Influence of β - cyclodextrin complexation on lovastatin release from osmotic pump tablets (OPT)

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ABSTRACT

An extended-release osmotic dosage form was designed and the effect of β-cyclodextrin (BCD) inclusion complexation on the solubility of lovastatin in aqueous media was investigated. The lovastatin BCD solid systems were prepared by kneading method. The elementary osmotic pumps (EOPs) were prepared with lovastatin BCD complex with cellulose acetate (CA) and polyethylene glycol as plasticizer. The effect of the BCD molar ratio on enhancement of lovastatin dissolution rate and the influences of various parameters (e.g. drug –BCD ratio, molecular weight and amount of PVP, coating weight gain) on drug release profiles were investigated. The solubility and dissolution rates of lovastatin were significantly increased by using inclusion complexation. It was found that PVP K90 was a suitable hydrophilic polymer with thickening effect and had profoundly positive effect on drug release. The present results confirmed that dissolution rate of lovastatin BCD were greatly enhanced and this system has suitable solubility behavior in EOP tablet formulations.

Keywords: β-Cyclodextrin, Lovastatin, Inclusion complex, Elementary osmotic pump .

INTRODUCTION

Osmotically controlled oral drug delivery systems are available in various designs to control the drug release based on the principle of osmosis. Osmotic tablets offer many advantages like zero–order delivery rate, improving patient compliance, a high degree of in vitro–in vivo correlation (ivivc) and they are simple in operation.

In the 1970s, the elementary osmotic pump (EOP) was introduced by Theeuwes (1). Oral osmotic pump tablets generally consist of a core including the active agent, an osmogent and other common excipients, coated with semi permeable membrane. A delivery orifice drilled through the coating, provides a passage way for drug release by hydrostatic pressure created from the core osmogent when exposed to an aqueous environment (1, 2).

The rates of drug release from osmotic pump depends on the drug solubility and the osmotic pressure of the core; hence, these systems are suitable for delivery of drugs with moderate water solubility (3) .The push-pull osmotic tablets were developed in the 1980s and were used to deliver drugs having low to high water solubility (4,5). Products such as Ditropan® XL (oxybutynin chloride), Procardia® XL (nifedipine) and Glucotrol® XL (glipizide) are based on this technology. These pumps are in the form of a two layer tablet with a drug and a push layer. When the system comes in contact with an aqueous environment, both layers absorb water. The lower part, which does not have an orifice, swells and pushes the drug through the orifice as a solution or suspension in the upper chamber (6,7). However, this system has some disadvantages; firstly, laser drilling technology should be employed to drill the orifice next to the drug compartment (8). Secondly, lag time for drug release from osmotic pumps after coming in contact with the aqueous media is long (9). In contrast to push–pull osmotic system, EOP tablets are prepared by a simple technology without any lag time for drug release however an EOP system requires that the drug to be in solution in order to be delivered in a controlled predictable manner. If the drug is insoluble, an EOP will not function properly. There are several techniques which can be used to solubilize drugs. Solubilization by cosolvents, crystal modification, prodrug formation and complexation can individually or in combination be extremely valuable means for solubilization of drugs (10). One approach to overcome pharmaceutical solubility problems is

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complexation. Drug/cyclodextrin (CD) complexation has received considerable attention in the pharmaceutical field for the past few years (11-18). CDs have been playing a very important role in formulation of poorly water – soluble drugs by improving apparent drug solubility and/or dissolution through inclusion complexation or solid dispersion by acting as hydrophilic solid carrier. Okimoto et al. has investigated poorly water – soluble drugs such as testestrone, prednisolone, chlorpromazine, indometacin and naproxen complexation utilizing (SBE) 7m-β-CD in osmotic tablets (19-22). It has been reported that Sulfobutylether (SBE) 7m-β-CD could serves both as a solubilizer and osmotic agent (22). Gan et al. have reported recently an oral osmotic pump of glipizide with BCD inclusion complexation (23). The objective of the present study was to investigate the possibility of improving the solubility and dissolution rate of lovastatin by complexation with BCD in the EOP tablets. The drug/BCD ratio was optimized on the basis of release rate of lovastatin.

MATERIALS AND METHOD

Materials

Lovastatin from Fermic (Mexico), β-cyclodextrine(BCD) from Roquette, Polyvinily pyrrolidone (PVP) from BASF (Germany), Lactose from DMW (Netherlands), Hydroxypropylmethylcellulose (HMPC) from Shiethsu (Japan), Cellulose acetate from Fluka (USA), Pregalatinized Starch from Colorcon (UK), Triacetine, MG stearate and PEG300 from Merck(Germany) were used in this investigation. All other chemicals were of analytical grades except for those used in HPLC analyses which were of HPLC grade.

Phase solubility studies

Solubility studies were carried out according to the method described by Higuchi and Connors (24). Accurately weighed sample of lovastatin in quantities exceeding its aqueous solubility was taken into vials to which 15 mL of distilled water containing various concentration of BCD (0.5%, 1%, 1.75%, 2.5%, 5%w/v) were added. The suspensions were shaken at room temperature for a period of 48 hours. This amount of time is considered sufficient to reach equilibrium and then filtered through a 0.45μm membrane filter to obtain a clear solution for HPLC assay. All samples were analyzed using a high performance liquid chromatography (HPLC) system consisting of a Waters solvent delivery pump, a Novapak® C18 column (5 micron, Waters Co.) attached to a UV detector. Mobile phase was composed of acetonitril, phosphate buffer of pH = 7 and methanol (5:3:1). The flow rate was 1 ml/min and the detection wave length was set at 230 nm. Each sample was determined in triplicates.

Preparation of core tablets

Preparation of solid complexes of lovastatin and BCD were performed by the kneading method. The kneaded powders were prepared by mixing and kneading accurate amount of drug and BCD in molar ratios of 1:1, 1:2, 1:4 and1:6 respectively as BCD1, BCD2, BCD4 and BCD6. Lovastatin and different molar quantities of BCD were wetted in mortar with 25 % (w/w) ethanol and the mixture was kneaded in a mortar. The effect of the kneading time on the complexation was also investigated and 2 hrs kneading showed a little change on the complexation. The pastes were then dried at 40°C for 6 hrs until 2% moisture was remained and finally they were passed through a 600μm sieve.

The basic tablet core composition and various amounts of all excipients are listed in Table 1. The ingredients of each formula were passed through 600μm sieve, mixed sufficiently and then compressed into tablets using single punch tabletting machine (Erweka, Germany) with normal concave 11 mm diameter round punches. Each tablet theoretically contained 20 mg lovastatin, and total tablet weights were 480±10mg with and average hardness between 80-100 N.

Coating and drilling of tablets

Tablets were coated using a coating pan. The pan specifications were as follows: spherical stainless steel having 220 mm diameter and rotating speed of 20 rpm. The composition of coating solution used for coating of lovastatin EOP tablets is given in Table 2. The coating has been done using a spray gun with a nozzle diameter of 1.3 mm, spray rate of 5–7 mL/min, spray pressure of 5 bars and the hot air blower was set at 45 °C. After coating, the coated tablets were dried at 50°C for 24 hrs. All formulations were drilled by a high speed mechanical drill in the center of each tablet to obtain a uniform orifice with 700μm diameters.

Drug release and analysis

Drug release was determined by evaluation of the cumulative amount of drug released from EOP tablets using USP dissolution apparatus type II (paddle) in 900 mL phosphate buffer pH 7 with 2% SLS as the dissolution media at 37±0.5 °C. The media were agitated at 50 rpm and samples were taken at specified time intervals and analyzed at 230 nm for lovastatin contents by HPLC. The mean of six determinations were used to calculate the amounts of drug released from the sample. The amounts of drug released were plotted versus time as percent dissolved drug.

Table 1. Basic tablet formulation and varying range of all ingredients.

Ingredients	Basic amount (mg)	Varying range (mg)
Lovastatin[1]	20	20
β-cyclodextrin[2]	112.2	56.1-336.6
Lactose	267.8	43.4 -323.9
Sodium lauryl sulfate (SLS)	10	10
PVP K30	46	46
Pregelatinized starch	20	20
Mg stearate	4	4

[1,2] were mixed as BC1 ,BC2 ,BC4 and BC6 inclusion complex with other excipients.

Table 2. Coating compositions for lovastatin core formulations

Ingredients	Amount (mg)
Cellulose acetate	5.4
Polyethyleneglycol 300 (PEG300)	1.6
Triacetin	1.0
Talc	1.6
Acetone	480

Composition given in terms of %w/w, (total solids in the coating compositions 2%), average of coating weight for each tablets 9.6 mg (2% weight gain)

RESULTS AND DISCUSSION

Phase solubility studies

Lovastatin is insoluble in water and solubility was found to be 0.4 µg/mL in water of pH 6 at 25° C which is in good agreement with literature values (25). The phase-solubility diagram for the complex formation between lovastatin and β-cyclodextrin is presented in Figure 1.

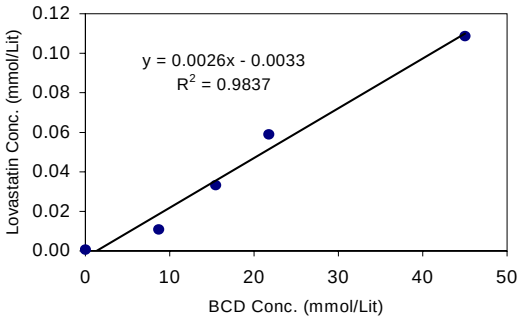

Figure 1. Phase solubility diagram for lovastatin in the presence of β-cyclodextrin in water at 25° ± 0.5°C

This plot shows that the aqueous solubility of the drug increases linearly as a function of β-cyclodextrin concentration. If the slope of the phase solubility diagram in general is less than 1, the complex stiochiometry will be assumed to be 1:1 and such profiles according to Higuchi and Connors are of A type. In the case of a 1:1 complex, using the following equation one may determine the equilibrium binding or association constant, $K_{1,1}$ from the slope of the linear portion of the curve.

$$K_{1..1} = \frac{slope}{S_o \circ (1 - slope)} \qquad \text{(Eq. 1)}$$

Where S_o is the intrinsic solubility of the drug under study. The value of the apparent stability constant obtained from the slope of phase solubility diagram was 2166 M^{-1} for many drug/CD complexes, binding constant values were in the ranges of 100 to 20000 M^{-1} which well within the range of 100 to 1000 M^{-1} are considered ideal (18). A small $K_{1:1}$ value indicates a too weak interaction, whereas a larger value indicates the possibility of limited drug release from the complex (26). The K showed that the lovastatin- β-cyclodextrin complexes are adequately stable at 1:1 ratios.

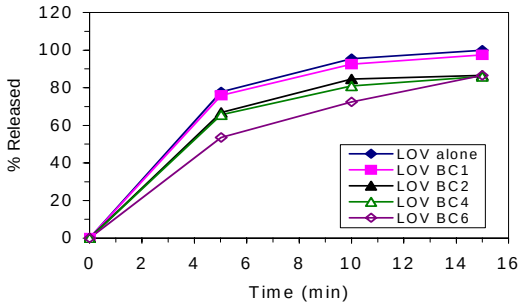

Figure 2. Dissolution of lovastatin alone and from lovastatin-BCD inclusion complex in phosphate buffer pH 7 with 2% SLS, N=3, data are presented as mean±SD.

Dissolution rate studies

The dissolution profiles of lovastatin alone and lovastatin β-cyclodextrin inclusion complex in four molar ratios (1:1, 1:2, 1:4 and 1:6) in pH 7 phosphate buffer solution (PBS) with 2% SLS are illustrated in Figure 2. It is clearly evident that lovastatin alone as well as LOV-BCD complexes exhibited high dissolution rate in PBS with 2%SLS; however, this dissolution media did not provide a discriminating power to distinguish solubility enhancement effect of BCD

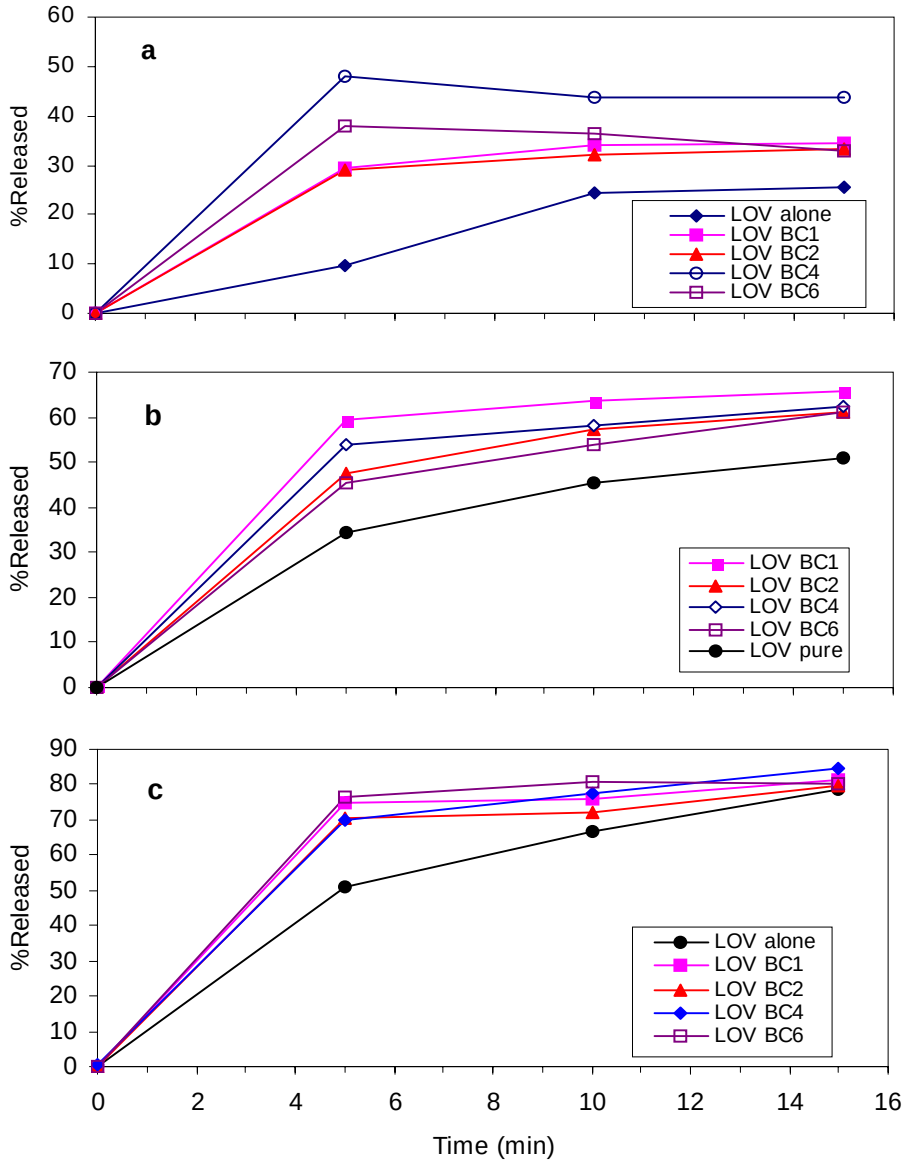

Figure 3. Effect of BCD ratio on lovastatin release from inclusion complex in various concentration SLS in PBS pH7 dissolution media comprised with lovastatin alone. (a: medium with 0.1% SLS, b: 0.2% SLS and c: 0.3% SLS)

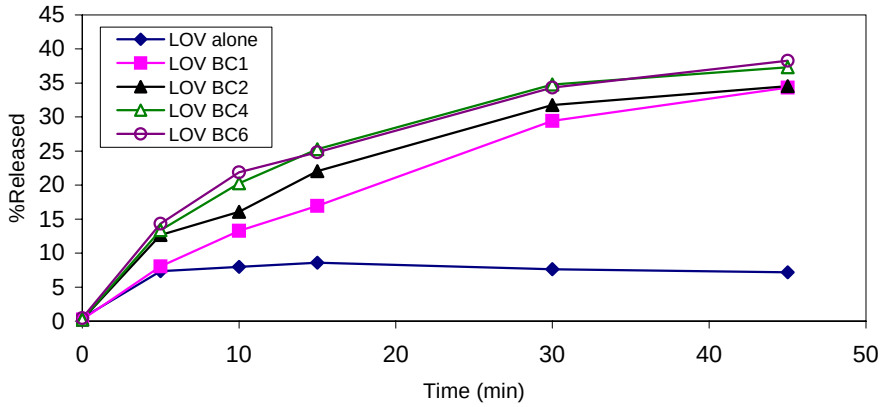

Figure 4. Effect of BCD ratio on lovastatin release from inclusion complex in PBS pH7 Dissolution media without SLS in comparison with lovastatin alone

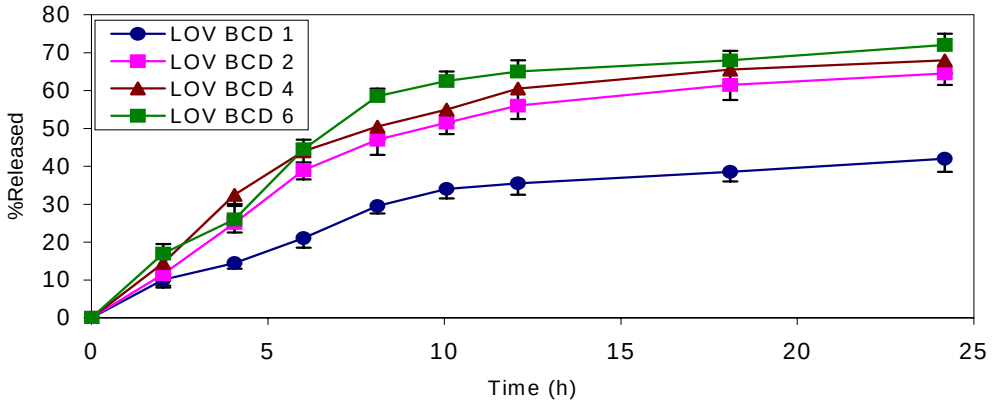

Figure 5. Influence of concentration of BCD on drug release from the EOP tablets, N=3, data are presented as mean±SD.

complexation. In selection a medium for dissolution testing the solubility characteristics of active ingredient must be considered. For water-insoluble and sparingly water soluble drug, use of a surfactant such as sodium lauryl sulfate is recommended (27). The need for surfactants, as well as their types and concentrations should be justified. To determine whether a dissolution method can discriminate different formulations, the method must be challenged. In conducting the challenge, the formulation change is evaluated versus the change of dissolution data and if the data show significant differences, the method may be considered as a discriminating test.

USP 28 describes PBS in pH7 with 2% sodium lauryl sulphate (SLS) as the dissolution medium for lovastatin tablets. Results showed that the high concentration of sodium lauryl sulphate in the USP dissolution medium does not allow the use of this test to distinguish between dissolution differences of the lovastatin and lovastatin BCD inclusion complexes. By decreasing the amount of sodium lauryl sulphate in the dissolution medium clear differences in the dissolution rates of the lovastatin and BCD complexes were observed. The effect of various concentrations of SLS in dissolution media on the dissolution profiles are shown in Figures 3a, 3b and 3c. The most discriminating medium was containing 0.2 % sodium lauryl sulphate. The release rate from lovastatin-BCD complex also increased by decrease in the concentration of SLS in the dissolution media. These results are consistent with the probability of having solubility competition between SLS and BCD in dissolution media. On the contrary, in the PBS without SLS the large, amount of BCD in lovastatin-BCD complexes exhibits higher dissolution rates as compared with SLS media (Figure 4). All the lovastatin-BCD complexes showed significant improvement in dissolution media as compared with lovastatin plain powder. This could be due to some probable interaction between lovastatin and BCD which might cause improved wettability, reduction in the crystalinity, and increase in surface area by inclusion into the hydrophobic cavity of the BCD.

Influences of tablet formulation variables on drug release

To study the effects of tablet formulation variables on the release profile, tablets with lovastatin β-cyclodextrin inclusion complex of four molar ratios (1:1, 1:2, 1:4 and 1:6) were prepared, coated with the same coating formulation and a 700 μm diameter orifice was drilled on one side of the tablets. Tablet cores consisted of drug-BCD complex and other conventional excipients such as osmogent filler (lactose), hydrophilic polymer and binder (PVP K30), filler and glident (pregelatinaized starch), wetting agent (SLS) and lubricant (Mg stearate) to form the core compartment.

Effect of lovastatin-BCD ratio on drug release in EOPs tablets

In vitro release profiles for BCDs elementary osmotic tablets are depicted graphically in Figure 5. It is clearly evident that the amount of BCD has a pronounced influence on the extent of the release profiles. BCD plays the role of hydrophilic carrier through inclusion complexation or solid dispersion to improve dissolution performance in EOP tablets. When EOP tablets are placed in the aqueous media, water penetrates into the core by diffusion through semi permeable membrane film. The solvation of the osmotic agents creates a constant osmotic pressure differences between the core contents and outside of the device and a viscous drug suspension is formed in situ within the coated tablets. The shell membrane is non-extensible and the hydration of the core causes increase in volume. This hydrostatic pressure pumps the suspension or solution out through the orifices. Depending on core ingredient

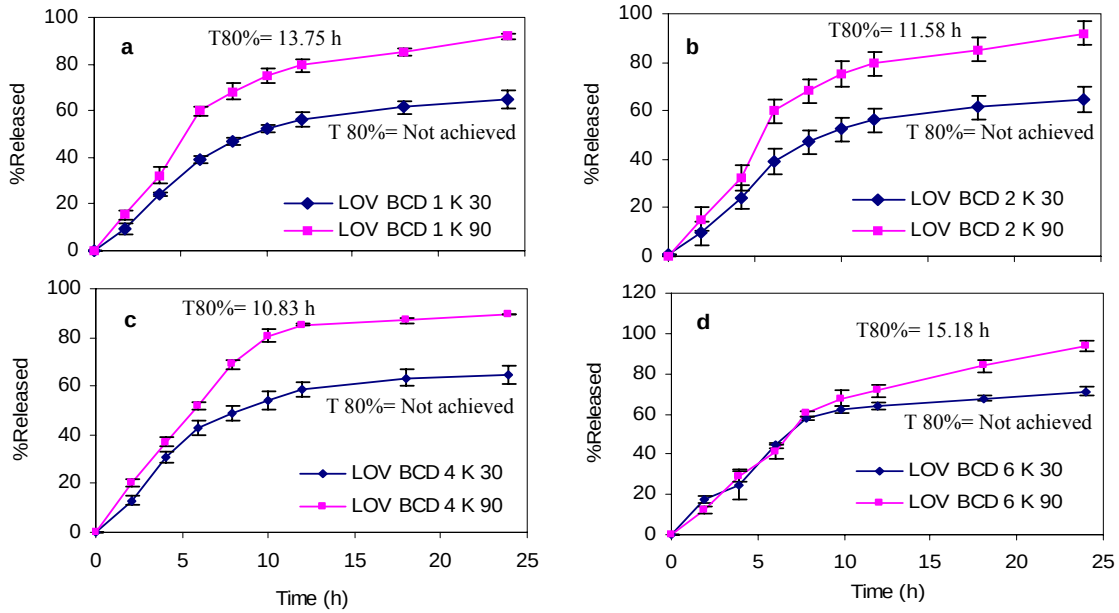

Figure 6. Effect of PVP molecular weight on lovastatin release in various BCD molar ratio from EOP tablets, N=3, data are presented as mean±SD.

solubility in the external media, internal contents can be released as either a solution or a suspension. As it is evident from, figure 5, the dissolution profiles shows higher and faster release profiles for BCD 2, BCD 4 and BCD compared to BCD 1 formulation. Two mechanisms have been proposed to be responsible for the increase in dissolution kinetics in this system. The first reason for this enhancement is better dissolution of lovastatin-BCD complexation and the second reason is the presence of higher amounts of BCD in formulation which enhances the viscosity of drug-polymer suspension; which increases stability of suspension as a result and inhibits precipitation of drug particles in suspension. The suspension is pumped out through the orifices and consequently, higher release rate could be obtained in the case of higher level of BCD. Similar results have also been obtained by other investigations (28, 29).

Influence of PVP molecular weights on drug release

Polyvinylpyrrolidone (PVP), a synthetic polymer made up of linear groups of 1-vinyl-2-pyrrolidone monomers forms molecular adducts with many substances and is frequently used in pharmaceutical formulation as a binder or hydrophilic carrier. This polymer is freely soluble in water and is available in different molecular weights, ranging from 10000 to 700000 Da. To study the influence of Mw of PVP on lovastatin release profile, PVP K30 and PVP K90 were incorporated into the tablets. Dissolution curves for BCD1, BCD2, BCD4 and BCD6 with PVP K30 and PVP K90 are shown in Figures 6a, 6b, 6c and 6d. These Figures show that PVP K90 had a marked effect on the rate and extent of lovastatin release. The $t_{80\%}$ values determined from percent cumulative drug release versus time plots and release curves confirmed effects of increase in viscosity of hydrophilic polymer on enhancement of dissolution rates described previously. It is obvious that the combination of inclusion complexation agent (BCD) and hydrophilic polymer with swelling behavior (e.g. PVP) had an appropriate and profound effect on the drug release.

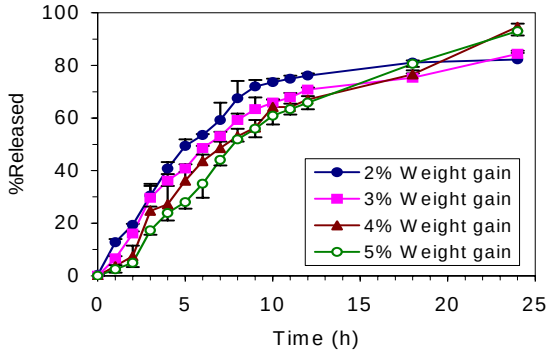

Figure 7. Effect of coating weight gain on lovastatin release from the developed EPO tablets. N=3, data are presented as mean±SD.

Influences of membrane variables on drug release

EOP core compartment is surrounded by a polymer which forms a membrane and contains water soluble additives as a pore former and at least one plasticizer which improves the properties of the film forming polymer. It is important to investigate membrane parameters responsible for drug release whereas the types and thickness of membrane have a profound effect on the drug release from EOP tablets. To study the influence of membrane

thickness on kinetics of lovastatin release, Eop tablets were coated with different weights of 2%, 3%, 4% and 5%, of the same coating solution. It was observed that the release rate decreased by increase in total weight gain and membrane thickness (Figure7). As the membrane thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased, which resulted in lowering the drug release rate. Figure 8 depicts the release rate, calculated from the zero–order release portions of the release profiles (mainly the first 8 hours), versus the inverse of membrane thickness.

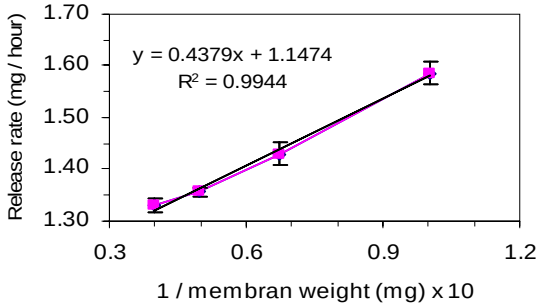

Figure 8. Relation between average release rates as a function of coating membrane weight, N=3, data are presented as mean±SD.

The plots are linear ($r^2 > 0.99$) in different formulations. The linearity of the plots exhibited a relation between the release rate and membrane thickness which can be described by an osmotic pressure driven release mechanism according to the following equation (30):

$$dm/dt = (AS / h)\ \sigma\ LP\ \Delta\pi$$

Where dm/dt is the zero order release rate of drug, A is the surface area of the film coated membrane, S is the solubility, h is the membrane thickness, σ LP is the hydraulic permeability of the membrane and Δπ is the osmotic pressure differences across the membrane at saturation state.

CONCLUSION

In the present study controlled release formulations of lovastatin were developed based on oral osmotic pump technology. The results obtained from solubility studies clearly indicate that the solubility of lovastatin increased by complexation with β-cyclodextrin. It was found that the ratio of β-cyclodextrin has profound positive effect on the drug release. Furthermore, the release rate of drug can be effectively modified using PVP with higher molecular weight. Moreover, the effects of coating weight gain on drug release were also investigated. The EOPs with thicker coating films showed longer dissolution time which is in agreement with the theoretical prediction. The properties of these systems, combining the benefits of a dispersion of lovastatin in an inclusion complex and using high molecular weights hydrophilic polymer, might results possibility of development a new formulation for controlled release purposes.

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