



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH

An official Publication of Human Journals

ISSN 2349-7203





Human Journals

Research Article

August 2016 Vol.:7, Issue:1

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

			
IJPPR		HUMAN	
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH		An official Publication of Human Journals	
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HUMAN JOURNALS

www.ijppr.humanjournals.com

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 3^2 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_{max} (2-4 hours) and $t_{1/2}$ (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 0.2 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 inclusion complexes by co-precipitation method

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 600 μ m 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 $\pm 0^{\circ}-001^{\circ}$ 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 600 μ m 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

Formulation Code	Drug: β -Cyclodextrin Ratio (mg)	KCl (mg)	Lactose (mg)	Mannitol (mg)	PVP (mg)	SLS (mg)	Talc (mg)	Magnesium Stearate (mg)	
TS1	1:0	156:0	30	318	318	10	10	5	3
TS2		156:0	50	308	308	10	10	5	3
TS3		156:0	70	298	298	10	10	5	3
TS4	1:1	156:361	30	137	138	10	10	5	3
TS5		156:361	50	127	128	10	10	5	3
TS6		156:361	70	117	118	10	10	5	3
TS7	1:1.5	156:542	30	47	47	10	10	5	3
TS8		156:542	50	37	37	10	10	5	3
TS9		156:542	70	27	27	10	10	5	3

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 $27\pm 2^{\circ}\text{C}$ 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°C to 35°C prior to dipping in the coating solutions. The air temperature of the blower was 45°C and 50°C . The coated tablets were dried at 55°C for 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 $37 \pm 0.5^\circ\text{C}$ 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.

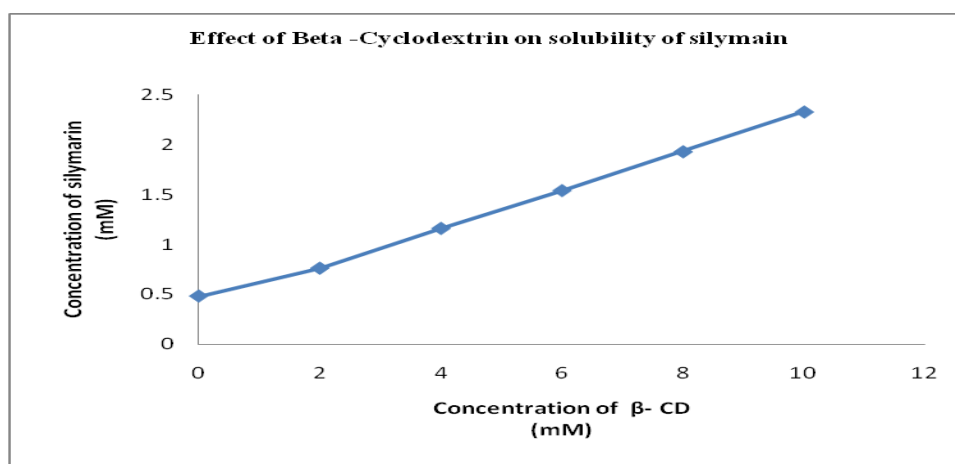


Fig. 1: Effect of β -cyclodextrin on solubility of silymarin

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.

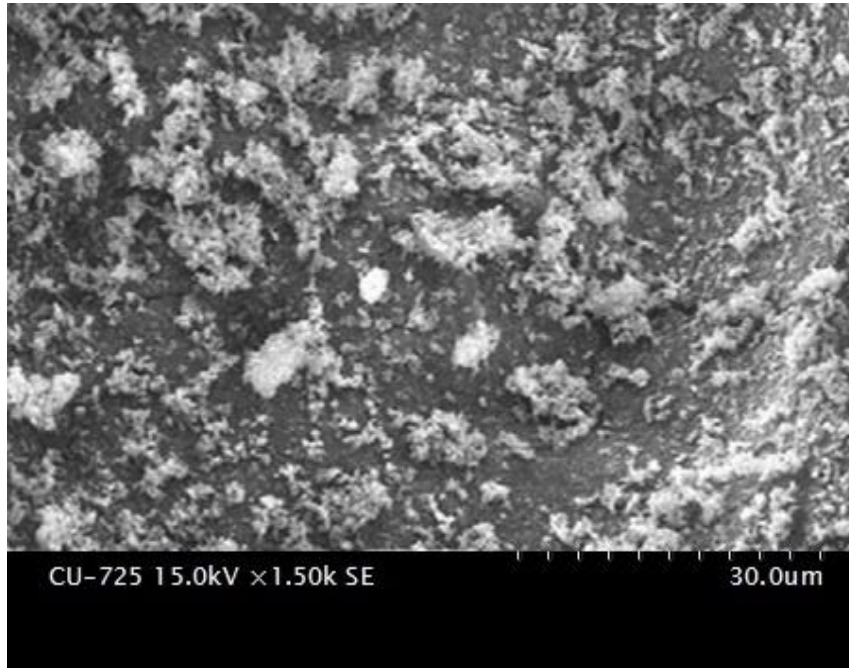


Fig. 2:SEM of silymarin drug

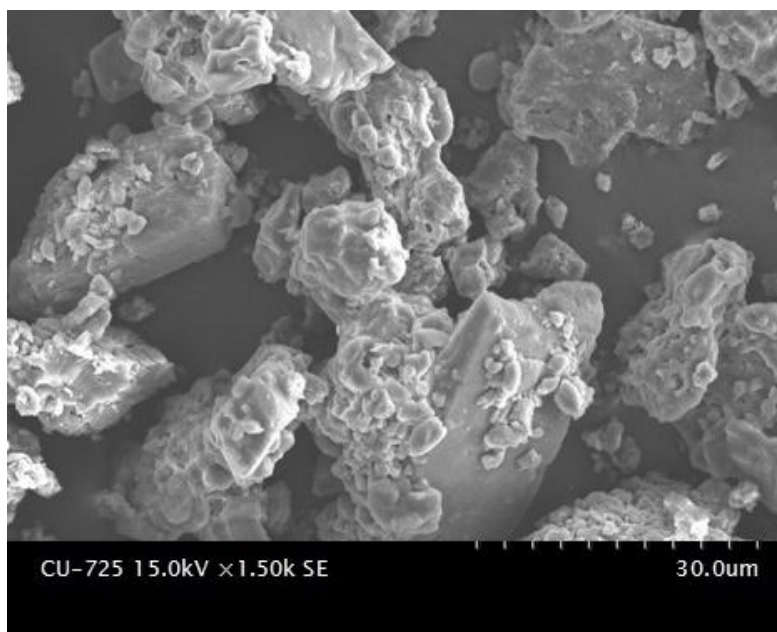
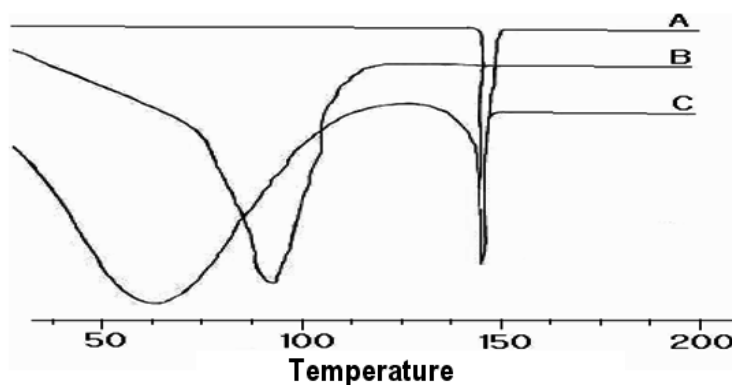


Fig. 3: Silymarin with β -cyclodextrin (Co-precipitation method)

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 : (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 coprecipitation method were represented in Fig 5. The peak position (angle of diffraction) is an indication of amorphous nature of the sample.

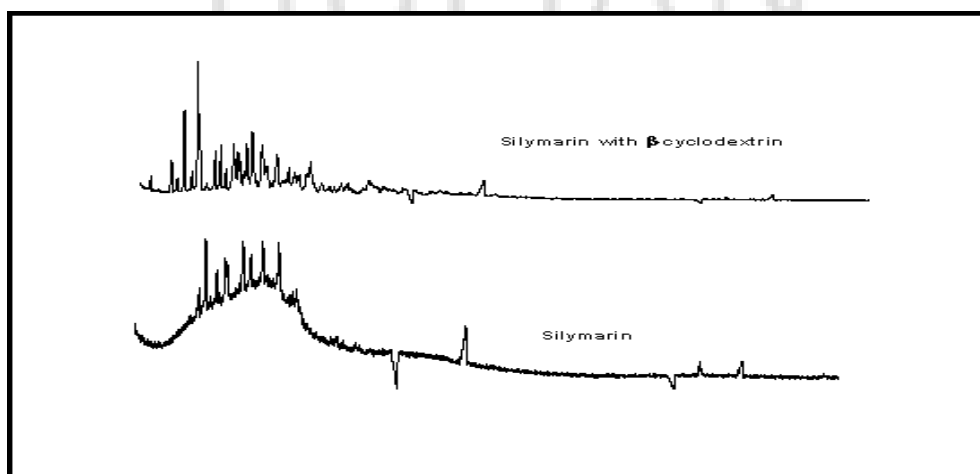


Fig. 5: X-Ray Diffraction Study on the Silymarin and Silymarin complexed with β -Cyclodextrin

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

Batch code	Weight variation (mg)	Diameter variation (cm)	Thickness variation. (cm)	Hardness. (kg/cm ²)	Disintegration Time (hr:min)	Friability (%)
TS1	849.13±0.315	1.40±0.01	0.55±0.00	6.12±0.21	0.51	0.002±0.00
TS2	850.42±0.721	1.41±0.03	0.57±0.12	6.45±0.23	0.55	0.001±0.00
TS3	848.05±0.432	1.39±0.07	0.54±0.01	6.03±0.12	0.52	0.000±0.01
TS4	851.22±0.231	1.39±0.20	0.56±0.04	5.98±0.5	0.49	0.002±0.01
TS5	847.32±0.247	1.40±0.06	0.55±0.11	5.92±0.14	0.48	0.003±0.02
TS6	849.11±0.618	1.38±0.03	0.55±0.00	5.96±0.19	0.45	0.001±0.03
TS7	852.10±0.163	1.38±0.02	0.57±0.05	5.57±0.5	0.40	0.003±0.03
TS8	849.01±0.215	1.42±0.12	0.54±0.03	6.12±0.3	0.58	0.004±0.01
TS9	853.81±0.284	1.38±0.03	0.57±0.05	6.23±0.16	0.65	0.002±0.03

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*

Batch code	Weight variation (mg)*	Diameter variation (cm)*	Thickness variation. (cm)*	Hardness. (kg/cm ²)*	Disintegration Time(hr:min)	Percentage Drug Content (%)
TS1	851.03±0.415	1.41±0.0	0.56±0.00	5.72±0.11	0.59	88.75
TS2	852.12±0.521	1.42±0.0	0.58±0.02	5.95±0.39	0.48	90.00
TS3	850.25±0.132	1.40±0.0	0.53±0.08	6.01±0.29	0.42	90.70
TS4	853.02±0.131	1.41±0.1	0.55±0.02	4.98±0.57	0.59	95.66
TS5	849.12±0.347	1.41±0.0	0.56±0.10	5.32±0.44	0.51	96.86
TS6	851.21±0.218	1.39±0.0	0.56±0.20	5.56±0.29	0.41	96.38
TS7	854.10±0.063	1.38±0.0	0.58±0.15	5.37±0.5	0.50	97.61
TS8	851.01±0.315	1.43±0.1	0.55±0.23	5.76±0.34	0.53	98.55
TS9	854.81±0.184	1.39±0.0	0.58±0.05	5.83±0.64	0.55	97.21

*n =3, mean±SD

Dissolution rate studies

Dissolution profiles of all controlled release osmotic pump formulations of silymarin β-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.

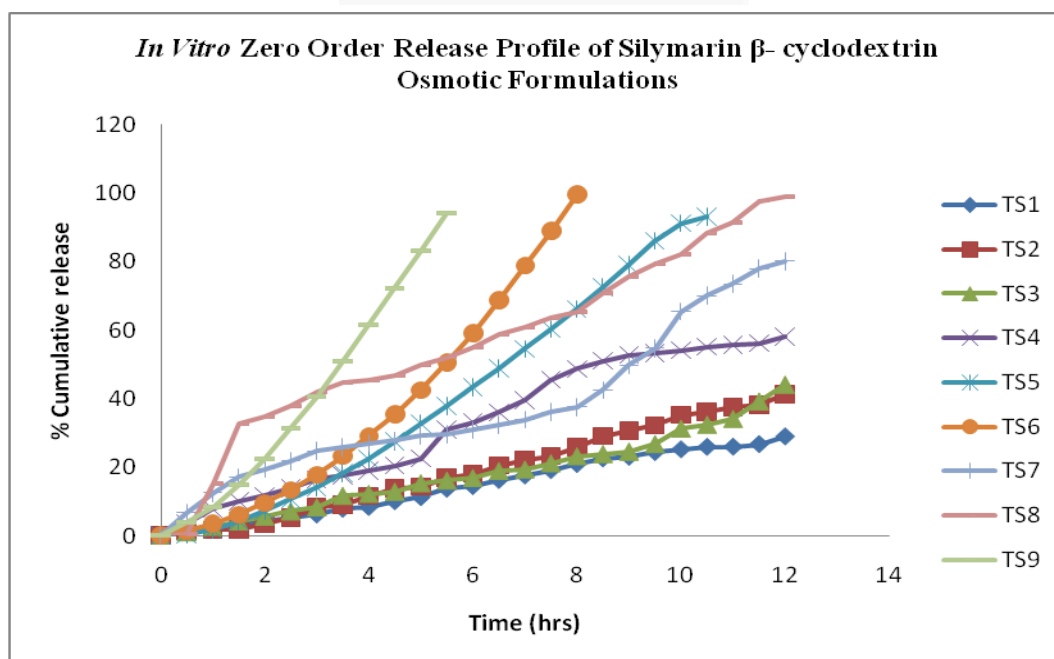


Fig. 6: *In Vitro* Zero Order Release Profile of silymarin β- CDosmotic formulations

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.

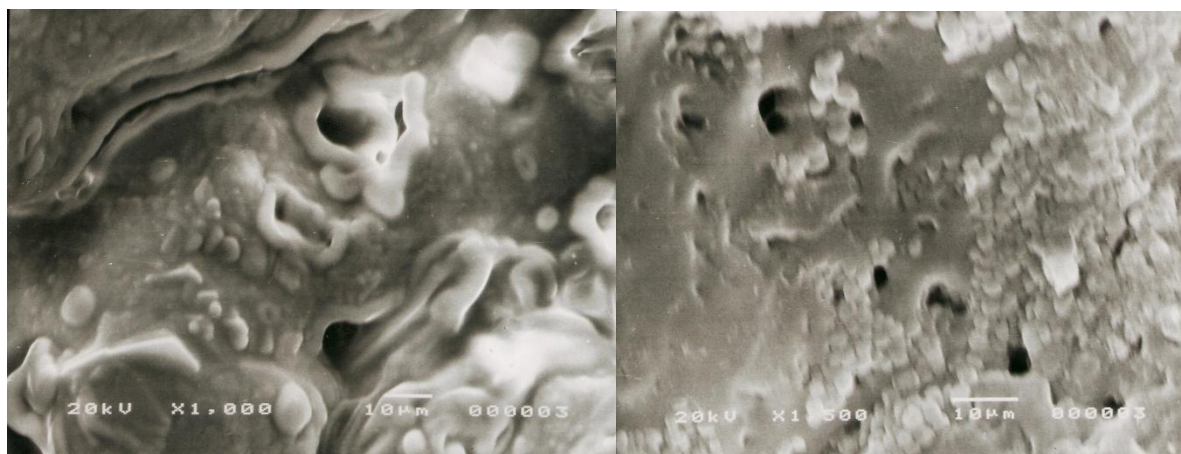


Fig. 6: SEM images of the coat after dissolution study

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

Kinetics	Formulation Code								
	TS1	TS2	TS3	TS4	TS5	TS6	TS7	TS8	TS9
Zero Order									
R²	0.991	0.992	0.984	0.974	0.980	0.949	0.910	0.947	0.982
First Order									
R²	0.989	0.979	0.950	0.971	0.844	0.641	0.754	0.936	0.820
Higuchi Kinetics									
R²	0.922	0.899	0.904	0.917	0.853	0.788	0.826	0.688	0.839
Hixson Crowell									
R²	0.944	0.946	0.937	0.944	0.946	0.991	0.838	0.917	0.979

Table 5: *n*-values and *b*-values obtained according to Korsmeyer-Peppas and Weibull kinetic model.

Formulation code	Phosphate buffer pH 6.8				
	Korsmeyer-Peppas model		b	T _{50%} (hrs)	T _{90%} (hrs)
	n	Mode of transport			
TS1	1.065	Case II Anomalous	0.313	19.91	35.79
TS2	1.280	Super Case II Anomalous	0.433	14.64	25.76
TS3	1.081	Case II Anomalous	0.350	16.48	29.47
TS4	0.917	Case II Anomalous	0.520	9.21	16.69
TS5	1.911	Super Case II Anomalous	0.682	6.33	10.48
TS6	1.589	Super Case II Anomalous	0.656	5.04	8.24
TS7	0.769	Non-Fickian Anomalous	0.477	8.40	15.58
TS8	1.123	Super Case II Anomalous	0.987	5.23	10.79
TS9	1.360	Super Case II Anomalous	0.697	3.31	5.58

DISCUSSION

Phase solubility studies were carried out in an aqueous system to calculate the stability constants, (K_c). 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. K_c value in the range of 200- 500 M^{-1} indicates stronger interactions between drug and β -cyclodextrin and the value of $K_c 479 M^{-1}$ here indicated 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 $150^{\circ}C$, which was observed for silymarin, decreased in the inclusion complex (1:1M). Furthermore, the wide peak at $90^{\circ}C$, which was observed for β -CD, shifted to $60^{\circ}C$ 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 where 1:1 Molar 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 patient compliance and decreasing the drug related adverse effects and toxicity.

ACKNOWLEDGEMENT

The authors wish to thank the department of pharmaceuticals, Himalayan Pharmacy Institute, Majhitar, East Sikkim, for allowing us to carry out the research work in their laboratories. We also wish to thank Jadavpur University for allowing us to utilize their DSC, SEM and XRD facilities.

REFERENCES

1. Pradhan SC and Girish C. Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine. *Indian J Med Res* 2006; 124:491-04.
2. Luper SA. Review of plants used in the treatment of liver disease, Part 1. *Altern Med Rev* 1998; 3: 410-21.
3. Reynolds JEF. *Martindale the Extra Pharmacopoeia*. London: Pharmaceutical Press;2002.
4. Pepping J. Milk Thistle: *Silybum marianum*. *Am J Health Sys Pharma* 1999; 56:1195-97.
5. Saller R, Meier R and Brignoli R. The use of silymarin in the treatment of liver diseases. *Drugs* 2001; 61:2035-63.
6. Kren V and Walterova D. Silybin and silymarin – new effects and applications. *Biomed Pap Med FacUnivPalacky Olomouc Czech Repub* 2005; 149:29-41.
7. Wu JW, Lin LC and Tsai TH. Drug-drug interactions of silymarin on the perspective of pharmacokinetics. *J Ethnopharmacol* 2009; 121:185-93.
8. Loftsson T, Brewster ME and Masson M. Role of cyclodextrins in improving oral drug delivery. *Am. J. Drug Deliv* 2004; 2:1-15.
9. Nagarsenkar MS, Meshram R and Ramprakash G. Solid dispersion of hydroxypropyl a cyclodextrin and ketorolac: enhancement of *in vitro* dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity in rats. *J.PharmPharmacol* 2000; 52: 949-56.
10. Reddy MN, Chowdary KPR and Diwan PV. β - Cyclodextrin complexes of celecoxib: molecular modeling, characterization and dissolution studies. *AAPS Pharm Sci* 2004;6: article 7.
11. Salsa T, Veiga F and Pina ME. Oral controlled release dosage forms I. Cellulose ether polymer in hydrophilic matrices. *Drug Dev Ind Pharm* 1997; 23:929–38.
12. Theeuwes F. Drug delivery systems. *Pharm Ther* 198;13:149–91.
13. Eckenhoff B, Theeuwes F and Urquhart J. Osmotically activated dosage forms for rate controlled drug delivery. *Pharm Technol* 1981; 5:35–4.
14. Eckenhoff B and Yum S. The osmotic pump; novel research tool for optimizing drug regimens. *Biomaterials* 1981; 2:89–7.
15. Bindschaedler C, Gurny R and Doelker E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. *J ContRel* 1986; 4:203–12.
16. Verma RK, Mishra B and Garg S. Osmotically controlled oral drug delivery. *Drug Dev Ind Pharm* 2000; 26:695–8.
17. Verma RK, Krishna DM and Garg S. Formulation aspects in the developments of osmotically controlled oral drug delivery system. *J ContrRel* 2002; 79:7–27.
18. Santus G and Baker RW. Osmotic drug delivery; a review of patent literature. *J ContrRel* 1995; 35:1–21.
19. Verma RK and Mishra B. Studies on formulation and evaluation of oral osmotic pumps of nimusulide. *Pharmazie* 1999; 54:74–5.
20. Ramakrishna N and Mishra B. Design and evaluation of osmotic pump tablets of naproxen sodium. *Pharmazie* 2001;56: 958–62.
21. Ozdemir N and Sahin J. Design of a controlled release osmotic pump system of ibuprofen. *Int J Pharm* 1997;158: 91–7.
22. Theeuwes F: Elementary osmotic pump. *J Pharm Sci* 1975; 64:1987–91.
23. Loftsson T and Brewster ME. Pharmaceutical application of cyclodextrin in drug solubilisation and stabilization. *J Pharm Sci* 1996; 85:1017-25.
24. Kamal D, Ramana MD, Himaja M, Agarwal A and Garg V. Investigation of enhancement of solubility of norfloxacin beta cyclodextrin in presence of acidic solubilizing additives. *Curr Drug Deliv* 2007; 4: 21-5.
25. Renju P, Janakiramank, Jyoti H. Formulation and evaluation of taste masked oral suspension of cefuroxime axetil using hydroxypropyl-beta-cyclodextrin. *Asian j pharmclin res* 2016;9: 90-2.
26. *Indian Pharmacopoeia*. Govt. of India, Ministry of health and family welfare. New Delhi: 1996.
27. *British Pharmacopoeia*. Appendix-XII C (A) 159, (II): 749-50.

28. Becket G, Schep LJ and Tan MY. Improvement of the *in vitro* dissolution of praziquantel by complexation with α -, β -, and γ -cyclodextrin. *Int J Pharm* 1999; 179:65-1.
29. Shah SK, Tyagi CK, Jhade D, Pandey P. Oral control release microparticulate drug delivery study of aceclofenac using natural polymer. *Asian j pharm clin res* 2016; 9:229-35
30. Ritu BD, Gupta RR and Patel HV. Formulation and characterization of sustained release matrix tablet of metformin hydrochloride. *Int J of Pharma R Res* 2009; 1:49-3.
31. Chandira M, Venkateswarlu BS, Shankarrao JA, Bhowmik D, Jayakar B and Narayana TV. Formulation and evaluation of extended release tablets containing metformin HCl. *Int J of Chem Tech Res* 2010; 2:1320-29.
32. Lafuente CS, Fauci MT, Arevelo MF, Fuentes JA, Rabasco AM and Mura P. Development of Sustained release tablets of didanosine containing methacrylic and ethylcellulose polymers. *Int J of Pharmaceutics* 2002; 234:213-21.
33. Roy A, Roy K, Roy S, Deb J, Ghosh A and Ali KA. Response Surface Optimization of sustained release metformin hydrochloride matrix tablets: Influence of some hydrophilic polymers on the release. *International Scholarly Research Notices [Internet]*. 2012 [cited 2014 May 12]. Article ID 364261:10 pages.

