combination of hydrophilic and hydrophobic matrix former. *AAPS Pharm. Sci. Tech.* **7**, 1-9.
8. Citation from web documents. The web address is-www.ijrdpl.com/upload/Quality%20Control%20of%20Tablets.doc
9. Higuchi, T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* **50**, 874-875.
10. Korsmeyer, R.W. and Peppas, N.A. 1983. In: Roseman, T.J. and Mansford, S.Z. (eds.), Controlled release delivery systems. Marcel Dekker, New York, pp. 77-90.