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EFFECTS OF ETHYL CELLULOSE & HYDROXY PROPYL METHYL CELLULOSE POLYMER ON THE RELEASE PROFILE OF DILTIAZEM HYDROCHLORIDE SUSTAINED RELEASE PELLETS

Nuzhat Mariam Elias, Shahana Sharmin*, Ishtiaq Ahmed

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

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***Correspondence for Author**
Shahana Sharmin
Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka -1000.

ABSTRACT

Objectives: In the present study, the effect of cellulose polymers Ethyl Cellulose (EC) & Hydroxy Propyl Methyl Cellulose (HPMC 5 cps) was evaluated on the release profile of drug from sustained release pellet. Diltiazem Hydrochloride, an antihypertensive, cardio protective agent and slow channel blocker was used as a model drug to evaluate its release characteristics from different pellets formulations. **Methods:** Diltiazem Hydrochloride sustained release pellets were prepared by drug loading (drug binder suspension) on neutral pellets followed by different percentages of spraying, i.e. 2%,4%, 6%, 8% and 10% coating suspension using Ethyl Cellulose & Hydroxy Propyl Methyl Cellulose polymer in a fixed 85:15 ratios respectively. The *in vitro* dissolution studies of Diltiazem Hydrochloride from these sustained release pellets were carried out in pH 7.2 phosphate buffer for 1,2,3,4,5,6,7 and 8 hr using USP-I method. **Results:** Statistically significant differences were found among the drug release profile from different formulations. Polymer content with highest concentration of Ethyl Cellulose on the pellets shows highest release retarding rate of the drug. The retarding capacity decreases with the decreased concentration of Ethyl Cellulose. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer's equations. **Conclusion:** Finally the study showed that the profile and kinetics of drug release were functions of polymer type, polymer concentration & the physico chemical properties of the drug.

KEYWORDS: Diltiazem Hydrochloride, Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose, release kinetics, sustained release pellets.

INTRODUCTION

Currently much emphasis has laid on multi-particulate dosage forms because of their multiple advantages over single unit dosage forms, like flexibility during formulation development and therapeutic benefits for their patients. These include increased bioavailability, predictable gastric emptying and reduced risk of local irritation and systemic toxicity due to dose dumping.[1] Now a day's pellets dosage form are being preferred as they have several biopharmaceutical advantages over tablet dosage forms like less possibility of dose dumping and their drug release is not affected by gastric emptying.[2] A number of design options are available for the preparation of controlled release formulations to modify oral absorption by pellets. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration.[3, 43] Process used for producing pellets, in general, is defined as "pelletization".

Pelletization is an agglomeration process that converts fine powder or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets.[5] Further, they can be tailored to target release of drug to specific areas within the gastrointestinal tract. Traditionally, pellets are prepared by drug layering (as powder, solution or suspension) on nonpareil seeds in a conventional coating pan, tangential fluid bed processor or Wurster coater and by extrusion-spheronization. The development of sustained release pellet dosage form of Diltiazem is of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of the drug over time. Because sustained-release pellet products not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficacy of bioactive agents.[6, 7] Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material. It is dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films.[8] Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating.

The objective of the this study was to prepare Diltiazem Hydrochloride sustained release pellets using Ethyl cellulose (EC) and Hydroxy propylmethyl cellulose (HPMC 5 cps) polymer and to evaluate the effect of these polymers with respect to polymer type and concentration.

MATERIALS AND METHODS

Materials

API (Active Pharmaceutical Ingredient) & Excipients: Diltiazem Hydrochloride USP (Nicholas Piramal India Ltd., India), Sugar powder BP & Sugar fine powder BP (Sugar Australia Pty Ltd., Australia), Povidone K30 BP (Hangzhou Zhongbao Imp. & Exp. Corp., Ltd. China), Hydroxy Propyl Methyl Cellulose 15 cps (HPMC 15 cps) USP (Deepak Cellulose Private Limited., India), Hydroxy Propyl Methyl Cellulose 5 cps (HPMC 5 cps) USP (United Pharma and Chemical Co., Ltd., China), Purified Talc BP (Asian Mineral Resources Co. Ltd., Thailand), Ethyl Cellulose 7 cps (EC 7 cps) BP (Colorcon Asia Pvt. Ltd., India).

Solvents: Isopropyl Alcohol BP (TAT Petroleum Pte. Ltd., Singapore), Methylene Chloride BP (Ineos Chor Limited., UK), Purified Water (ACI Limited, Narayanganj).

Equipments: Coating Pan (Pharmachine, India), Fluid Bed Processor APCG 225 (Pharmaseal, India), USP Type- I Dissolution Apparatus (LOGAN UDT 804, Logan Instruments Corp, USA), Scanning Electron Microscope (Hitachi S-3400 N, Japan), Electronic balance (Shimadzu AX 200, Japan and Ohaus Champ II Bench Scale, Japan), Sonicator (Ultrasonic Bath, Villain Motorsports, Canada), pH meter (HANNA pHep4 Meter, HANNA instruments, USA), Water Suction Filtration (India), Bulk Density Apparatus (India).

Preparation of sustained release pellets

The Neutral Pellets were manufactured using Coating Pan Method. Using ASTM (American Society for Testing and Materials), initially the sugar powder was sifted using 60# mesh followed by mesh 45# to achieve the targeted size distribution (45-60) # as mentioned in Tablet-1. This sugar powder was incorporated in the Coating Pan. Solution of Povidone K30 was used as the binder solution. During this process, sugar fine powder was added gradually with interval of 5 min while the binder solution was sprayed through spray gun. After that wet spherical particles were dried in the Tray Dryer for 6-8 h to achieve moisture content

<2.0. After drying, spherical particles were passed through Vibratory Sifter to achieve different size distribution. These are the Neutral Pellets with different size (20-24#).

Table 1: Formulation of Diltiazem Hydrochloride Coated pellets

Materials	Qty (g)
Nuclei formula	
Sugar Powder (Size#45-60)	130.890
Povidone K30	q.s.
Sugar Fine Powder	104.710
Purified Water	q.s.
Diltiazem HCl 50% sustained release pellets formula	
Neutral pellets (Size# 20-24)	235.600
Diltiazem Hydrchloride	315.000
Hydroxy propyl methyl cellulose 15 cps	37.400
Purified talc	6.400
Purified Water	q.s.
Coating formula	
Ethyl cellulose 7 cps	57.600
Hydroxy propyl methyl cellulose 5 cps	9.800
Isopropyl Alcohol	6.784
Methylene Chloride	6.340

A drug binder suspension was prepared by mixing two homogenous mixer of Diltiazem Hydrochloride and HPMC 15 cps with purified water as mentioned in Table-1. Finally talc was added into it with continuous stirring for approximately 10 min. This suspension is known as the drug binder suspension.

The parameters were set down of the machine Fluid Bed Processor (APCG-225) according to Table-2. The weighted Neutral Pellets were loaded in the machine. After that the Fluid Bed Processor was well sealed and started to pre-warm the Neutral Pellets for approximately 5 min. After pre-warming, drug binder suspension was started to spray on the neutral pellets. Full procedure will take approximately 32 h. After completion of spraying, the pellets were dried in the Fluid Bed Processor for 30 min at 45 ^{0}C bed temperature. The 50% drug loaded pellets were sifted through vibratory sifter using 20 mesh followed by 14 mesh to achieve (size 14-20) # pellets.

Isopropyl alcohol & Methylene chloride were taken to prepare coating suspension. HPMC-5cps was added slowly into the region of vortex slowly with continuous stirring for approximately 2 min. Thereafter, Ethyl Cellulose-7cps was added into it with continuous

stirring for approximately 30 min. This suspension is known as the Coating suspension. The prepared coating suspension was weighted and equally divided into five separate buckets.

The parameters were set down of the machine Fluid Bed Processor (APCG-225) according to Table-2. The weighted Diltiazem HCl 50% pellets were loaded in the machine. After that the Fluid Bed Processor was well sealed and started to pre-warm the Diltiazem HCl 50% pellets for approximately 5 min. After pre-warming, coating suspension from one bucket was started to spray on the Diltiazem HCl 50% pellets. The Diltiazem HCl 50% pellets were coated using Ethyl Cellulose and HPMC containing coating suspension in a ratio of 85:15 to a thickness equivalent to theoretical coating load 2%, 4%, 6%, 8%, 10% .The spraying procedure will continue till the coating suspension of the bucket is over. The above procedure will take approximately 40 min.

After completion of spraying the coated pellets were dried in the Fluid Bed Processor APCG-225 for 5 min at 45 °C bed temperature. After that, approx. 20 g coated pellets were withdrawn without opening the machine and sifted through vibratory sifter using 18 mesh followed by 14 mesh to achieve (size 14-18) # pellets. The coated pellets were stored in poly bags placed inside a plastic / fiber board drum. The same procedure will continue for four times where each time 85E:15H polymer coating suspension was sprayed on the pellets. For each time, approx. 20 g coated pellets were withdrawn following same procedure.

Table 2: Machine parameter set up during coating.

Sl. No.	Parameters	Specifications
1.	Spray gun nozzle diameter	1.22 mm
2.	Silicon tube dia (ID / OD)	6mm / 9mm
3.	Atomizing air pressure	2.5±0.5kg/cm²
4.	Inlet air temperature	(50-55) °C
5.	Product bed temperature	(40-45) °C
6.	Inlet air humidity	50 -55 % RH
7.	Spray rate	25-100 ml/min

Control tests for pellets

The sustained release pellets which were coated with different percentages of coating suspension were evaluated for particle size distribution of pellets, bulk density (tapped) and drug content. Size distributions of formulated pellets were done by Vibratory sifter using mesh # 14 – 18 according to ASTM & by SEM (Scanning Electron Microscope) as well. Bulk density (tapped) were tested by the ratio of weight of coated pellets into a measuring

cylinder which was tapped for 100 strokes using bulk density apparatus & volume occupied by the pellets. Drug content for Diltiazem Hydrochloride 50% pellets was carried out by injecting prepared sample solution of Diltiazem HCl through Zorbax Eclipse XDB-C18, 150mm × 4.6mm, 5µ column using Shimadzu HPLC- prominence integrated with spectrophotometric UV Detector and comparing both the peak areas of active Diltiazem HCl present in the standard solution & sample solution in the same medium.

***In vitro* dissolution study of pellets**

Dissolution studies were conducted in USP Type-I dissolution apparatus (LOGAN UDT 804, Logan Instruments Corp) using 900 ml of pH 7.2 Buffer solution in the metallic drive shaft rotated at a speed of 50 rpm and the temperature was maintained at 37 °C ± 0.5 ^{0}C. This operation was continued for 8 h. At every 1-hr interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 237 nm for Diltiazem HCl by UV spectrophotometer (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of straight-line equation obtained from the calibration curves for respective drug. The dissolution study was continued for 8 h 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 (h) curve. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism.

Kinetic analysis of release data: To study the release kinetics, data obtained form in vitro drug release study were tested with the following mathematical model.

Zero order equation

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows: $C = K_0t$---------- (1)

Where, K_0 is the zero order rate constant expressed in unit of concentration/time and t is the time in hour. A graph of cumulative amount of drug release vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order equation

The release behavior of first order equation is expressed as log cumulative percentage of drug remaining vs. time. The equation may be as follows[9]

$\text{Log } C = \text{Log } C_0 - K_1t / 2.303$ ---------- (2)

Where, C = the amount of drug un-dissolved at t time,

C_0 = Drug concentration at t = 0,

K_1= Corresponding release rate constant.

Higuchi square root law

The Higuchi release model describes the cumulative percentage of drug release vs. square root of time. The equation may be as follows[10]

$Q = K_H\sqrt{t}$ ---------- (3)

Where, Q = the amount of drug dissolved at time t. K_H is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer–Peppas equation

Korsmeyer et al developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time. The equation may be as follows:

$Q/ Q_0 = Kt^n$ ---------- (5)

Where, Q/ Q_0 = the fraction of drug released at time‘t’.

K = Constant comprising the structural geometric characteristics.

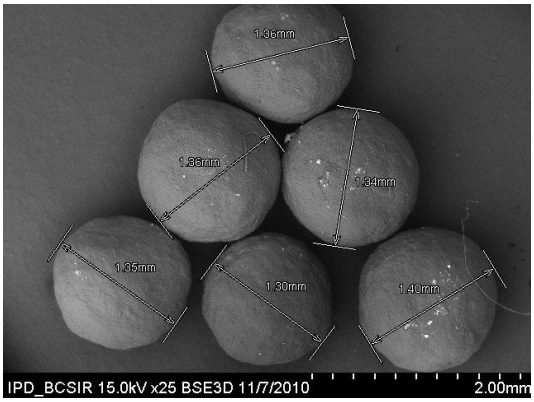
n = the diffusion exponent that depends on the release mechanism.

A value of $n \leq 0.45$ indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.[11]

RESULTS AND DISCUSSION

Scanning electron microscope analysis

Diltiazem HCl 50% pellets were coated with a composition of 85% of Ethyl cellulose & 15% hydroxy propyl methyl cellulose (HPMC 5 cps) at different coating load of polymer. Morphology and surface properties of the pellets were examined with a Scanning Electron Microscope “SEM” (HITACHI, Model: S-3400N, Japan) (Fig. 01, Fig. 02, Fig. 03). Pellets were taken using different magnifications. The magnifications used for taking pellets were 25-2000 (SE-Secondary Electron).



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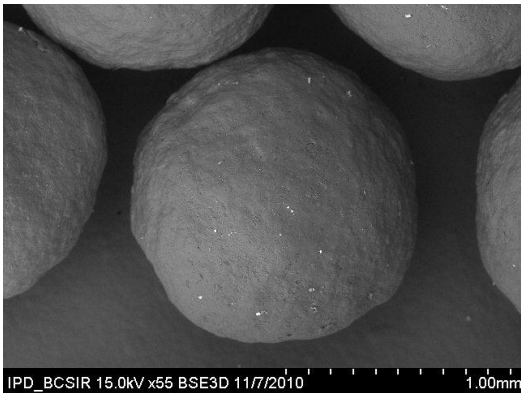

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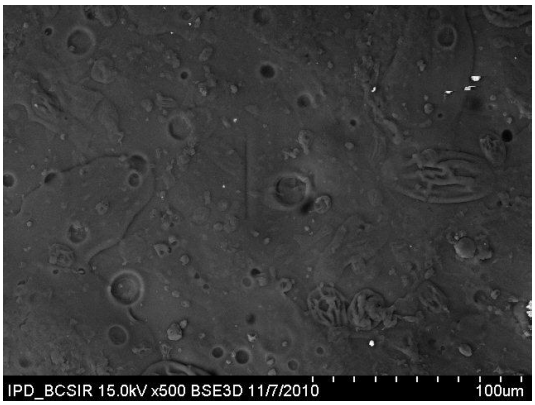

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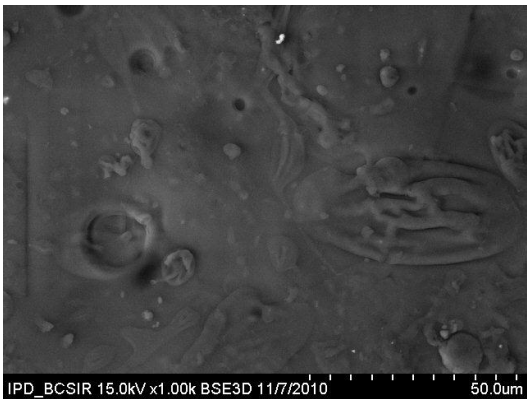

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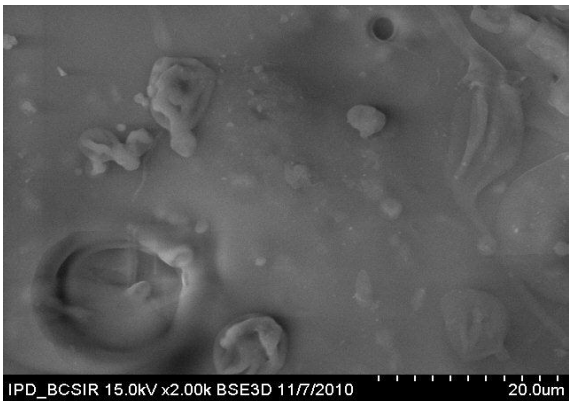
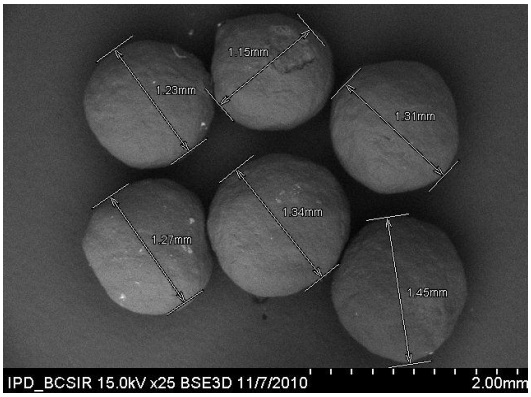


(E)

Fig. 1: Scanning Electron Micrographs of Diltiazem Hydrochloride 50% SR Pellets [coated with 85% Ethyl Cellulose & 15% HPMC where Loaded Coating Suspension is 4%] magnification at: (A)X 25; (B) X 55; (C) X 500; (D) X 1000 (E) X 2000.



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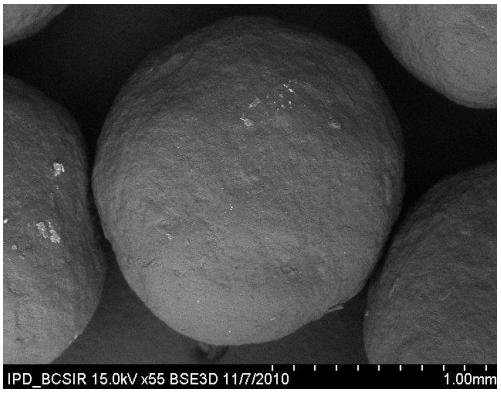

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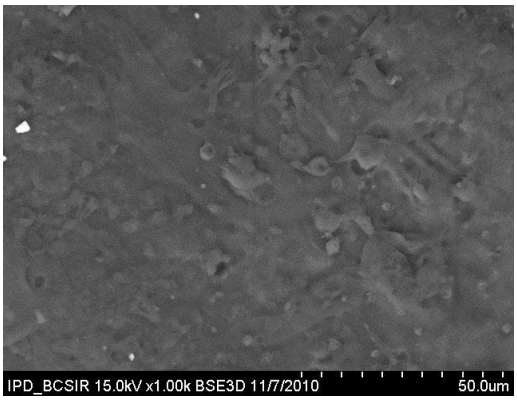

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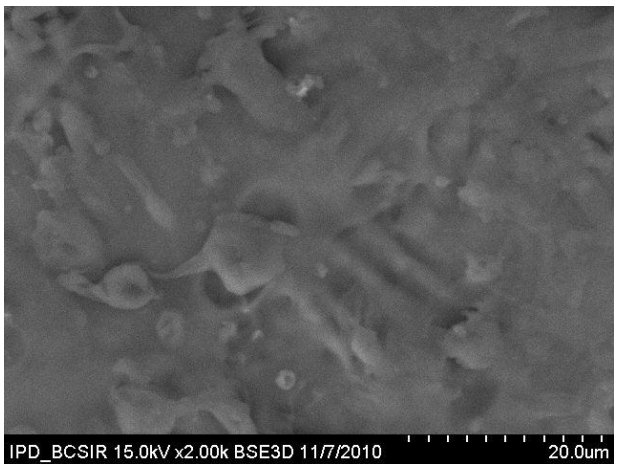
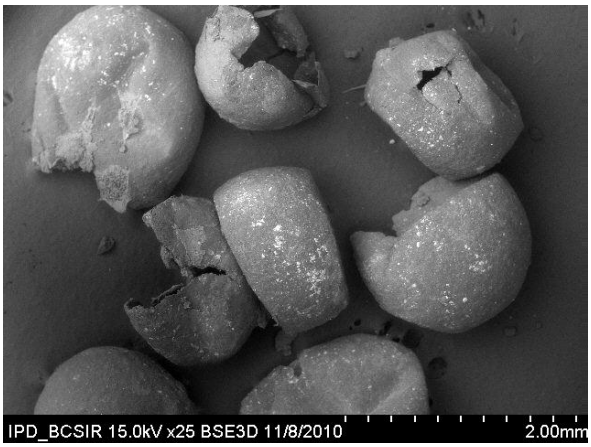


(E)

Fig. 2: Scanning Electron Micrographs of Diltiazem Hydrochloride 50% SR Pellets [Coated with 85% Ethyl Cellulose & 15% HPMC where Loaded Coating Suspension is 6%] magnification at: (A)X 25; (B) X 55; (C) X 500; (D) X 1000 (E) X 2000.



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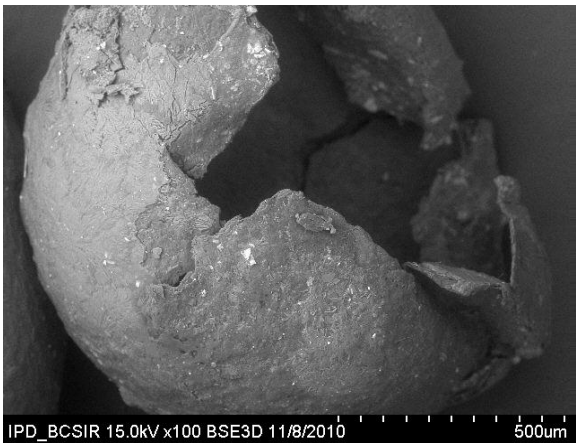

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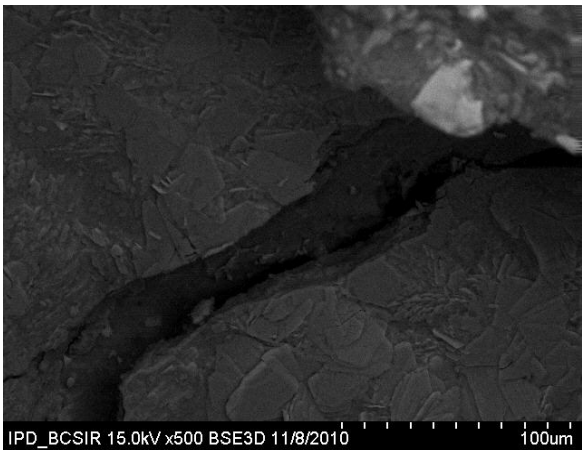

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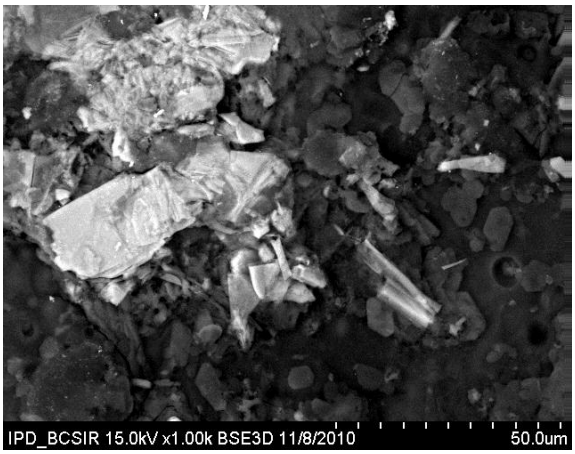

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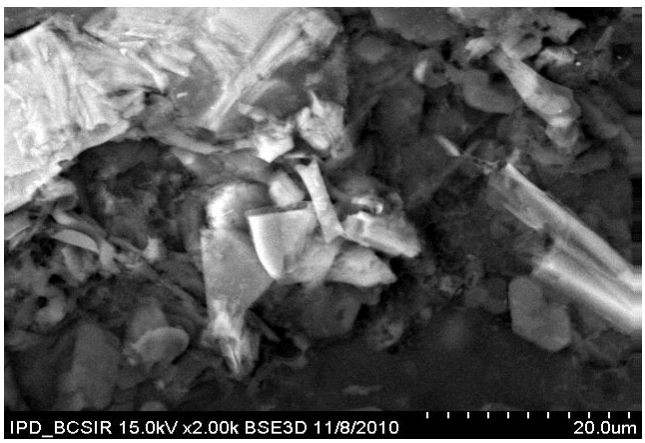

(E)

Fig. 3: Scanning Electron Micrographs of remaining Diltiazem Hydrochloride 50% SR coated Pellets from which the drug has been released magnification at: (A)X 25; (B) X 100; (C) X 500; (D) X 1000 (E) X 2000.

Physical Evaluation of Diltiazem Hydrochloride sustained release pellets

The sustained release pellets which were coated with different percentages of coating suspension were evaluated for particle size distribution of pellets, bulk density (tapped) and drug content. The particle size was ranged from 1150-1540 µm (range for 14-18 # mesh is 1000-1550 µm). The bulk density of all batches ranged from 0.89 to 0.95 g/cm^3. Drug content among different batches of pellets ranged from 46.908 mg to 50.075 mg. Thus, all the physical parameters of the pellets were practically within control.

Effect of Ethyl cellulose & Hydroxy propyl methyl cellulose polymer on release pattern of Diltiazem Hydrochloride

After completion of coating on Diltiazem hydrochloride pellets an assay test was done by HPLC method. Then the dissolution studies of above coated samples were carried out in Basket method (USP 1) at 50 rpm in 900ml pH 7.2 Buffer Solution at 37 ° C (± 0.5 °C) for 8 h, results are shown in Table-3. The increased percentage of drug release after 8 h is directly proportional to the increased percentage of coating suspension sprayed which is shown in Table-3. A correlation coefficients values and Release rate constants for different release kinetics of Diltiazem HCl 50% SR pellets using different % of coating suspension shown in Table-4. The film coated beads showed moderate swelling and when the drug was slowly released at a consistent rate. Six samples were used from each sample in dissolution study. The average release pattern (Zero Order Plot - average percent drug released vs. time) is shown in Figure-4. First order release pattern has been shown in Figure-5 that was drawn by plotting log of cumulative percent drug remaining vs. time. Figure-6 represents the Higuchi impact that was obtained by plotting the % of drug released vs. square root of time (SQRT). Korsmeyer′s release pattern was obtained by plotting log cumulative percent drug released vs. log time shown in Figure-7. The percent of drug released from these five formulations at 8 h are shown by plotting a bar diagram in the Figure-8. The release profile of Diltiazem Hydrochloride from coated pellets with different polymer load can be explained from the diagram.

The ‘n’ value (release exponent) from Korsmeyer-Peppas equation from different sample of coated pellets were 0.430, 0.892, 1.366, 1.454 and 1.456 for 2%, 4%, 6%, 8% and 10% coating load respectively which indicated super Case II type of release except at lower coating load (2%).At lower coating load the drug release mechanism is similar to Fickian release meaning the drug is released due to the diffusion through the porous membrane. As

the coating load increases the release mechanism gradually shifted from Fickian to super Case II type transport. Super Case II type of release generally refers to erosion of the polymeric chain controlled drug release.[11]

The release of Diltiazem Hydrochloride from coated pellets not only depended on the nature of polymer but also on the amount of coating load. Increasing polymer level changed the release profile of drug from coated pellets. The gradual increase of polymer level decreases the drug release as expected due to decreased porosity of the films. Mean dissolution time (MDT) values were determined to characterize the drug release rate from the coated pellets and the retaining efficiency of the polymer (Table 4). A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa.[12] The Higuchi release kinetics data of Diltiazem hydrochloride of coated pellets data has been shown by plotting a bar diagram in the Figure-9.

Table 3: % of Cumulative Drug Released after spraying of different % of coating suspension of Ethyl Cellulose and HPMC (85E:15H) at different times

Time (h)	Cumulative % of Drug released				
	2%	4%	6%	8%	10%
0	0	0	0	0	0
1	42.614	12.046	4.299	2.755	2.324
2	45.856	25.494	10.197	9.138	7.913
3	70.212	45.015	25.132	13.584	10.232
4	76.099	56.640	36.012	24.219	19.205
5	88.355	65.643	47.693	33.654	25.150
6	90.845	68.698	54.658	41.314	34.655
7	92.951	70.494	58.471	47.466	41.242
8	93.970	75.233	66.049	57.240	49.489

Table 4: Correlation coefficients values and Release rate constants for different release kinetics of Diltiazem HCl 50% SR pellets using different % of coating suspension of Ethyl Cellulose and HPMC (85E:15H).

Batch	Zero order		First order		Higuchi		Korsmeyer		MDT
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n	(h)
2%	0.835	10.584	0.978	0.159	0.968	34.748	0.928	0.430	1.627
4%	0.921	9.722	0.973	0.080	0.947	30.059	0.951	0.892	4.167
6%	0.980	8.970	0.982	0.062	0.889	26.054	0.976	1.366	5.736
8%	0.985	7.459	0.960	0.046	0.846	21.063	0.993	1.454	6.924
10%	0.976	6.385	0.948	0.037	0.821	17.847	0.991	1.456	7.957

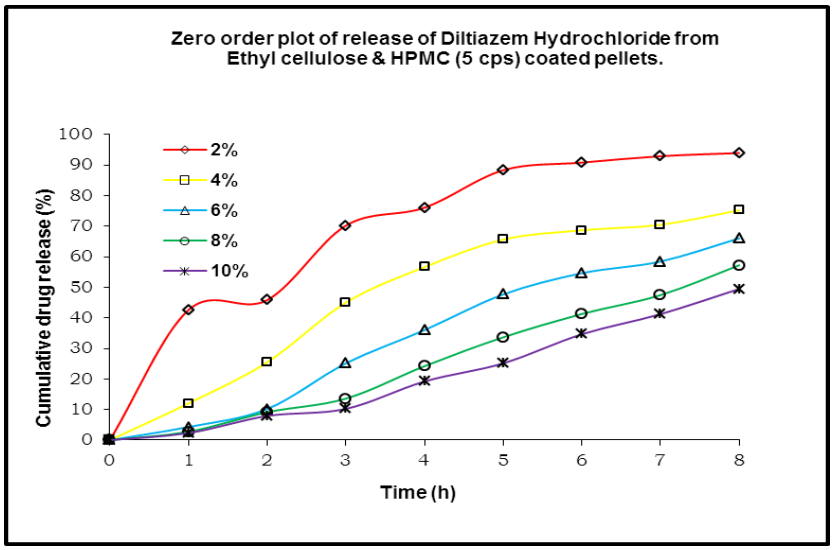

Fig. 4: Zero Order Plot of Release kinetics of Diltiazem HCl sustained release pellets.

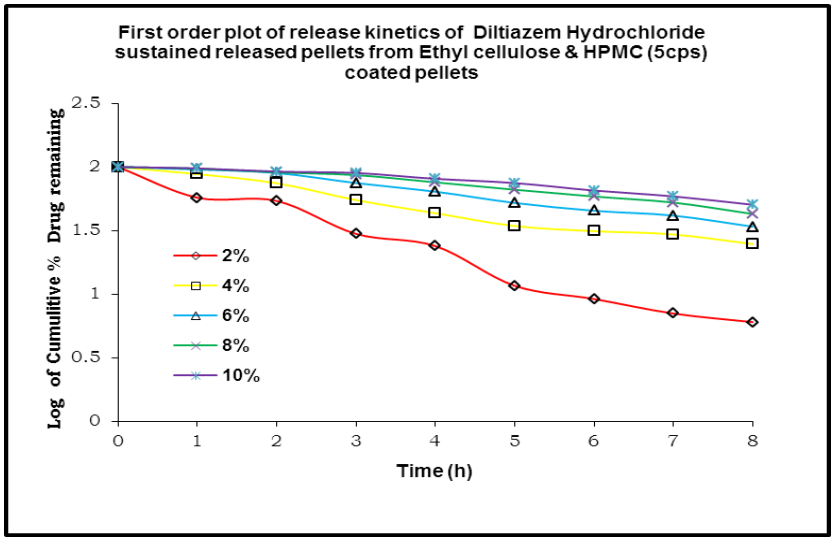

Fig. 5: First Order Plot of Release kinetics of Diltiazem HCl sustained release pellets.

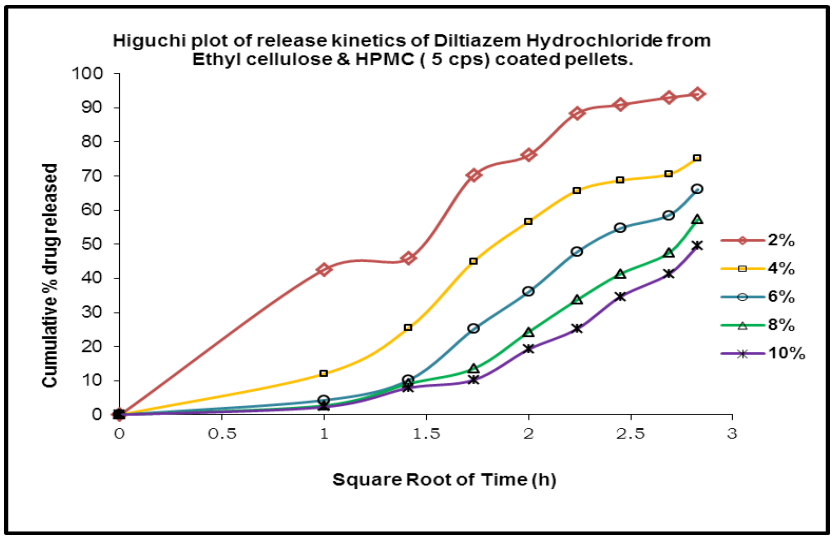

Fig. 6: Higuchi Plot of Release kinetics of Diltiazem HCl sustained release pellets.

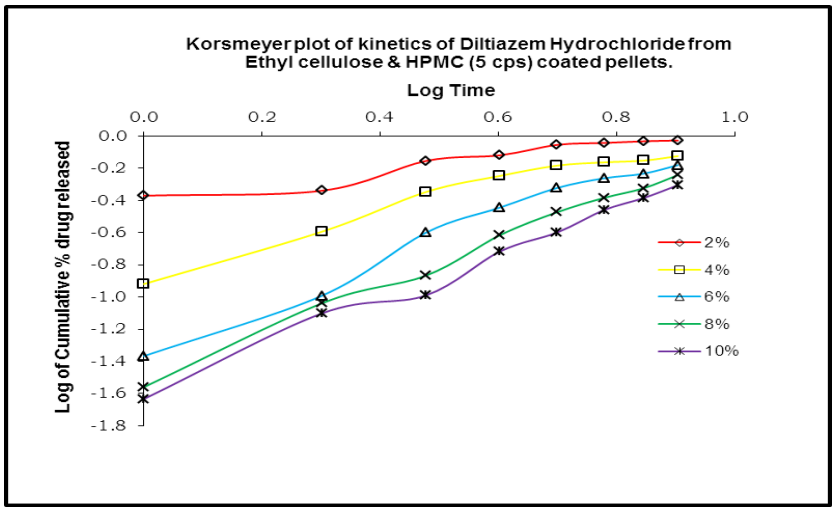

Fig. 7: Korsmeyer Plot of Release kinetics of Diltiazem HCl sustained release pellets.

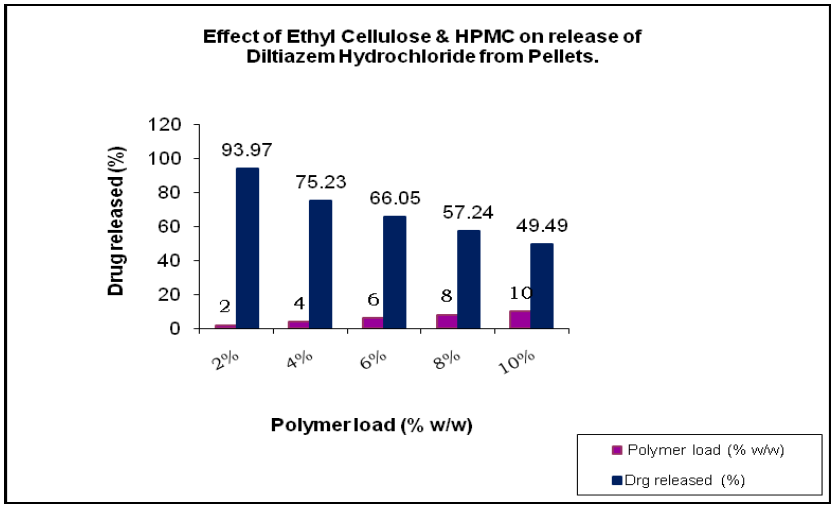

Fig. 8: Effect of 2%, 4%, 6%, 8% & 10% Polymer Load on the release of Diltiazem HCl SR Pellets using 85 % Ethyl Cellulose & 15 % HPMC at 8 h

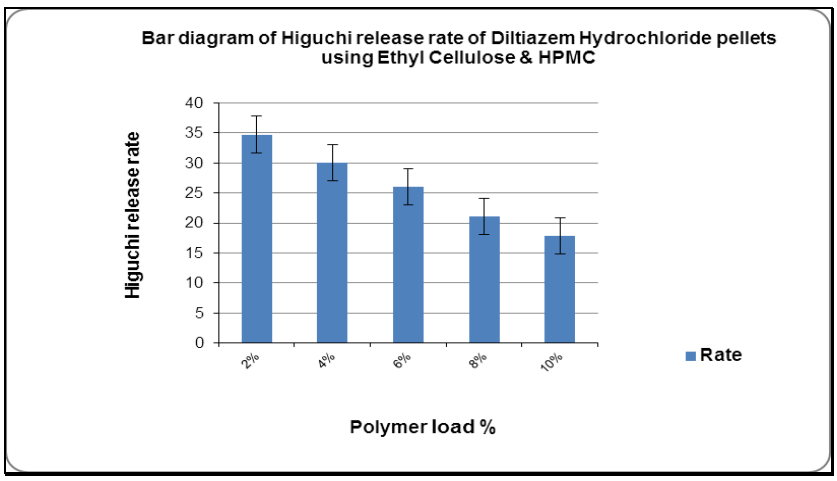

Fig. 9: Higuchi release rate of Diltiazem HCl SR Pellets using 2%, 4%, 6%, 8% & 10% Polymer Load of 85 % Ethyl Cellulose & 15 % HPMC at 8 h

CONCLUSION

Diltiazem Hydrochloride pellets loaded with Ethyl Cellulose & Hydroxy Propyl Methyl Cellulose as rate retarding polymer could be prepared by using layering technique in a fluidized bed bottom sprayer coater. After exploring the release mechanism with zero order, first order, Higuchi equation, Korsmeyer's equation it can be said that there was a correlation found between *in vitro- in vivo* study. This study also illustrated that the profile and kinetics of drug release were basically the functions of polymer type which ultimately can lead to establish a successful formulation from biopharmaceutical view point.

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CONFLICT OF INTEREST

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