Development and Biopharmaceutical Evaluation of Controlled Porosity Osmotic Formulations of Silymarin β-Cyclodextrin Inclusion Complex

Keywords: Silymarin, bioavailability, inclusion complexes, controlled porosity osmotic pump tablet

ABSTRACT

The objective of the present work is to formulate and characterize controlled porosity osmotic pump (CPOP) tablets of silymarin β-cyclodextrin(β-CD) molecular inclusion complexes for prolonged and controlled delivery of the drug. The silymarin β-CD solid systems were prepared in three molar ratios by co-precipitation method. The complexes formed were characterized by SEM, DSC and XRD studies. CPOP tablets were prepared using 3² factorial designs with two variable being silymarin β-cyclodextrin inclusion complexes and concentration of osmogen, KCl along with adjusted concentration of lactose, mannitol, polyvinylpyrrolidone, and SLS. Coating was done using acrycoat E30D along with 10% PEG-400 as pore formers.

Influences of variables i.e. drug β-CD ratio and the amount of KCl on drug release profiles were investigated. The pores formed were confirmed by SEM studies. The release of the drug from the formulations was fitted into different kinetic models (Zero Order, First Order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas, and Weibull) to understand the mechanism of drug release. The solubility and dissolution rates of silymarin were significantly increased by using inclusion complexation. It was found that concentration of both the variables has a profound effect on the release of the drug from the osmotic pump tablets. With a high concentration of KCl, faster dissolution was observed probably due to the high pressure generated inside the tablet due to high concentration of osmogen along with high concentration of drug β-cyclodextrin ratio. The present results confirmed that CPOP tablets of silymarin may be prepared for effective delivery of the drug for 10-12 hrs with higher solubility and bioavailability.
INTRODUCTION

*Silybummarianum*, generally called as milk thistle is classified in the family of Asteraceae. It is one of the oldest and thoroughly researched plants of ancient times for the treatment of liver and gallbladder disorders, hepatitis, cirrhosis, jaundice, and protection against Amanita phalloides mushroom poisoning and other toxin poisonings[1-5]. Silymarin, the active component of this plant, is a standardized extract consisting of approximately 70 to 80% silymarin flavonolignans and flavonoids, and the remaining 20-30 % consisting of a chemically undefined fraction comprised of polymeric and oxidized polyphenolic compounds[6]. Silybin is the primary and most active component of the silymarin complex. All pharmacokinetic parameters of silymarin are referred to and standardized as silybin. Orally administered silymarin (silybin) is rapidly absorbed with a t<sub>max</sub> (2-4 hours) and t<sub>1/2</sub> (6-8 hours). Only 20-47% of oral silymarin is absorbed from the gastrointestinal tract where it undergoes extensive enterohepatic circulation. Therefore, absorption of silymarin from the gastrointestinal tract is low, making bioavailability poor [7]. The poor aqueous solubility of the drug may lead to dissolution related bioavailability problems. Cyclodextrin and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability, and absorption of a drug[8]. Nagarsenkar et al. reported faster dissolution and better bioavailability of ketorolac solid dispersion with HP-β-cyclodextrin [9]. Reddy et al. reported enhanced solubility and dissolution rate of Celecoxib by complexation with β-CD [10]. Studies of the controlled release of drugs for their extended and safe use have become an important field of research [11]. Among controlled-release devices, osmotically driven systems to hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods [12-17]. Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery [18-20]. Preparation of CPOP consists of the core containing the active material and a semipermeable membrane that coats the core, having some percentage of pore formers in order to release the active materials. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane pores that are formed and dissolves the active material. The osmotic pressure generated inside the tablet induces the release of the drug outside through the pores formed at a slow but constant rate [21, 22].

The objective of the study was to investigate the possibility of improving the solubility and dissolution rate of silymarin by complexation with β-CD and then to formulate CPOP for controlled delivery of the drug for 10-12 hrs. The novelty of the study is in the fact that no
such attempt to improve the solubility and bioavailability of silymarin (BCS class II drug) along with controlled release formulation for 12 hours is being reported till now. Most of the studies done were focused on improving the solubility of the drug in GIT for faster absorption which leads to nucleation and crystal growth from the supersaturated solution of the drug, and an ultimately large portion of the dosed drug is not absorbed into the systemic circulation. Here, we attempt to improve as well as deliver the drug in a controlled manner from the CPOP for a longer duration of time.

MATERIALS

A gift sample of silymarin was obtained from AGAPE Pharmaceutical, Majhitar, East Sikkim; β-CD was obtained from Zim laboratories Ltd, Nagpur; Acrycoat E-30D was obtained from Corel Pharma, Ahmadabad. HCl, methanol potassium dihydrogen phosphate and sodium hydroxide used were of analytical grade (Merck, Mumbai). All other chemicals and reagents used were of analytical grade.

METHODS

Phase Solubility Analysis for Silymarin

Phase solubility studies of silymarin with different concentrations of β-CD were performed according to the method described by Higuchi and Connors to determine stoichiometric proportions of silymarin with β-CD [23, 24]. The data were used to determine stability constant of the complexes. For this, the stock solution of 10 mM β-cyclodextrin were prepared using triple distilled water. The stock solution was diluted with triple distilled water to give millimole solutions in the range of 02 to 10 mM β-cyclodextrin solutions. Five ml of each solution was filled in screw capped vials and the excess quantity of the drug was added to each vial separately. The vials were kept for shaking at ambient temperature for 72 hrs using a lab shaker (Remi RSB-12). After 72 hrs of shaking to achieve equilibrium, 2 ml aliquots are withdrawn at 1 hr interval and filtered through Whatman no.1 filter paper. The filtered samples are diluted suitably and assayed for drug content by specific UV method against a blank in the same concentration of β-CD in water so as to cancel any absorbance that may be exhibited by the cyclodextrin molecules. Shaking is continued until the consecutive estimations are the same.
Preparation of solid complexes of silymarin and β-CD was performed by the co-precipitation method. Required molar ratios 1:0.5M, 1:1M and 1:1.5M quantities of drug and β-CD was dissolved in methanol: water respectively. The solution of the drug was added dropwise into cyclodextrin solution. The contents were continuously stirred for 6 hours using a magnetic stirrer and finally the pastes were then dried at 40°C for 6 hrs until 2% moisture remained and finally they were passed through a 600µm sieve [25].

Characterization of inclusion complexes

Scanning Electron Microscope

The morphology of the drug and inclusion complex prepared by co-precipitation method was studied using a scanning electron microscope (JSM- 5610 LV Jeol, Japan). The samples were coated with platinum to provide a conductive layer for observing images at 15 kV.

Differential Scanning Calorimetry

This scanning was performed using DSC model (Perkin Elmer, DSC 4000 System). The samples were placed in a closed platinum crucible and DSC thermograms were recorded at a heating rate of 10°C/minute in the range of 20°C to 310°C [25].

X-Ray Diffractometry Study

The X-ray diffraction pattern of the selected inclusion complex was compared with that of pure silymarin. This was performed by measuring 2θ in the range of 40° to 50° with reproducibility of ± 0°–001° on an X-ray diffractometer (Phillips PW 1800).

The core tablet formulation design: full 3² factorial design

The tablets were prepared by full 3² factorial designs. Two variables, with variations at three levels, namely, high, medium, and low, were done by varying the concentrations of the drug: β-CD ratio and the concentration of osmogen KCl. Low, medium, and high levels of the drug: β-CD ratio was selected as 1:0.5M, 1:1M, and 1:1.5M, respectively, and as 30mg, 50mg and 70mg for KCl. The formulation design is tabulated in Table 1. All ingredients except talc and magnesium stearate were passed through 600µm sieve, mixed sufficiently and using wet granulation technique converted into granules, and after drying, compressed into tablets using
rotator 8 stations tableting machine (Rimek, India) with normal concave round punches. Each tablet theoretically contained 156mg Silymarin.

Table 1: Basic core tablet formulation and varying range of all ingredients

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug: β-Cyclodextrin Ratio (mg)</th>
<th>KCl (mg)</th>
<th>Lactose (mg)</th>
<th>Mannitol (mg)</th>
<th>PVP (mg)</th>
<th>SLS (mg)</th>
<th>Talc (mg)</th>
<th>Magnesium Streate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>1:0</td>
<td>156:0</td>
<td>30</td>
<td>318</td>
<td>318</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS2</td>
<td>1:0</td>
<td>156:0</td>
<td>50</td>
<td>308</td>
<td>308</td>
<td>10</td>
<td>10</td>
<td>5</td>
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<tr>
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<td>156:0</td>
<td>70</td>
<td>298</td>
<td>298</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS4</td>
<td>1:1</td>
<td>156:361</td>
<td>30</td>
<td>137</td>
<td>138</td>
<td>10</td>
<td>10</td>
<td>5</td>
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<td>TS5</td>
<td>1:1</td>
<td>156:361</td>
<td>50</td>
<td>127</td>
<td>128</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS6</td>
<td>1:1</td>
<td>156:361</td>
<td>70</td>
<td>117</td>
<td>118</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS7</td>
<td>1:1.5</td>
<td>156:542</td>
<td>30</td>
<td>47</td>
<td>47</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS8</td>
<td>1:1.5</td>
<td>156:542</td>
<td>50</td>
<td>37</td>
<td>37</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TS9</td>
<td>1:1.5</td>
<td>156:542</td>
<td>70</td>
<td>27</td>
<td>27</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Evaluation of core tablets

The tablets were evaluated for appearance, weight variation, thickness, diameter, friability and hardness of the tablet to meet the pharmacopoeia standard.

Determination of the weight variation of the tablets

Twenty tablets were selected at random from each batch and were weighed accurately and the average weight was calculated. Then the deviation of individual weights from the average weight and the standard deviation were calculated[26].

Determination of thickness and diameter

Thickness and diameter of ten randomly selected tablets from each batch were measured with a slide caliper. Then the average diameter and thickness and standard deviation were calculated[26].
Determination of hardness of the tablets

Five tablets were sampled randomly selected from each batch and the hardness of the tablets was determined by the help of the Monsanto Hardness Tester. Then average hardness and standard deviation were calculated.

Determination of Friability of tablets

The friability test was done using Roche’s Friabilator. Twenty tablets were selected and weighed individually. Then the friability test was carried out at 25 rpm for 4 minutes. These tablets were then again weighed and percentage loss in weight was calculated.[26,27]

Determination of disintegration time of tablets

Disintegration is defined as the state in which no residue of the tablet or capsule remains on the screen of the apparatus, or if a residue remains, it consists of a fragment of the insoluble coating of the tablet or capsule shells or is a soft mass with no palpable core. In vitro disintegration time of 6 tablets from each of the formulation was determined by using a digital Tablet Disintegration apparatus (Electrolab Disintegration apparatus ED-2L). In vitro disintegration was carried out at 27±2°C in a 900 ml phosphate buffer at pH 6.8[27].

Coating of tablets

The coating solution used for sustained release osmotic tablet for 12 hrs of drug release was Acrycoat E30D. Acrycoat E30D contains 30% solids which is prepared by emulsion polymerization and consist of neutral copolymers of ethyl acrylate and methyl methacrylate esters that are insoluble over the entire physiological pH range. The films are formed which swell in water, buffer or gastric fluid and are permeable in these fluids. Acrylcoat E30D film imparts plasticizing effect and thus there is no need for the addition of plasticizer. Along with acrylcoat E30D, 10% PEG-400 were used as pore formers. The coating was performed by dip coating method with a hot air blower. Core tablets were heated up to 30°Cto 35°Cprior to dipping in the coating solutions. The air temperature of the blower was 45°Cand 50°C. The coated tablets were dried at 55°Cfor 24hr.

Evaluation of coated tablets

The tablets after coating with Acrylcoat E30D were evaluated for appearance, weight variation, thickness, diameter, friability and hardness of the tablets and drug content [26, 27].
Dissolution study of the CPOP tablets

**In vitro** drug release from controlled porosity osmotic pump tablets was studied using paddle type apparatus (Electro lab dissolution apparatus TDT 08L, USP type II) with 900ml of phosphate buffer pH 6.8 solution (PBS) as dissolution medium at a temperature of 37±0.5°C for 12 hrs. The paddle was rotating at 50 rpm. The release of drug was analyzed by UV absorption spectroscopy (Shimadzu UV 1700) at 287nm. The release kinetic of the drug was studied from plot of % cumulative drug release against time [28,29].

Characterization of osmotic coat

**Scanning electron microscope**

The morphology of the coat after dissolution studies were performed to check the formation of pores on the coat of CPOP tablets was studied using a scanning electron microscope (JSM-5610 LV Jeol, Japan). The samples were coated with platinum to provide a conductive layer for observing images at 15 kV.

RESULTS AND DISCUSSION

**Phase solubility analysis of silymarin**

The complexation of the drug with β-CD, the effect of β-CD on the solubility, the type of phase solubility diagram and the stability constant of β-CD complex formed was investigated by phase solubility studies. The phase solubility diagram for the complex formation between silymarin and β-CD is shown in Fig 1.

![Effect of β-cyclodextrin on solubility of silymarin](image)

**Fig. 1: Effect of β-cyclodextrin on solubility of silymarin**
Characterization of inclusion complexes

Scanning Electron Microscope

The morphology of the pure drug, and silymarin-β-CD inclusion complex was studied. The representative photographs are shown in Fig 2 and 3.

Fig. 2: SEM of silymarindrug

Fig. 3: Silymarin with β-cyclodextrin (Co-precipitation method)
Differential Scanning Calorimetry

The DSC thermal curves of silymarin, β-CD and inclusion complex (1:1 molar ratio) are shown in Fig 4. The DSC curve of silymarin shows one characteristic sharp endothermic peak at around 150 indicating the melting point of the drug.

![DSC Curves](image)

DSC Curves: (A) Silymarin alone; (B) β-Cyclodextrin; (C) Inclusion complex

**Fig. 4: DSC Study of Silymarin, β-Cyclodextrin, and Silymarin – β-Cyclodextrin complex**

X-Ray Diffraction Study

The X-ray diffraction patterns of pure Silymarin and Silymarin - β-CD complex by co-precipitation method were represented in Fig 5. The peak position (angle of diffraction) is an indication of amorphous nature of the sample.

![X-Ray Diffraction](image)

**Fig. 5: X-Ray Diffraction Study on the Silymarin and Silymarin complexed with β-Cyclodextrin**
Evaluation of core tablets

All formulations are having good physicochemical characteristics. The weight variation of each formulation was well within the I.P. limits. The tablets from each formulations showed good hardness and optimum disintegration time (Table 2).

Table 2: Physicochemical evaluation of core Tablets

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Weight variation (mg)</th>
<th>Diameter variation (cm)</th>
<th>Thickness variation (cm)</th>
<th>Hardness (kg/cm²)</th>
<th>Disintegration Time (hr:min)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>849.13±0.315</td>
<td>1.40±0.01</td>
<td>0.55±0.00</td>
<td>6.12±0.21</td>
<td>0.51</td>
<td>0.002±0.00</td>
</tr>
<tr>
<td>TS2</td>
<td>850.42±0.721</td>
<td>1.41±0.03</td>
<td>0.57±0.12</td>
<td>6.45±0.23</td>
<td>0.55</td>
<td>0.001±0.00</td>
</tr>
<tr>
<td>TS3</td>
<td>848.05±0.432</td>
<td>1.39±0.07</td>
<td>0.54±0.01</td>
<td>6.03±0.12</td>
<td>0.52</td>
<td>0.000±0.01</td>
</tr>
<tr>
<td>TS4</td>
<td>851.22±0.231</td>
<td>1.39±0.20</td>
<td>0.56±0.04</td>
<td>5.98±0.5</td>
<td>0.49</td>
<td>0.002±0.01</td>
</tr>
<tr>
<td>TS5</td>
<td>847.32±0.247</td>
<td>1.40±0.06</td>
<td>0.55±0.11</td>
<td>5.92±0.14</td>
<td>0.48</td>
<td>0.003±0.02</td>
</tr>
<tr>
<td>TS6</td>
<td>849.11±0.618</td>
<td>1.38±0.03</td>
<td>0.55±0.00</td>
<td>5.96±0.19</td>
<td>0.45</td>
<td>0.001±0.03</td>
</tr>
<tr>
<td>TS7</td>
<td>852.10±0.163</td>
<td>1.38±0.02</td>
<td>0.57±0.05</td>
<td>5.57±0.5</td>
<td>0.40</td>
<td>0.003±0.03</td>
</tr>
<tr>
<td>TS8</td>
<td>849.01±0.215</td>
<td>1.42±0.12</td>
<td>0.54±0.03</td>
<td>6.12±0.3</td>
<td>0.58</td>
<td>0.004±0.01</td>
</tr>
<tr>
<td>TS9</td>
<td>853.81±0.284</td>
<td>1.38±0.03</td>
<td>0.57±0.05</td>
<td>6.23±0.16</td>
<td>0.65</td>
<td>0.002±0.03</td>
</tr>
</tbody>
</table>

n=3, mean ±SD

Evaluation of coated tablets

All formulations after coating also showed good physicochemical characteristics. The weight variations of each of the formulations are well within the I.P. limitation. The tablets of each of the formulations are having good hardness and optimum disintegration time. Also the drug content of each of the tablets was performed (Table 3).
Table 3: Physicochemical Characteristics of Tablets after coating*

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Weight variation (mg)*</th>
<th>Diameter variation (cm)*</th>
<th>Thickness variation. (cm)*</th>
<th>Hardness. (kg/cm²)*</th>
<th>Disintegration Time(hr:min)</th>
<th>Percentage Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>851.03±0.415</td>
<td>1.41±0.0</td>
<td>0.56±0.00</td>
<td>5.72±0.11</td>
<td>0.59</td>
<td>88.75</td>
</tr>
<tr>
<td>TS2</td>
<td>852.12±0.521</td>
<td>1.42±0.0</td>
<td>0.58±0.02</td>
<td>5.95±0.39</td>
<td>0.48</td>
<td>90.00</td>
</tr>
<tr>
<td>TS3</td>
<td>850.25±0.132</td>
<td>1.40±0.0</td>
<td>0.53±0.08</td>
<td>6.01±0.29</td>
<td>0.42</td>
<td>90.70</td>
</tr>
<tr>
<td>TS4</td>
<td>853.02±0.131</td>
<td>1.41±0.1</td>
<td>0.55±0.02</td>
<td>4.98±0.57</td>
<td>0.59</td>
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<tr>
<td>TS5</td>
<td>849.12±0.347</td>
<td>1.41±0.0</td>
<td>0.56±0.10</td>
<td>5.32±0.44</td>
<td>0.51</td>
<td>96.86</td>
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<tr>
<td>TS6</td>
<td>851.21±0.218</td>
<td>1.39±0.0</td>
<td>0.56±0.20</td>
<td>5.56±0.29</td>
<td>0.41</td>
<td>96.38</td>
</tr>
<tr>
<td>TS7</td>
<td>854.10±0.063</td>
<td>1.38±0.0</td>
<td>0.58±0.15</td>
<td>5.37±0.5</td>
<td>0.50</td>
<td>97.61</td>
</tr>
<tr>
<td>TS8</td>
<td>851.01±0.315</td>
<td>1.43±0.1</td>
<td>0.55±0.23</td>
<td>5.76±0.34</td>
<td>0.53</td>
<td>98.55</td>
</tr>
<tr>
<td>TS9</td>
<td>854.81±0.184</td>
<td>1.39±0.0</td>
<td>0.58±0.05</td>
<td>5.83±0.64</td>
<td>0.55</td>
<td>97.21</td>
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</tbody>
</table>

*n =3, mean±SD

Dissolution rate studies

Dissolution profiles of all controlled release osmotic pump formulations of silymarin ß-CD inclusion complexes prepared by co-precipitation method for three molar ratios (1:0.5, 1:1 and 1:1.5M) in pH 6.8 phosphate buffer solution (PBS) are illustrated in Fig 6.

Fig. 6: In Vitro Zero Order Release Profile of silymarin ß- CDosmotic formulations
Scanning Electron Microscope of the coat

The pores that are formed on the surface of the formulations prepared are characterized by SEM studies. Figure 7 shows the pore formed by dissolving the PEG 400 that was mixed with the osmotic coat solution Acrylcoat E30D as pore former.

Fig. 6: SEM images of the coat after dissolution study

Kinetics of dissolution studies

The final sets of nine formulations (TS1–TS9) were subjected to the dissolution study in phosphate buffer pH 6.8. The release profile of the formulations was subjected to the Zero Order, First Order, Higuchi, and Hixson-Crowell models.

Table 4: Values of different kinetic models

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>Formulation Code</th>
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<tr>
<td></td>
<td>TS1</td>
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<tr>
<td>Zero Order</td>
<td></td>
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<tr>
<td>R²</td>
<td>0.991</td>
</tr>
<tr>
<td>First Order</td>
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<tr>
<td>R²</td>
<td>0.989</td>
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<tr>
<td>Higuchi Kinetics</td>
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<td>R²</td>
<td>0.922</td>
</tr>
<tr>
<td>Hixson Crowell</td>
<td></td>
</tr>
<tr>
<td>R²</td>
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Table 5: n-values and b-values obtained according to Korsmeyer-Peppas and Weibull kinetic model.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Phosphate buffer pH 6.8</th>
<th>Korsmeyer-Peppas model</th>
<th>b (hrs)</th>
<th>T_{50}% (hrs)</th>
<th>T_{90}% (hrs)</th>
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<tr>
<td>TS1</td>
<td></td>
<td>n=1.065</td>
<td>0.313</td>
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<td>35.79</td>
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<tr>
<td>TS2</td>
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<td>n=1.280</td>
<td>0.433</td>
<td>14.64</td>
<td>25.76</td>
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<tr>
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<td>9.21</td>
<td>16.69</td>
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<tr>
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<td>n=1.911</td>
<td>0.682</td>
<td>6.33</td>
<td>10.48</td>
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<td></td>
<td>n=1.589</td>
<td>0.656</td>
<td>5.04</td>
<td>8.24</td>
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<tr>
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<td>0.987</td>
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<td>10.79</td>
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<tr>
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<td>n=1.360</td>
<td>0.697</td>
<td>3.31</td>
<td>5.58</td>
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</table>

DISCUSSION

Phase solubility studies were carried out in an aqueous system to calculate the stability constants, (Kc). The phase solubility diagrams made at ambient temperature showed that the solubility of silymarin increased linearly along with the concentration of β-CD, therefore they can be considered as AL-type diagrams, suggesting the formation of 1:1 complexes. Kc value in the range of 200- 500 M\(^{-1}\) indicates stronger interactions between drug and β-cyclodextrin and the value of Kc479M\(^{-1}\) hereindicated that the complex formed between silymarin and β-CD is quite stable. SEM studies of the prepared complex confirmed that the pure drug particles were small in size with reduced effective surface area due to agglomeration. They remained dispersed and physically adsorbed on the surface of β-CD in the co-precipitation method. Co-precipitated systems showed homogeneity, signifying the inclusion complex formation. DSC curve showed that the sharp endothermic peak at around 150\(^0\) C, which was observed for silymarin, decreased in the inclusion complex (1:1M). Furthermore, the wide peak at 90\(^0\) C, which was observed for β-CD, shifted to60\(^0\) C in the inclusion complex, indicating that the inclusion complex did not contain a much residue of Silymarin or β-CD.
and thus suggesting that the drug is well dispersed in the β-CD cavity. XRD study shows the
diffractogram of pure silymarin with intense peaks which are indicative of crystallinity. But
in the case of silymarin complexed with β-CD, diffractogram attributes to a new solid phase
with low crystallinity indicates inclusion complex formation (more water soluble). A reduced
number of signals, of markedly low intensity, are noticeable in the complex, indicating more
amorphous nature of the inclusion complex compared to the free molecules. The evaluation
of the core formulations, as well as osmotic coated formulations, showed all physicochemical
properties within IP limits in terms of hardness, friability, weight variation, disintegration
time and drug content. From dissolution study, it is seen that, there is a reflective effect of
both the variables i.e. drug- β- CD ratio and KCl concentration on the rate of dissolution of
the drug from the osmotic tablets. In formulation of TS1, TS2, and TS3, though the
concentration of KCl was in low, medium and high concentration respectively, there was
ineffective drug release from these formulations which may be due to less drug: β-CD
concentration. The concentration of drug release also reflects that this release may not be
enough to show profound pharmacological effect. In formulations where1:1Molar ratio of
drug β-CD was (TS4, TS5 and TS6) used along with 30mg, 50mg, 70 mg of KCl, there is
an increase in drug release, though the release of drug in TS4 is also not enough for effective
pharmacological effect. In TS5 and TS6 the drug release is faster in comparison to earlier
formulations. In formulation TS7 and TS8 where the concentration of drug: β-CD is 1:1.5M
and concentration of KCl is 30mg and 50mg, respectively, there is a steady release of drug for
11.5 hrs. This concludes that, formulations containing 1: 1.5 molar ratios of drug:β-CD ratio
along with 30mg or 50mg of KCl is optimum concentration to formulate a controlled porosity
osmotic tablet for around 10-12 hrs of drug release. In the case of TS9 due to high
concentration of both the variables there may be burst of the tablet which accounts for release
of drug in 5.5hrs. This also shows that the higher the concentration of β-CD ratio in inclusion
complexes, faster the dissolution. Same is in the case of concentration of osmogen. KCl,
higher the concentration of osmogen, more the internal pressure and faster the pore formation
and quicker the drug- β-CD coming out of the osmotic tablet. SEM studies of the coated
formulations confirmed generation of pores as PEG 400 gets dissolved, and through these
pores generated in the coat, the dissolution medium enters the core of the tablet where
osmotic pressure increases due to the presence of osmogen, KCL which then force the drug
complex outside to the dissolution medium through these pores that are generated.
Calculation of $R^2$ values confirms almost all formulations to show zero order release kinetics with Hixson-Crowell release pattern as predicted and valid as far as literatures. In order to verify the release pattern the Korsmeyer-Peppas and Weibull kinetic was employed. According to the n-value of the Korsmeyer-Peppas model, all formulations were following Case II Anomalous or Super Case II Anomalous law of diffusion. Case II generally refers to the erosion of the polymeric chain (Case-II release is the drug transport mechanism associated with stresses and state-transition in hydrophilic polymers which swell in water or biological fluids) and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

Further intrinsic study was performed to consider variation in the shape factor, so Weibull equation was employed. The shape factor ‘$b$’ as a Weibull function was determined for each of the formulations, which reveals a new story regarding the release pattern of the drug. Formulations TS2, TS4, TS5, TS6 and TS7 showed the $b$- value ranging between 0.39-0.69 suggesting diffusion in fractal or disorder substrate different from percolation cluster. The $b$ value of TS8 suggests diffusion in normal euclidean substrate with contribution of another release mechanism. TS9 suggest diffusion in normal Euclidean space whereas TS1 shows $b$ value less than 0.35 which is not found in simulation studies may occur in a highly disordered spaces that must be different from the percolating cluster. TS3 suggest diffusion fractal substrate morphological similar to the percolated cluster. [30-33]

CONCLUSION

Though the study reported here is preliminary step towards CPOP of silymarin still this study suggests that the CPOP formulations of Silymarin β-CD inclusion complex could be prepared which may reduce the current 140mg thrice a day dose to 156mg twice a day dose reducing the drug intake, improving the patience compliance and decreasing the drug related adverse effects and toxicity.

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