DILTIAZEM HCL MICROCAPSULES USING ETHYL CELLULOSE ETHER DERIVATIVE POLYMER AS RELEASE RETARDING AGENT: IN-VITRO CHAPTER

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ABSTRACT

This study presents sustained release microencapsulation of Diltiazem HCL. Its in-vitro dissolution study in phosphate buffer pH 7.4 as dissolution medium and in vivo behaviour in animal subjects. The microcapsules were prepared using polymers Ethocel 7P and Ethocel 7FP at two different drug to polymer (D: P) ratios i.e. 1:5 and 1:10 and the effect of concentration was observed on drug release behaviour. The prepared microcapsules were evaluated for different physical characteristics i.e. Bulk density, Tap density, Compressibility index, Hausner’s ratio and Angle of repose. Characterization of the developed microcapsules was carried out using Differential Scanning Calorimetry and Fourier Transform Infrared Spectroscopy while Scanning Electron Microscopy was performed to observe the morphology of the microcapsules. Model dependent and dependent approaches were used to find out the drug transport mechanism and to compare the drug release profiles with standard formulation respectively.

All the formulations show anomalous, non-Fickian diffusion mechanism and the data was best fitted in Korsmeyer’sPeppas equation.

While carrying out in vivo studies, simple and rapid HPLC methods were developed which revealed optimum serum concentration (Cmax) levels for the developed microcapsules predicting least chances of side or adverse effects.

Keywords:
Diltiazem HCl, Microencapsulation, Kinetic models, Drug release rate.

1. INTRODUCTION

The patients with chronic diseases are increasing day by day. These patients are prescribed a lot of medicines at a time for a long time period for full therapy which leads to patient noncompliance. Such type of noncompliance is more in drugs with shorter half-lives because they have high dosage frequencies to maintain the blood plasma drug concentrations in therapeutics levels. These problems demand the development of such type of drug delivery systems which are acting for a long time period with constant blood drug plasma levels. Microencapsulation is one of the recent discoveries in developing controlled release drug delivery systems [1, 2]. In microencapsulation, a thin layer is applied to a drug moiety having particle size ranging between 5-5000 µm [2, 3]. This coating delayed the release of drug from the microcapsule and also alter the physic-chemical properties of the core and also modify the photosensitivity and heat sensitivity of the core [3, 4]. Microencapsulation develops a barrier between the core component and other components of the product. Several methods are used for the preparation of microcapsules including spray drying, spray cooling, spray chilling, air suspension coating, extrusion, centrifugal extrusion, freeze drying, coacervation, co-crystallization, liposome entrapment and molecular inclusion etc. [5]. Microencapsulation can successfully reduce the side effects of a drug and can enhance the drug absorption from GIT [3]. Recently with the help of microencapsulation technologies, many commercial products have been developed [6].

The objective of the present study was to encapsulate Diltiazem HCl by using Ethocel 7 Premium and 7FP polymer and to study the physical characteristics of these microcapsules by using Scanning Electron Microscope, in vitro dissolution behaviour and in vivo data.

2. MATERIAL AND METHODS

MATERIALS

Diltiazem HCl (Velour Pharma Islamabad, Pakistan, Ethocel 7P and 7FP (Dow Chemical Co., Midland USA), Acetone (Fisher Chemicals, UK), Dilzem SR tablet 90 mg by Parke Davis taken from local market, Spray Dryer (Labultima LU 228 Advanced, India), PharmaTest Dissolution Apparatus (D-63512, Hainburg), UV-Visible spectrophotometer (UVDEC-1601 Shimadzu, Japan), water bath.

CALIBRATION CURVE

For standard calibration curve of Diltiazem HCl, a 20 mg of each drug was taken in 100 ml solvent (phosphate buffer pH 7.4) and was kept for complete dissolution in ultra sonifier for 1-2 hrs. Several dilutions were prepared from this stock solution in decreasing order as shown in table 1.1 and were analysed using UV-visible spectrophotometer (UVDEC-1601 Shimadzu, Japan) at $\lambda_{\text{max}}$ 237 nm and the values of its absorbance’s were recorded and a plot was drawn using MS Excel format as shown in figure 1.1.
Table 1.1: Concentrations versus Absorbance of Diltiazem HCl

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Concentration (mg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 mg/ml</td>
<td>3.711</td>
</tr>
<tr>
<td>2</td>
<td>0.05 mg/ml</td>
<td>1.956</td>
</tr>
<tr>
<td>3</td>
<td>0.025 mg/ml</td>
<td>0.971</td>
</tr>
<tr>
<td>4</td>
<td>0.0125 mg/ml</td>
<td>0.489</td>
</tr>
<tr>
<td>5</td>
<td>0.00625 mg/ml</td>
<td>0.241</td>
</tr>
</tbody>
</table>

Figure 1.1: Standard Curve of Diltiazem HCl

\[ y = 37.207x + 0.0268 \]
\[ R^2 = 0.9993 \]

PARTICLE SIZE ANALYSIS

To determine the particle size distribution, the particle size analysis of the drug was performed using Particle Size Analyser (LA-300, Horiba, Japan) and Distilled Water was used as a solvent. The mean particle size of the drug was determined using a sufficient quantity of the drug incorporated in the loading chamber of the instrument. Some parameters were set accordingly like (Circulation Speed: 2 minutes, Ultra Sonic Time: 5 minutes and Standard R.R.Index: 1.18-0.00i).

PREPARATION OF MICROCAPSULES

Diltiazem HCl microcapsules were prepared using two different drug to polymer (D: P) ratios i.e. 1:5, 1:10 as shown in table 1.2. Given quantities of drugs and polymers were dissolved in specified quantity of acetone with constant stirring. After preparation all the solutions were then passed through the spray dryer (Labultima LU 228Advanced, India) using closed or inert loop containing Nitrogen gas and having the inlet temperature constant at 60°C. The collected microcapsules from the main chamber and cyclones of the dryer were then filled in capsule shells each having 90mg of Diltiazem microcapsules for further evaluation.
**Table 1.2:** Formulation of Diltiazem HCl Microcapsules with Different Polymers and D: P ratios

<table>
<thead>
<tr>
<th>S/No</th>
<th>Batch #</th>
<th>D: P Ratio</th>
<th>Polymer</th>
<th>Drug Quantity</th>
<th>Polymer Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Batch #1</td>
<td>1:5</td>
<td>Ethocel 7 Premium</td>
<td>1 gram</td>
<td>5 grams</td>
</tr>
<tr>
<td>2</td>
<td>Batch #2</td>
<td>1:10</td>
<td>Ethocel 7 Premium</td>
<td>1 gram</td>
<td>10 grams</td>
</tr>
<tr>
<td>3</td>
<td>Batch #3</td>
<td>1:5</td>
<td>Ethocel 7 FP Premium</td>
<td>1 gram</td>
<td>5 grams</td>
</tr>
<tr>
<td>4</td>
<td>Batch #4</td>
<td>1:10</td>
<td>Ethocel 7 FP Premium</td>
<td>1 gram</td>
<td>10 grams</td>
</tr>
</tbody>
</table>

FT-IR Spectrophotometry and DSC thermo gram were used for the characterization of developed sustained release Diltiazem HCl microcapsules. Scanning Electron Microscope (SEM; Joel JSM-5910, Japan) was used to take electron micrographs of the above samples by placing the samples on a metal stub having adhesive tape and then coating with gold for good conductivity. The micrographs were taken at different magnifications.

**MICROCAPSULE SOLVATION**

Microcapsule solvation was determined by the following formula which was performed at the end of each microencapsulation process[3]. Microcapsules were weighed immediately after preparation before drying (M₁) and after drying (M₂).

Microcapsule Solvation (%) = \((M₁/M₂) \times 100\)

**BULK DENSITY**

Bulk density was determined, according to method as was recorded by [7]. The following formula was used to determine bulk density of microcapsules:

Bulk Density = Sample weight/Sample Volume

**TAP DENSITY**

To determine tap density of microcapsules, the conventional tapping method was used. A 10 ml cylinder was taken and the tapping number was reduced to 100 because this number was sufficient to bring a plateau condition [8]. The following formula was used to calculate tap density:

Tapped density = Weight of Microcapsules/Volume of microcapsules after 100 tapping’s

**COMPRESSIBILITY INDEX**

The following formula was used to determine compressibility index[8]:

\[ Ci = \left(\frac{\text{Initial Volume} - \text{Final Volume}}{\text{Initial Volume}}\right) \times 100 \]
HAUSNER’S RATIO

As reported by [9], the Hausner’s ratio of microcapsules was determined by the following formula:

Hausner’s ratio = Volume before Tapping/Volume after tapping

ANGLE OF REPOSE

To determine the angle of repose for microcapsules, the microcapsules were passed through a horizontal surface of funnel. The height of the formed heap and the radius (r) of cone base was measured[3]. The angle of repose (θ) was determined by the following formula as stated by [10].

θ = tan⁻¹ h/r

Where (r) is radius and (h) is height of funnel.

IN VITRO DISSOLUTION STUDIES

PharmaTest dissolution apparatus (D-63512, Hainburg) having 6 stations, was used for the in vitro studies of Diltiazem HCl microcapsules. For this purpose USP method-II (rotating paddle method) was used by using phosphate buffer pH 7.4 as dissolution solvent and the rotating speed was 100 rpm. Each station was containing 900 ml of the dissolution solvent and the temperature was kept constant at 37 °C. Capsules having a specific amount of microcapsules equivalent to 90 mg pure Diltiazem HCl were added to each station. Samples of 5ml each were withdrawn from the stations at specific time intervals and were replaced with fresh buffer kept at the same temperature. The samples were analysed for drug concentration through UV-visible spectrophotometer (UVIDEC-1601, Shimadzu Japan) at 237 nm wavelength and were compared with standard reference Dilzim 90mg immediate release tablets.

IN VIVO STUDIES

In vivo study for Diltiazem HCl sustained release microcapsules was performed on 10 healthy Himalayan Angora rabbits according to a randomized two way crossover design. The in vivo study in rabbits was approved by the Ethical Committee of Gomal University, D.I.Khan (KPK) Pakistan. The average weight of rabbits was 2 ± 0.3 kg. The 10 rabbits were divided into two groups (Group A& Group B) each group having 5 rabbits.

IN VITRO DRUG TRANSPORT MECHANISM

A model dependent approach was used to investigate the drug release mechanism from the microcapsules into the dissolution medium. For this KorsmeyerPeppas equation was used.

\[
\frac{M_t}{M_\infty} = Kt^n[11]
\]

In KorsmeyerPeppas kinetic model an (n) value which is a diffusional exponent represents drug transport mechanism. When the value of n = 0.5 then drug diffuses with a quasi-Fickian diffusion
mechanism. When the value of n > 0.5 then anomalous or non-Fickian diffusion mechanism of drug occurs and when n = 1 then non-Fickian, Zero order or case-II release kinetics occurs[12].

**SIMILARITY FACTOR f₂**

The similarity factor f₂ is used to compare the drug release profiles of a formulation from the test with a reference standard formulation and is approved by FDA. Its value ranges from 50 to 100. The values greater than (50) show similarities while smaller than (50) show dissimilarities.

\[
f₂ = 50 \log \left\{ \frac{1}{1/n} \sum_{t=1}^{n} (R_t - T_t)^2 \right\}^{0.5} \times 100
\]

3. **RESULTS AND DISCUSSION**

**PARTICLE SIZE AND PARTICLE SIZE DISTRIBUTION**

Horiba particle size analyser was used to determine the particle size analysis. The particle size and particle size distribution of any drug plays a very vital role in the release mechanism from controlled release systems or dosage forms [13]. Particle size is inversely proportional to the surface area and the effect of drug release [14]. It’s been witnessed that the particle size of the drug and the polymer play a very important role in the powder compressibility and hence can produce even and uniform matrices which have uniform water channels that helps in controlling the diffusion and dissolution of drug in a controlled manner. Figure 1.2 show the histogram for Diltiazem HCl having the median particle size was 232.5647 µm.
PHYSICAL PROPERTIES OF MICROCAPSULES

The bulk density, tapped density, compressibility index, Hausner’s ratio and angles of repose express the rheological properties of powders and microcapsules. The bulk density of batch 1 was 0.28 g/ml while that of batch 2, 3 and batch 4 was 0.24 g/ml and 0.29 g/ml and 0.23 g/ml respectively. It could be seen that the bulk density was decreased by increasing polymer concentration which was also defined by [16], which reported that by increasing the polymer concentration bulk density decreased vice versa. The tapped density was 0.32 g/ml, 0.30 g/ml, 0.29 g/ml and 0.28 g/ml for batch 1, 2, 3 and batch 4 respectively. The compressibility index was 11.23%, 9.13%, 8.79% and 9.01% for batches 1, 2, 3 and batch 4 respectively which shows good flow properties of the microcapsules. The Hausner’s ratio was 1.22, 1.13, 1.27 and 1.17 for the four batches i.e. batch 1, batch 2, batch 3 and batch 4 respectively indicating good flow properties. The angle of repose was 29.33°, 28.79°, 25.55° and 30.76° for the said four formulations respectively again showing good flow properties.

FOURIER TRANSFORM INFRA-RED ABSORPTION SPECTROSCOPY (FTIR)

FTIR spectroscopy of Diltiazem HCl, Polymer i.e. Ethocel standard 7 Premiumalone and their formulations were conducted in order to investigate any interaction between the drug and polymer. As shown in Fig 1.2 and 1.3, Diltiazem HCl has two carbonyl groups around 1679 and 1745 cm\(^{-1}\) [15]. The Infra-red studies reveal that both of the characteristics bands around 1679 and 1745 cm\(^{-1}\) were present in the physical mixture with Ethocel polymer and no new bonds or shifts in the bands appeared which confirms the development of microcapsules and represents no interaction or alteration. The FTIR study was done in order to investigate drug polymer compatibility and the confirmed undisturbed structures of the Diltiazem HCl indicate no drug polymer interaction.

![Figure 1.2: FTIR spectra of Pure Diltiazem HCl](image-url)
DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

Figures 1.5 to 1.7 show the DSC thermograms for Diltiazem HCl, Ethocel 7 P and their developed microcapsules. As depicted from the figures, Diltiazem HCl has a characteristic endothermic peak around 217°C, which in case of physical mixture with Ethocel polymer is at the same position indicating that there is no interaction between the drug and the polymers and confirms the development of Diltiazem HCl microcapsules[15].

Figure 1.3: FTIR spectra of Diltiazem HCl with Ethocel 7 P Microcapsules

Figure 1.4: Differential Scanning Calorimetric Thermogram of Diltiazem HCl
Figure 1.5: Differential Scanning Calorimetric Thermogram of Ethocel 7 P

Figure 1.6: Differential Scanning Calorimetric Thermogram of Ethocel 7 P with Diltiazem HCl Prepared Microcapsules

SCANNING ELECTRON MICROSCOPY (SEM)

The figures 1.7, 1.8, 1.9, 1.10, 1.11 and 1.12 show SEM images of Diltiazem HCl, Ethocel polymer and Diltiazem HCl microcapsules from batch 1, batch 2, batch 3 and batch 4 respectively with two different grades of polymer Ethocel i.e. 7 Premium and 7 FP Premium at two different D: P ratios i.e. 1:1 and 1:2. The images were taken at different resolutions. These SEM images shows regular
spherical shaped microcapsules of Diltiazem HCl. The microcapsules were round spherical structures where the drug particles were embedded within the polymer matrix and could account for the slow release of the drug from the microcapsules [17]. In similar studies while performing in vitro studies of Diltiazem HCl microcapsules with Chitosan, the prepared microcapsules were clearly visible with definite spherical geometrical shapes with smooth surfaces with little deposits [14].

**Figure 1.7:** SEM image of Diltiazem HCl

**Figure 1.8:** SEM image of Ethocel Polymer

**Figure 1.9:** SEM image of Diltiazem with Ethocel 7 Premium (batch 1)

**Figure 1.10:** SEM image of Diltiazem with Ethocel 7 FP Premium (batch 2)
**IN VITRO DISSOLUTION STUDIES**

The dissolution studies of Diltiazem microcapsules were carried out in phosphate buffer pH 7.4. The effect of three different concentrations of polymer was also investigated on drug release profiles from microcapsules. Fig.1.13 shows the *in vitro* drug release data of Diltiazem from microcapsules. A biphasic drug release was observed from Diltiazem HCl microcapsules, during which an initial burst release was observed which was then followed by a sustained release of the drug. Similar phenomenon was observed by [2]. Drug release from batch 1 and batch 3 was in comparatively shorter time i.e. 4 hrs while from batches 2 and 4, the drug was released in 5 hrs. From the figure it could be seen that by increasing the concentration of polymer the drug release time was increased and vice versa. The formulation with high concentration of polymer was having the longest drug release time i.e. 5 hrs. approximately while the formulation with lowest concentration of polymer was having smaller drug release time i.e. approximately 4 hrs. Thus by increasing concentration of polymer extends the drug release rates from polymeric dosage forms [18]. Similar results were found while performing in vitro dissolution behaviour of Diltiazem HCl microcapsules in phosphate buffers pH 1.2 and pH 7.4 separately in which the increase of Chitosan concentration in all the formulations results in decrease of drug release or increase of drug release time from the prepared microcapsules[14].
DRUG TRANSPORT MECHANISM AND DISSOLUTION EQUIVALENCY

The values of $R^2$ (coefficient of determination) of the batches were best fit in Korsmeyer-Peppas equation. The ‘n’ values which indicate the drug transport mechanism of the four batches in Korsmeyer-Peppas equation were 0.491, 0.543, 0.509 and 0.511 indicating anomalous non-Fickian diffusion release kinetics. Significant differences were found in release rates of all the four batches ($P<0.05$).

The in vitro dissolution results were compared with a reference standard conventional dosage form (Diltiazem 90 mg tablets). The values of dissolution equivalency $f_2$ of all the four batches as compared to a conventional dosage form were 39, 42, 33 and 36 ($<50$) indicating differences from the reference conventional formulation.

PHARMACOKINETICS OF DILTIAZEM HCL MICROCAPSULES

In the present study, animal models (Himalayan Angora Rabbits) were used to study the in vivo performance of Diltiazem HCl microcapsules which showed that the developed sustained release formulations maintain a constant blood plasma level for approximately long period of time as compared to a reference conventional dosage form which gain a rapid peak plasma concentration but could not maintain it. The extended half-life $t_{1/2}$ and the time which is required to achieve peak plasma concentration $T_{\text{max}}$ were representative of a slower drug release rate and an extended time period. The AUCs of both the test and reference formulations were not significantly different indicating that the formulations were bioequivalent. Ethocel was found to be a significant rate controlling polymer giving a nearly Zero order drug release and maintaining a nearly constant peak plasma level in desired therapeutic range thus minimizing the risk of reaching drug plasma concentrations above MTC (Maximum toxic concentration), therefore, avoiding drug toxicity and side effects and improves permissibility [19].

Figure 1.13: Dissolution profiles of Diltiazem HCl microcapsules with two different ratios of polymer Ethocel and a reference standard formulation
As shown in the table 1.3, Diltiazem HCl sustained release microcapsules showed significantly different $T_{\text{max}}$ (4 ± 2.7 hours) as compared to $T_{\text{max}}$ of reference standard (30± 0.5 minutes), where $P<0.05$. Significantly higher values of peak time were observed. The half-life $t_{1/2}$ of test SR formulation was observed to be 5.93 ± 0.96 hours as compared to reference conventional tablet 2 ± 1.3 hours, where $P<0.05$. The higher values of $T_{\text{max}}$ and half-life $t_{1/2}$ for test SR formulations indicate the extended absorption phase and the presence of drug for a long time in the body. Moreover, significantly optimized values of peak concentration ($C_{\text{max}}$) were observed for test SR microcapsules (44.7 ± 1.34ng/ml) as compared to reference conventional formulation (78.32 ± 2.19ng/ml), where $P<0.0001$. Similarly, AUC₀₅ for test formulation was 2251 ± 19 ng.hr/ml as compared to reference standard conventional formulation being 1962 ± 24 ng.hr/ml and AUC₀∞ was 2157 ± 27 ng.hr/ml and 2297 ± 21 ng.hr/ml for test formulation and reference standard respectively which were not significantly different having $P<0.05$. Nearly similar values of $C_{\text{max}}$, AUC₀₅ and AUC₀∞ indicate bioequivalence of the test SR formulations to the reference standard conventional tablets. Elimination rate constant $K_{\text{el}}$and total Clearance $Cl_{\text{Total}}$for Diltiazem HCl microcapsules were found to be 0.034±0.023 h⁻¹ and 0.012±0.004 μg×hr/(μg/mL) for test formulations and 0.145±0.005 h⁻¹ and 0.012±0.004 μg×hr/(μg/mL) for the reference tablet. Different authors have performed In vivo studies on Diltiazem HCl SR formulations but the in vivo data results we got were somewhat different with respect to pharmacokinetic parameters that might be due to subject and formulation variations.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Reference Tablet</th>
<th>Test (SR) Formulation</th>
<th>Statistical Test ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Plasma Concentration $C_{\text{max}}$ (ng/ml)</td>
<td>78.32 ± 2.19ng/ml</td>
<td>44.7 ± 1.34ng/ml</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Maximum Plasma Conc. Time $T_{\text{max}}$ (hours)</td>
<td>30± 0.5 Min</td>
<td>4 ± 1.5 hours</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Half Life $T_{1/2}$ (hours)</td>
<td>2hrs ±1.3hours</td>
<td>5.93hrs ±0.96 hours</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Area under the Curve AUC₀₅</td>
<td>1962 ± 24 ng.hr/ml</td>
<td>2251 ± 19 ng.hr/ml</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Area under the Curve AUC₀∞</td>
<td>2297 ± 21 ng.hr/ml</td>
<td>2157 ± 27 ng.hr/ml</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Apparent Volume of Distribution ($V_{d/f}$)</td>
<td>16.9 L/kg</td>
<td>22.33 L/kg</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elimination rate Constant $K_{\text{el}}$(hour⁻¹)</td>
<td>0.145±0.005 h⁻¹</td>
<td>0.034±0.023 h⁻¹</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total Clearance $Cl_{\text{Total}}$(Liter/hour)</td>
<td>0.012±0.004 μg×hr/(μg/ml)</td>
<td>0.087±0.004 μg×hr/(μg/ml)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Diltiazem HCl SR microcapsules were also evaluated for relative bioavailability and were found to be 95% indicating 95% relative bioavailability for both the test formulation and reference formulation but the test formulation having a stable and constant peak plasma concentration for an extended period of time as compared to the reference conventional dosage form.
The plasma serum concentration of Diltiazem HCl versus time profile from reference conventional formulation and test formulation could be seen from the figure 1.14 given below. It could be seen that plasma concentrations of Diltiazem HCl were detectable even at 12 h. A gradual increase in serum concentration was observed reaching the peak plasma concentration at about 3 hours after drug administration via oral route and maintained for about 12 hours reflecting a sustained release formulation. It was observed that the reference formulation had a higher and faster peak plasma concentration in short time as compared to test CR formulation indicating a slow and steady rate of drug absorption from the SR test formulation. A similar result was found by investigating Olanzapine in rabbit serum after administering a test CR formulation and a reference conventional formulation [19].

Figure 1.14: Mean Comparative plasma concentrations versus time profiles of Diltiazem HCl Microcapsules and reference standard conventional tablets

4. CONCLUSIONS

Diltiazem HCl microcapsules were produced using Ethocel as polymer and encompassing spray drying technique. Various physical characterization procedures like DSC, FTIR and SEM studies confirmed the successful development of CPM solid dispersions. Effect of variable i.e. drug to polymer ratio (D: P) on Diltiazem microcapsules was studied, which revealed that the drug to polymer ratio has a prominent role in the development of microcapsules. It was found that the release rate of the drug was decreased with increasing the concentration of the polymer which may be due to the reason that more polymer particles surround the drug particles, whereas Ethocel is insoluble in analytical grade water. Other reason could also be due to the cross-linked structure of the polymers that resists the drug diffusion in spite of its amorphous molecular state. The current study suggests that the preparation of Diltiazem HCl microcapsules formulated with ethyl cellulose ether derivative polymer Ethocel® and using spray drying technique contributes to good and simple sustained release dosage formulations. The simple microcapsules designed could effectively be used as potential sustained release formulation in the market.
5. REFERENCES


