

# The Fabrication And Evaluation of the Formulation Variables of a Controlled-Porosity Osmotic Drug Delivery System with Diltiazem Hydrochloride

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Diltiazem hydrochloride (HCl) is an ideal candidate for a zero-order drug delivery system because it is water-soluble and has a short half-life. The study presented in this article used a controlled-porosity osmotic pump, which was prepared in the form of a bilayered tablet containing a drug compartment (pull compartment) and an osmogen layer (push compartment), for the delayed release of diltiazem HCl. The effects of various formulation and process variables such as the agitation rate, the pH of the dissolution medium, membrane thickness, surface porosity, and the concentration and nature of plasticizers were analyzed.

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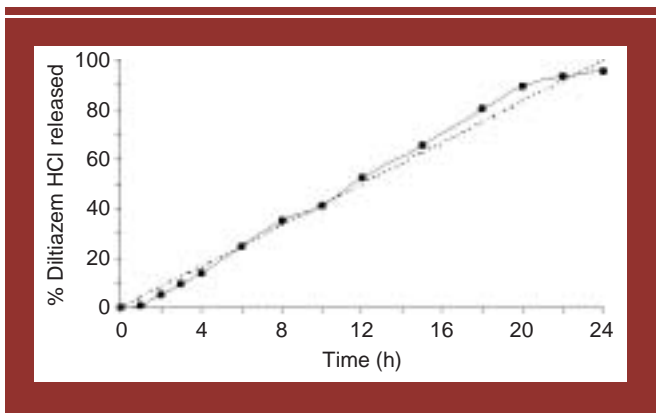
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**D**iltiazem hydrochloride (HCl) is a calcium channel-blocker drug used for the treatment of chronic stable angina pectoris and for angina pectoris caused by a coronary arterial spasm. Although ~90% of an orally administered dose of diltiazem HCl is absorbed, only 40% of the oral dose reaches systemic circulation in an unchanged form. The mean absolute bioavailability of diltiazem in normal subjects ranges from 33 to 44%. The drug undergoes rapid elimination that causes a short half-life (2–3 h), which dictates dosing at three times per day. Therefore, diltiazem HCl, with its low oral bioavailability, short half-life, and multiple daily dosing, is appropriate for a formulation in an extended-release, once-a-day dosage form.

Many drug delivery systems have been devised by various researchers to modulate and release a drug over an extended period of time. The majority of these systems are matrix-based, and their principal drug-release mechanism is based on drug diffusion through the matrix system. This diffusion is altered by the pH of the medium, the presence of food, and the body's physiological factors, all of which can cause difficulty in controlling the drug release rate. Another delivery method used is the osmotic drug delivery system. Unlike matrix systems, osmotic systems use the principle of osmosis as a driving force to release the drug from the system, and the release rate is unaffected by the body's pH and other physiological factors.

A survey of the literature indicates that extensive work was conducted in the development and fabrication of an osmotic drug delivery system for pharmaceutically active materials such as nifedipine, metoprolol, theophylline, and ciprofloxacin. Also, many attempts were made to develop osmotic pumps, which provide zero-order drug delivery for an extended period of time for many active drug substances (1–6). The drug-release mechanism from such systems can be explained by diffusion, osmotic pumping, and a combination of both (7).

Hence, in the study presented in this article, an osmotic drug delivery system for diltiazem HCl was devised and studied to reduce the drug's dosing frequency and to produce a zero-order drug release system. To begin this experiment, scientists explored using a microporous-membrane coating because of its



**Figure 1:** A dissolution profile (% diltiazem HCl released) of an optimized formulation in water. The dotted line represents a zero-order drug-release profile.

advantages such as a high flux of water into tablets, better control of the permeability and porosity of the membrane, and ease of formulation (8). Then, bilayered tablets of 240 mg of diltiazem HCl were prepared. The drug was incorporated with other excipients into one layer, and a suitable osmogen was incorporated into the other layer. The tablets were then coated with a microporous membrane consisting of plasticizers and a pore

former. Researchers studied the effects of various formulation variables, including the pH of the dissolution medium, agitation rate, porosity of the membrane, the type and concentration of the plasticizers, membrane thickness, and the osmotically active medium, on the performance of the dosage system.

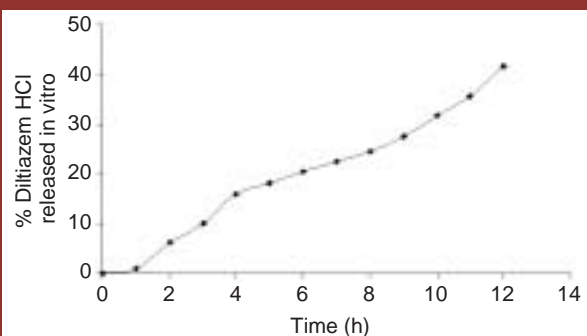
## Materials and methods

**Materials.** Diltiazem HCl was received from Cadila Healthcare Ltd. (Ahmedabad, India). Sodium chloride (S.D. Fine Chemicals, Mumbai, India), guar gum (H.B. Gum, Kalol, India), Carbopol 71G (Goodrich International, Bangalore, India), polyvinylpyrrolidone (PVP) K30M (ISP, Wayne, NJ), cellulose acetate (Eastman Chemical Company, Kingsport, TN), dibutylphthalate and glycerol (S.D. Fine Chemicals), polyethylene glycol 400 (India Glycols Ltd, Kashipur, Uttarpradesh, India), and triethylcitrate were used as received.

**Preparing a controlled-porosity osmotic pump.** Microporous membrane-coated bilayered osmotic tablets of diltiazem HCl were prepared by conventional wet granulation technology. Granules of the osmogen layer and drug layer that were equivalent to 2000 tablets were prepared with PVP K30M as a binder. Prepared granules were compressed as bilayer tablets using 11.9-mm standard concave round-shape punches in a 16-

**Table I:** The effect of sodium chloride and viscolyzing polymer concentrations (in the drug compartment) on the drug-release rate from the controlled-porosity osmotic pump.

Composition	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8
<b>Drug compartment composition, mg/tablet (variable)</b>								
Diltiazem HCl	240	240	240	240	240	240	240	240
Sodium chloride	20	40	60	80	60	60	60	60
Guar gum	—	—	—	—	25	50	75	100
Microcrystalline cellulose	125	105	85	65	60	35	10	20
PVP K30M	10	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
<b>Average weight</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>400</b>	<b>435</b>
<b>Push compartment composition, mg/tablet (constant)</b>								
Sodium CMC	100	100	100	100	100	100	100	100
Sodium chloride	50	50	50	50	50	50	50	50
Carbopol 71 G	50	50	50	50	50	50	50	50
Microcrystalline cellulose	55	55	55	55	55	55	55	55
PVP K30M	10	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
<b>Average weight</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>
<b>Coating composition, mg/tablet (constant)</b>								
Cellulose acetate	51.6	51.6	51.6	51.6	51.6	51.6	51.6	54.8
Dibutylphthalate	18.1	18.1	18.1	18.1	18.1	18.1	18.1	19.2
Glycerin	10.3	10.3	10.3	10.3	10.3	10.3	10.3	11.0
Drug-release rate (mg/h)	18.4	16.7	16.4	16.3	15.1	14.3	13.3	12.8



**Figure 2:** The effect of the dissolution medium's osmosis on in vitro drug release from a controlled-porosity osmotic pump with diltiazem HCl.

station rotary tablet press (Cadmech Machinery, Ahmedabad, India).

Diltiazem HCl and excipients that were required to produce 2000 tablets were blended together. The alcoholic solution of PVP was added to produce a damp mass. The wet mass was passed through a #16 sieve and dried in a hot-air oven at 60 °C for 2 h. The dried granules were passed through a #20 sieve and blended with lubricants. Granules for the push compartment

were prepared similarly. The tablets were compressed at an average weight of 670 mg. The weight of the push compartment was adjusted to 270 mg, and the pull compartment weight was adjusted to 400 or 435 mg. The tablets were coated with cellulose acetate along with suitable plasticizers and a pore-forming agent in a 12-in. diameter perforated stainless steel coating pan (Gans coater, Ganson Limited, Mumbai, India). A mixture of isopropyl alcohol and acetone in equal proportions was used as a coating solvent. A 12% (by weight) solid dispersion of a polymer was sprayed onto the tablets using the following conditions: Pan speed was 32 rev/min, inlet temperature was 40–45 °C, bed temperature was 35–40 °C, spray rate was 10 g/min, and atomization pressure was 2 bar. A coating was applied to the tablets to the amount of the required weight gain.

**In vitro drug release study.** Tablets were subjected to an in vitro drug release study using the USP Type II dissolution test apparatus. Operating conditions were  $37 \pm 0.5$  °C and a paddle speed of 100 rev/min with 900 mL of distilled water as the medium. Samples of 5 mL were withdrawn at every hour, and the same amount of liquid was replaced with fresh dissolution medium. Samples were filtered and suitably diluted, and the absorbance was measured at 237 nm in a double-beam UV–visible spectrophotometer (Shimadzu, Kyoto, Japan).

#### The effect of formulation variables on drug release.

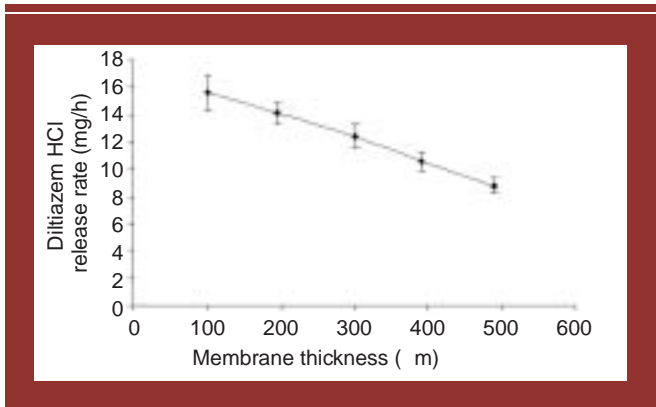
Drug release from osmotic tablets is affected by formulation variables. In this study, tablets were evaluated to analyze the effects of variables such as the presence of a viscolyzing polymer and an ionic compound in the pull compartment, membrane thickness, surface porosity, concentration and type of plasticizers, pH of the dissolution medium, agitation rate, and osmotic activity of the dissolution medium.

#### Results and discussion

**Operation of a controlled-porosity osmotic pump.** In a majority of cases, osmotic systems have a preformed passageway (pore formed by a laser beam) in the membrane from which the drug release takes place. Controlled-porosity osmotic pumps contain water-soluble additives in the coating membrane, which dissolve after coming in contact with water,

**Table II:** The effect of sodium chloride and sodium CMC concentrations (in the push compartment) on the drug-release rate from the controlled-porosity osmotic pump.

Composition	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
<b>Drug compartment composition, mg/tablet (constant)</b>							
Diltiazem HCl	240	240	240	240	240	240	240
Sodium chloride	60	60	60	60	60	60	60
Guar gum	100	100	100	100	100	100	100
Microcrystalline cellulose	20	20	20	20	20	20	20
PVP K30M	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2
<b>Average weight</b>	<b>435</b>	<b>435</b>	<b>435</b>	<b>435</b>	<b>435</b>	<b>435</b>	<b>435</b>
<b>Push compartment composition, mg/tablet (variable)</b>							
Sodium CMC	50	75	100	150	75	75	75
Sodium chloride	50	50	50	50	75	100	125
Carbopol 71G	50	50	50	50	50	50	50
Microcrystalline cellulose	105	80	55	5	55	30	5
PVP K30M	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2
<b>Average weight</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>	<b>270</b>
<b>Coating composition, mg/tablet (constant)</b>							
Cellulose acetate	54.8	54.8	54.8	54.8	54.8	54.8	54.8
DibutylPhthalate	19.2	19.2	19.2	19.2	19.2	19.2	19.2
Glycerin	11.0	11.0	11.0	11.0	11.0	11.0	11.0
Drug-release rate (mg/h)	8.4	10.5	12.8	13.6	12.6	13.7	14.2



**Figure 3:** The influence of controlled-porosity coating film thickness on the in vitro diltiazem HCl release rate (mg/h) from a controlled-porosity osmotic pump with diltiazem.

thereby resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes, and the drug release from these systems was found to be caused primarily by osmosis with simple diffusion playing a minor role (9–11).

**The effect of a viscolyzing polymer and sodium chloride in the drug compartment.** A preliminary trial with common excipients revealed a fast drug release rate at 20.6 mg/h from the system. Therefore, scientists attempted to retard the drug release from the system as suggested by McClelland et al. (12–13). Incorporating excipients that modulate the solubility of the drug within the system can be an ideal approach to control drug release. In this study, sodium chloride and guar gum were added to the drug compartment to alter the solubility of diltiazem in an aque-

ous medium and to alter the diffusion of the drug, respectively (see Table I). Preliminary batches were prepared by incorporating sodium chloride into the drug compartment. Sodium chloride was added to the drug compartment in 20-, 40-, 60-, and 80-mg increments. The push-compartment composition, which consisted of Carbopol 71 G (75 mg), sodium carboxymethyl cellulose (CMC) (100 mg), sodium chloride (75 mg), microcrystalline cellulose (40 mg), and lubricants, was kept constant during the preliminary study. The coating composition, % weight gain ( $12 \pm 0.7\%$  w/w), and membrane thickness ( $0.4 \pm 0.02$  mm) were also kept constant. The results revealed that incorporating sodium chloride at a concentration of 60 mg/tablet retarded the drug-release rate from 20.6 to 16.3 mg/h during a period of >12 h. No further improvement was achieved with a higher concentration of sodium chloride in the drug compartment. A viscolyzing polymer (guar gum) was added with the sodium chloride to the drug compartment for further retardation of drug release during a period of 15–16 h. Guar gum was added to the drug compartment in 25-, 50-, 75-, and 100-mg/tablet units along with 60 mg of sodium chloride as a solubility-modulating agent. A significant change in dissolution was observed with an increase in the viscolyzing agent's concentration in the tablets. The drug release rate decreased from 16.3 to 12.8 mg/h with an increase in guar gum concentration. In vitro drug release studies revealed that the formulation prepared with 100 mg of a viscolyzing agent (guar gum) and 60 mg of sodium chloride in the drug compartment fulfills the requirement for prolonging drug release during a period of 16 h.

The solubility of diltiazem HCl is >590 mg/mL at 37 °C. Be-

cause of its very high water solubility, the majority of the drug fraction was released predominantly at a first-order rate rather than the desired zero-order rate. Diltiazem HCl's solubility was reduced by incorporating sodium chloride into the pull compartment. Its solubility was 148 mg/mL in presence of 1 M sodium chloride. Furthermore, the presence of a viscolyzing agent retards the drug diffusion from the viscous matrix. The formulation prepared by a combination of a viscolyzing agent and

sodium chloride resulted in >85% of the drug released by zero-order kinetics during a 16-h period. Further change in the viscolyzing agent–sodium chloride concentration does not yield zero-order kinetics beyond 16 h. Hence, to keep the composition of the drug compartment constant, the push compartment was optimized to achieve the desired drug release.

**Optimizing the push compartment.** Osmogen and swellable ionic polymer concentrations were changed in the push compartment to select the optimum composition (see Table II) that provided sufficient pressure on the pull compartment for an extended period of time to achieve 24-h drug release from the system, which could mimic zero-order drug release kinetics. The results showed that both sodium chloride and sodium CMC

**Table III:** The influence of sodium chloride's concentration in the push compartment on the drug-release rate and  $Y_{720}^*$ .

Amount of sodium chloride	$Y_{720}$	Drug-release rate (mg/h)
50 mg	52.6	10.5
75 mg	55.9	12.6
100 mg	64.3	13.7
125 mg	67.8	14.2

\*% of drug release after 720 min.

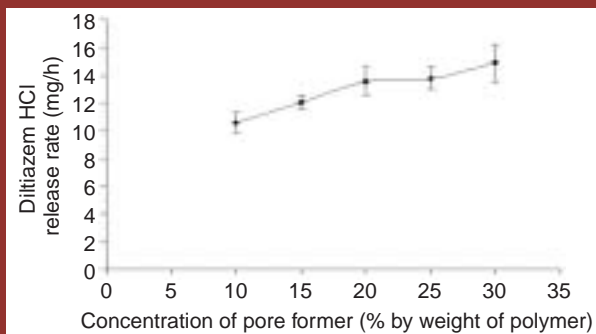
**Table IV:** The influence of sodium CMC's concentration in the push compartment on the drug-release rate and  $Y_{720}^*$ .

Amount of sodium CMC	$Y_{720}$	Drug-release rate (mg/h)
50 mg	43.6	8.4
75 mg	52.7	10.5
100 mg	59.8	12.8
150 mg	63.4	13.6

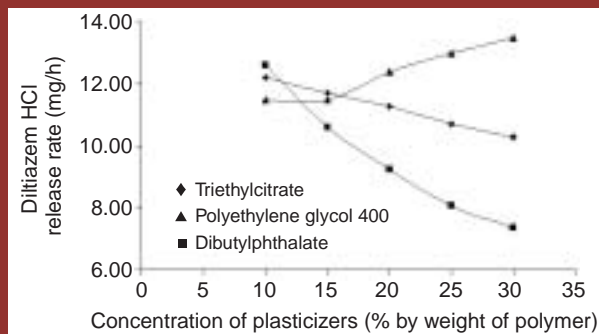
\*% of drug release after 720 min.

**Table V:** The effect of a pore former's concentration on drug release kinetics.

Concentration of pore former (% by weight of polymer)	Concentration of dibutylphthalate (% by weight of polymer)	Ratio of osmotic release kinetic to diffusion kinetic
10	35	3.8
15	35	4.0
20	35	3.7
25	35	2.4
30	35	2.1



**Figure 4:** The influence of a pore former's concentration (glycerol, % [by weight] of polymer) in the film on the diltiazem HCl release rate from a controlled-porosity osmotic pump.



**Figure 5:** The influence of concentrations and types of plasticizers (triethylcitrate, dibutylphthalate, and PEG 400) on the diltiazem HCl release rate from a controlled-porosity osmotic pump.

influence drug release (see Tables III and IV). Higher concentrations of sodium chloride and sodium CMC increased the release rate from the tablets because there was more pressure on the pull compartment. Water uptake increased with an increase in the concentration of sodium chloride and the swelling of sodium CMC by imbibing water to its maximum capacity to exert pressure on the pull compartment. A composition containing 75 mg of sodium CMC and 50 mg of sodium chloride (Batch A2) in the push compartment showed zero-order drug release kinetics for 24 h (see Figure 1). Carbopol 71G was added to the push compartment to maintain the integrity of the swellable hydrogel matrix. Carbopol 71G produced a stiff gel-like matrix in the tablets' push layer. This gel-like matrix helped maintain an integrated consistency in the push compartment without much loss of the water-soluble constituents from the compartment because of its gel-forming properties.

**The effect of an osmotically active dissolution medium on the drug release rate.** In vitro dissolution studies of tablets were conducted in osmotically active media. The external osmotic pressure was maintained at higher levels than the osmotic pressure generated inside the tablet. The drug release rate was tested in a 2.4% (by weight) magnesium sulfate solution (6 atm pressure) and water (0 atm pressure). An in vitro release rate was found to be 2.2 mg/h in a magnesium sulfate solution, although in water it was 10.6 mg/h. In the magnesium sulfate solution, the drug release rate was mainly attributed only to diffusion through the membrane, although in water, the drug release rate was mainly attributed to diffusion and osmosis. High in vitro drug release was mainly attributed to osmotic pressure generated inside the osmotic tablets. In an osmotically active medium, the osmosis phenomenon is stopped. These results were further confirmed by performing an in vitro drug release study by changing the medium instead of the method. An in vitro drug release study was conducted for 0–4 h in water (0 atm pressure) followed by 4–8 h in a 2.4% (by weight) magnesium sulfate solution (~6 atm pressure) followed by 8–12 h in water (see Figure 2). The results show a significant difference in the release rate in a different medium. From the previously mentioned results, one may conclude that the drug release from the tablets was mainly caused by diffusion in an osmotically active medium (14).

**The effect of membrane thickness.** The drug release rate from a microporous membrane was affected by overall membrane thickness (15). Tablets with varying coating thicknesses were prepared to demonstrate the effect of coating thickness on drug release. The drug release rate (mg/h) was measured using purified water as a dissolution medium. The drug release rate changed considerably with a change in coating thickness from 0.1 to 0.5 mm. A higher drug release rate (15.6 mg/h) was observed for tablets having a 0.1-mm coating thickness. On the other hand, for tablets with a 0.39-mm coating thickness, the drug release rate was 10.6 mg/h. Beyond a 0.39-mm membrane thickness, the initial lag phase for drug release was as long as 3 h, and the drug release rate was too slow at the terminal phase of the dissolution profile. An in vitro dissolution profile of tablets with varying coating thicknesses is shown in Figure 3. From this study, one can conclude that membrane thickness has a profound effect on drug release from an osmotic system. The release rate from an osmotic system is inversely proportional to membrane thickness. Increased membrane resistance to water diffusion resulted in a decreased drug release rate (16–17).

**The effect of surface porosity.** Drug release from controlled-porosity osmotic systems takes place through pores formed in situ. A microporous-membrane coating appears to be the key factor with respect to release kinetics. A change in the concentration of pore-forming substances in the membrane can alter the surface porosity of the membrane. Incorporating water-soluble additives into the membrane wall is the most preferred method for the formation of pores in a controlled-porosity osmotic pump (18). A water-soluble pore former dissolves on contact with water, leaving behind pores in the membrane through which drug release takes place. Drug release from such a system is independent of pH and has been shown to follow zero-order kinetics.

In this study, glycerol was used as a pore-forming additive at 20, 25, 30, 35, and 40% w/w concentrations of a film former. An in vitro dissolution study in water and magnesium sulfate was performed to study the effect of the pore former's concentration. The ratio of drug released by osmosis and diffusion was calculated at 3:8 when the glycerol content was 20% w/w of the polymer concentration (see Table V). At a higher concentration of glycerol (40% w/w), the ratio was 2:1. The results showed



that with a low concentration of pore former, drug release was mainly caused by osmosis; however, with a high concentration of pore former, the diffusion component increased (19). Furthermore, the drug release rate increased linearly as the pore-forming substance increased in the coating membrane (see Figure 4).

**Types and amounts of plasticizers.** Plasticizers modify the physical properties of polymers and improve their film-forming characteristics by changing their viscoelastic behavior. Plasticizers turn a hard and brittle polymer into a softer, more-pliable material and possibly make it more resistant to mechanical stress. These changes also affect the aqueous permeability of polymer films. The water permeability of a cellulose acetate film is relatively high and can be easily adjusted by selecting the proper concentration and type of plasticizers. Incorporating plasticizers into a cellulose acetate film lowers the glass transition temperature, increases the polymer-chain mobility, enhances the film's flexibility, and affects the film's permeability (20). In this study, three plasticizers were evaluated for their effect on a controlled-porosity osmotic pump with diltiazem HCl. The literature reports that an antiplasticization effect was observed at a low concentration of plasticizers (21–22). Plasticizer concentrations of 30% w/w and higher were used in this study to investigate the effect of the plasticizers' concentration on the drug release rate. Furthermore, at a low plasticizer concentration (below 30% by weight), the film was produced with low mechanical strength, which ruptured during an in vitro dissolution study. A significant difference was observed in the drug release rate with plasticizers such as polyethylene glycol (PEG)-400, triacetin, and dibutylphthalate. Figure 5 shows the relationship of the drug release rate to the concentration of different plasticizers. The diltiazem HCl release rate was found to be inversely proportional to the concentration of the dibutylphthalate, although it was directly proportional to the concentration of PEG-400. Hydrophilic plasticizers such as PEG-400 were found to increase drug release, whereas hydrophobic plasticizers (e.g., dibutylphthalate) were found to decrease drug release from the osmotic pump. A film that was produced with an increased concentration of PEG-400 was porous, whereas a film produced with a high proportion of dibutylphthalate developed pores only at the surface (23–24).

## Conclusion

Diltiazem HCl is released from a controlled-porosity osmotic pump predominantly by osmosis. Glycerin used as a pore former at a 20% (by weight) concentration of the polymer that contained 35% (by weight) water-insoluble plasticizers showed a zero-order release kinetic. The drug release rate decreased with an increase in dibutylphthalate and triethylcitrate concentrations; however, the release rate increased with an increase in the PEG-400 concentration. The coating thickness of 0.39 mm plasticized with 35% (by weight) polymer was found to be optimum as it showed a zero-order drug release rate for 24 h. Controlled-porosity osmotic tablets released the drug at a constant rate irrespective to the pH of the medium and the agitation rate.

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