Development of an osmotic pump system for controlled delivery of diclofenac sodium

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ABSTRACT: Based on an elementary osmotic pump, controlled release systems of diclofenac sodium (DS) were designed to deliver the drug in a zero-order release pattern. Osmotic pump tablets containing 100 mg DS were prepared and coated with either semipermeable (SPM) or microporous (PM) membranes. The tablet coats were composed of hydrophobic triacetin (TA) or hydrophilic polyethylene glycol 400 (PEG 400) incorporated in cellulose acetate (CA) solution, for SPM and PM, respectively. Variable tablet core compositions such as swelling polymers (PEO and HPMC) and osmotic agents (lactose, NaCl, and KCl) were studied. An optimized, sensitive and well controlled in vitro release design, based on the flow-through cell (FTC), was utilized to discriminate between preparations. The results revealed that the presence of PEG 400 in the coating membrane accelerated the drug release rate, while TA suppressed the release rate of DS. In the case of SPM, the amount of DS released was inversely proportional to the membrane thickness, where 5% (w/w) weight gain gave a higher DS release rate than 10% (w/w). Results of different tablet core compositions revealed that the release rate of DS decreased as PEO molecular weight increased. HPMC K15M showed the lowest DS release rate. The presence of lactose, KCl, or NaCl pronouncedly affected DS release rate depending on polymer type in the core. Scanning electron microscopy (SEM) confirmed formation of pores in the membrane that accounts for faster DS release rate. These results revealed that DS could be formulated as an osmotic pump system with a prolonged, zero-order release pattern.

Keywords: Cellulose acetate, polyethylene glycol 400 (PEG 400), controlled release, flow-through cell

1. Introduction

Controlled release (CR) drug delivery systems have received considerable attention in the past two decades with numerous technologically sophisticated products in the marketplace. The major benefits of CR products lie in the optimization of drug input rate into the systemic circulation in order to achieve an appropriate pharmacodynamic response. This in turn should add to product safety and reduce the extent and incidence of major adverse drug reactions due to more strict control of blood levels. Furthermore, with less frequent dosing, it is speculated that this should improve patient compliance and possibly maximize drug product efficacy in therapeutics (1). A number of designs are available to control or modulate drug release from dosage forms. The majority of oral CR dosage forms falls in the category of matrix, reservoir, or osmotic systems (2).

Osmotic drug delivery systems utilize osmotic pressure as the driving force for delivery of drugs. The pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrices and reservoirs), whereas drug release from oral osmotic systems is independent of these factors to a large extent (3-5). Thus, an appropriately designed osmotically controlled oral drug delivery system can be a major advance towards overcoming some problems associated with traditional CR systems. Osmotic pump systems have many advantages including reducing risk of adverse reactions, improving compliance of patients, and could exhibit comparable in vitro/in vivo drug release (6). In 1955, Rose and Nelson utilized the principle of osmotic pressure in drug delivery for the first time (7). In 1975, Theeuwees (6) further simplified the Rose-Nelson pump and developed a system known as the "Elementary Osmotic Pump" (EOP). In the EOP system, an active agent, having suitable osmotic pressure, is compressed in the form of a tablet, and then coated with a semipermeable membrane (SPM), and a small orifice is created in the membrane. In operation, the osmotic agent draws water through the SPM because...
of the osmotic pressure gradient and forms a saturated solution. As the membrane is non extensible, the increase in volume caused by imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. The EOP is simple to design and is well suited for drugs with intermediate water solubility (2,3,8,9). For delivery of poorly or highly soluble drugs, several modifications of the EOP were done, with the introduction of different systems based on principles of osmotic pressure such as the sandwiched osmotic tablet system (SOTS) (3), the push-pull osmotic pump (PPOP) (2,3,10), controlled porosity osmotic pumps (CPOP) (2,5,11,12), asymmetric membrane osmotic pumps (13-15), and the single composition osmotic tablet, SCOT (16).

Diclofenac sodium (DS) is a non steroidal anti-inflammatory analgesic with potent cyclooxygense inhibition activity and is commonly used for pain control and the treatment of rheumatic diseases. DS has biological half life of 2 h and is absorbed throughout the intestinal tract. The drug shows linear pharmacokinetics. DS is considered a good candidate for CR preparations due to its relatively short biological half life, also it would be advantageous to slow down its release in the gastrointestinal (GI) tract not only to prolong its therapeutic action but also to minimize possible side effects encountered with frequent administration (17).

Some efforts have been made to prepare osmotically controlled release DS tablets (18-22). These studies used polymers such as HPMC K4M and microcrystalline cellulose (19,21,22) in the tablet core with other additives such as sodium lauryl sulfate and talc (18-21). Different osmotic agents were incorporated in the tablet core such as potassium chloride (18-21), potassium bicarbonate (18,19), potassium carbonate (21), sodium chloride (21,22) and sodium carbonate (21). The tablet core was coated with a cellulose acetate (CA) membrane containing either castor oil (19-21), triacetin (TA) (18) or polyethylene glycol (PEG 400) (18-22) as plasticizers. It is worthy to mention that the in vitro evaluation of the prepared DS osmotic tablets have been carried-out using the conventional USP dissolution apparatus I (22) or USP II (18-21).

A previous in vitro release study to evaluate DS sustained release tablets of Voltaren Retard (Novartis – Switzerland) and Voltaren SR (Novartis – Egypt), using the more advanced flow-through cell (FTC) dissolution apparatus (USP IV), was carried out (23). This study describes an optimum condition for the FTC that is sensitive and capable of discriminating between different products and detecting variations in DS dissolution rate due to change of the manufacturing site of the product.

Thus, the objective of the present study was development of osmotically controlled release tablets of DS with different polymers in the tablet core such as HPMC K15M and polyethylene oxide (PEO) in the presence of lactose, potassium chloride, or sodium chloride as osmotic agents. Also, variations in coat thickness and membrane composition were studied. The in vitro evaluation of the prepared DS osmotic tablets were carried-out using our previously optimized FTC dissolution apparatus (23).

2. Materials and Methods

2.1. Materials

DS powder, polyethylene oxide (PEO) [M.W. 300,000, 900,000], hydroxypropylmethyl cellulose HPMC K15M (the viscosity of 2% water solution is 15,000 cps), and cellulose acetate (M.W. 30,000, 39.8% acetyl content) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Polyvinylpyrrolidone K-30 (PVP K-30) (M.W. 40,000), sodium chloride (NaCl), potassium chloride (KCl), sodium hydroxide pellets, potassium dihydrogen orthophosphate, mannitol, and polyethylene glycol 400 (PEG 400) were purchased from Rasayan Laboratories, Gujarat, India. Lactose was purchased from BDH, Poole, UK. Triacetin (TA) was purchased from Fluka, Buchs, Switzerland. Distilled water (Milli RO plus 10, Millipore, Billerica, MA, USA) was used. All other ingredients were of analytical grade.

2.2. Development of diclofenac sodium osmotic pump system

2.2.1. Tableting

DS powder was weighed, granulated with an alcoholic solution of PVP K-30, and then sieved through a 355 μm standard sieve (mesh number 42, US standard sieves, Fisher-Brand, USA). Granules were dried for 4 h at 50°C (drying oven, Heraeus, USA). All other ingredients were weighed to their specified amounts (composition of core tablets are listed in Table 1), sieved through a 710 μm standard sieve (mesh number 24, US standard sieves, Fisher-Scientific, Pittsburgh, PA, USA), then mixed with dried granules of DS. Blending of all ingredients was carried out simultaneously, after which, the blends were compressed into concave tablets (Single Punch Press Model 511-7-A, Strokes-Merrill, Bristol, PA, USA) with a round die (13 mm diameter) and a concave-face punch. The average tablet weight was adjusted to 400 mg, with each containing 100 mg DS.

2.2.2. Tablet coating and orifice formation

Coating solutions were prepared by dissolving cellulose acetate (CA) in acetone solution containing known levels of plasticizers (10% (w/v) total solids in acetone). The types and amounts of plasticizers for different formulations are listed in Table 1.

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The latter design of the FTC was previously designed and validated to carry-out the release rate studies because it was found to achieve optimal drug release i.e. large dissolution cell, free tablet position with turbulent flow conditions, 8 mL/min flow rate of dissolution medium. Dissolution medium consisting of phosphate buffer pH 6.8 was filtered (0.45 μm), degassed, and used throughout the study. Volume fractions were collected every half-hour for 6 h and analyzed spectrophotometrically (UV-Visible spectrophotometer DU-650, Beckman-Coulter, Brea, CA, USA) for DS content by measuring the absorbance at λ max 275 nm against phosphate buffer pH 6.8 as a blank.

2.4. Kinetic study of drug release data:

In order to describe the kinetics of drug release from DS osmotic tablets, various mathematical equations were applied such as:

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Core composition (mg)</th>
<th>Membrane composition (%)</th>
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<td>F2</td>
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Table 1. The compositions of osmotic pump tablets of diclofenac sodium (100 mg/tablet)

* PEO 300 000; PEO 900 000; HPMC K15M; NaCl (sodium chloride); KCl (potassium chloride); CA (cellulose acetate); TA (triacetin); PEG (polyethylene glycol 400).

Core tablets were coated with either a semipermeable membrane (SPM) using TA as a hydrophobic plasticizer or with a microporous membrane (PM) consisting of hydrophilic PEG 400 incorporated in CA. The coating was done using the dip-coating technique as described in other studies (13,24,25). Coating was continued several times until the desired weight gain was obtained (5 or 10% weight gain). For removal of the residual solvent, the coated osmotic tablets were allowed to dry in a drying oven at 50°C overnight. For SPM, an orifice was drilled manually on one side or both sides of the tablet with a sharp needle (3,8,26-28). The size of the delivery orifice was kept in the range of 550-600 μm diameter.

The prepared osmotic tablets were evaluated by visual inspection of the film smoothness, uniformity of coating, edge coverage, and luster. Thickness and diameter of tablets were measured before and after coating with a standard screw gauge (Shimadzu, Kytoto, Japan).

2.3. In vitro release study

The release rates of DS from the prepared osmotic tablets were determined, in triplicate, by employing the open system of the flow-through cell (FTC) dissolution tester (USP Apparatus IV, Dissotest CE-6 equipped with piston pump CY 7-50, Sotax, Basel, Switzerland) (23). Each tablet was placed in the 22.6 mm diameter cell according to the design described in Figure 1. A built-in filtration system (0.7 μm Whatman GF/F and GF/D glass micro-fiber, and glass wool) was used throughout the study. Temperature of the dissolution medium was kept at 37 ± 0.5°C. The latter design of the FTC was previously designed and validated to carry-out the release rate studies because it was found to achieve optimal drug release i.e. large dissolution cell, free tablet position with turbulent flow conditions, 8 mL/min flow rate of dissolution medium. Dissolution medium consisting of phosphate buffer pH 6.8 was filtered (0.45 μm), degassed, and used throughout the study. Volume fractions were collected every half-hour for 6 h and analyzed spectrophotometrically (UV-Visible spectrophotometer DU-650, Beckman-Coulter, Brea, CA, USA) for DS content by measuring the absorbance at λ max 275 nm against phosphate buffer pH 6.8 as a blank.

2.4. Kinetic study of drug release data:

In order to describe the kinetics of drug release from DS osmotic tablets, various mathematical equations were applied such as:

Table 1. The compositions of osmotic pump tablets of diclofenac sodium (100 mg/tablet)
Zero-order equation: \( \frac{dQ}{dt} = K_0 \)  \( (29) \)
First-order equation: \( \frac{dQ}{dt} = K_1 Q \)  \( (29) \)
Higuchi release model: \( Q_i = k_H t^{1/2} \)  \( (30, 31) \)

Where, \( Q \) is fraction of drug release at time \( t \); \( k_0, k_1 \), and \( k_H \) are release rate constants for zero-order, first-order, and Higuchi square root of time model, respectively.

2.5. Scanning electron microscopy (SEM) studies

A scanning electron microscope (JXA-840A, JEOL, Tokyo, Japan) was employed to observe the cross section of the semipermeable and the microporous membranes of the tablets before and after the release study. Each sample was sputter coated with gold using gold Sputter (S150A, Edwards, West Sussex, UK) before the SEM observation.

3. Results and Discussion

The release of drug from the oral osmotic system (OROS) is governed by i) total solubility and osmotic pressure of the core, ii) the hydraulic permeability of the membrane, iii) thickness and surface area of the membrane, and iv) the internal pressure (18). Osmotically CR systems require only osmotic pressure to be effective and are essentially independent of its environment. Thus, in light of the rather harsh and inconsistent conditions of pH and mixing in the digestive tract, this appears to be a good CR system for oral dosage forms (32). In this study, we investigated the effect of certain formulation variables on the release rate of DS from OROS including type and composition of coating membrane, the number of delivery orifices as well as variation of tablet core components.

3.1. Influence of membrane variables

The choice of the membrane components is an important aspect in the development of OROS. The membranes used for osmotic systems are categorized as: i) Semipermeable membrane (SPM) which allows the osmotic passage of water but do not allow solute molecules to pass to any appreciable extent. ii) Microporous membrane (PM) which allows free flow of water but offers a diffusion barrier to solutes. The release from these membranes is controlled by: i) the concentration difference and/or osmotic pressure difference across the membrane, ii) the permeability of the membrane to water and drug, and iii) the thickness of the membrane. Plasticizers can change visco-elastic behavior of polymers significantly; they can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes can affect the permeability of polymer films (33). The effect of type and amount of plasticizers as well as different membrane weight gain (membrane thickness) on the release of DS from OROS were studied.

The optimization of dissolution design might greatly affect the release rate results. Differentiating between formulations depends on the optimum choice of the criteria of the dissolution conditions (23). In this study, the selection of the dissolution design was chosen depending on a previous study describing the effect of different FTC designs on the release of DS sustained release tablets (23). The results revealed that turbulent flow of the dissolution medium pumped at a flow rate of 8 mL/min using either the large or small tablet cells was the ideal design for sustained release DS products. This design was capable of properly discriminating between products among other designs tested.

3.1.1. Effect of type of plasticizers

In this study SPM and PM were prepared and studied. For SPM, TA was incorporated in CA solution, two orifices were drilled (orifice size ~600 μm) on the side surfaces of the tablet using a sharp needle. For PM, PEG 400 was incorporated in CA solution. The total weight gain was adjusted to 10% (w/w).

Figure 2 compares the release profiles of DS from PEO 300,000 tablets with no osmotic agent, either coated with SPM or PM (F1 and F3, respectively). The figure shows that the amount of DS released was 16.23% versus 26.29% in the case of SPM (F1) and PM (F3), respectively. Thus, incorporation of PEG 400 into the coating solution gave a faster release rate of DS compared to TA, which might be due to the difference in hydrophilicity and hydrophobicity of the two plasticizers. Because PEG 400 is a hydrophilic plasticizer, it could be leached out easily leading to the formation of pores within the membrane, which increases the membrane permeability, thus, enhance drug release rate. In contrast, because TA is a hydrophobic plasticizer, with a low solubility of 1 part in 14 parts of water, and thus it would resist water
diffusion and, as a consequence, the drug release was less (33). This result was confirmed in a previous study done by Rani and Mishra (18), who reported that a higher rate and extent of DS release rate was observed from osmotic matrix tablets (containing HPMC K4M in the core) using PEG 400 compared to TA as plasticizers (porosigenic agents). Liu et al. (26) studied the influence of nature and amount of plasticizers on the release rate of nifidipine from osmotic pump tablets. Their results showed that films plasticized using PEG developed a completely porous structure after 24 h leaching, whereas films plasticized with TA retained their dense structure. Therefore, in our study a porous membrane was suggested to give a higher DS release rate than the non-porous semipermeable membrane.

Figure 3 compares the release profiles of DS from F1 and F2 containing PEO 300,000 with no osmotic agent, using two different ratios of CA:TA (2.0:1.5 and 2.0:3.0, respectively (Table 1). The results reveal that increasing the amount of TA to CA led to a decrease in DS release rate, where the amount of DS released was 16.23% versus 4.45% upon increasing the amount of TA. These results might be due to a decrease of the water permeability of SPM when increasing the amount of hydrophobic plasticizers (e.g. TA). Increasing the hydrophobic plasticizer led to a decrease in the molecular mobility of CA (2), thus, a decrease in the penetration of water into the system, and as a consequence, a lower osmotic pressure gradient and slower drug release was observed.

On the other hand, Figure 4 shows the release profiles of DS from F12 and F13 containing PEO 900,000 and KCl as an osmotic agent, using two different ratios of CA:PEG 400 (2.0:1.5 and 2.0:3.0, respectively). The results show that increasing the amount of PEG 400 in CA led to a simultaneous increase in the release rate, where the amount of DS released was doubled (viz. 25.68% versus 57.41% for F12 and F13, respectively) when the amount of PEG 400 was doubled. A previous study by Mishra et al. (21) was carried-out to evaluate the effect of membrane types on DS release from osmotic tablets using semipermeable (CA containing castor oil) and microporous (CA containing PEG 400) membranes. Drug release results showed that the microporous membrane coated batches gave more drug release. In addition, the PEG 400 (20%) containing batch gave a much higher drug release than the PEG 10% containing batch (21). The same results were obtained by Lu et al. (34), who studied the influence of the amount of PEG 400 incorporated in the coating membrane on the release of water insoluble naproxen. Their results showed that increasing the PEG 400 level, led to increased drug release rate, as the more PEG 400 incorporated in the coating solution, the more void space formed after leaching and, as a result, higher membrane permeability and higher release rate. However, the study clarified that a high percentage of PEG 400 (50%) in CA would make the membrane fragile, which was not observed in our study, where the two ratios of CA:PEG 400 (2.0:1.5 and 2.0:3.0) produced a relatively strong membrane. These membranes were capable of keeping their shape and integrity during the 6 h release study without any observed deformation or rupture of the membranes.

In general, in case of SPM, the membrane becomes stronger on addition of a high level of TA, and thus, slower drug release will be observed. On the contrary, in the case of PM, the membrane becomes more porous on addition of PEG, which in turn accounts for a faster release rate. These findings could be considered as important key factors and should be taken into account during manufacture of osmotic devices, as the osmotic device should release drug quickly and at the same time give a sufficiently high burst strength to prevent premature rupture and the attendant dose dumping in the GI tract (35).
3.1.2. Effect of membrane weight gain and number of delivery orifices

The osmotic delivery systems should contain at least one delivery orifice in the membrane for drug delivery, which should be optimized in order to control drug release from osmotic systems. Delivery orifices in osmotic systems can be created with the help of a mechanical drill (33), but for a commercial production scale, tablets need to be produced using a continuous process, and therefore, laser drilling is considered to be one of the most valuable techniques to create delivery orifices in osmotic tablets. However, due to the expense of using a laser-drilling machine, its use is limited to large-scale production, whereas, for research scale, reports have studied the use of other techniques, e.g. systems with passage ways formed in situ, use of modified punches, and indentation of the core which is not covered during coating (8,28,33).

To study the effect of membrane weight gain (membrane thickness) on DS release rate, tablets containing PEO 300,000 as a swelling polymer and mannitol as an osmotic agent, were coated with SPM to obtain tablets with two different weight gains (viz. 5% and 10% (w/w), F7-F10, respectively) (Table 1). The release profiles of DS from these formulations are shown in Figures 5A and 5B. It was clearly evident that the drug release rate decreased upon increasing the membrane weight gain. This result was observed in the presence of one or two delivery orifices (Figures 5A and 5B, respectively). On the other hand, it was found that increasing the number of delivery orifices increases DS release rate, which was clearly observed only in the case of tablets having 5% weight gain. The increase in membrane weight resulted in the increase of resistance of the membrane to water diffusion and a decrease in the rate of water imbibition, therefore, a simultaneous decrease in the rate of drug liquefaction, and as a result, drug release decreased (33). Similar results were obtained in previous studies (19,21), where a DS release rate from osmotic tablets was decreased with an increase in coating thickness of the semipermeable membrane. Therefore, tablet coat thickness might be a critical property of osmotic pump preparations and should be optimized to safeguard both the integrity of the system, during its trip through the GI tract, and the required release rate of the drug. However, the presence of two orifices was preferred, in case one orifice gets blocked. Also, Figure 5 showed a shorter lag time period in the presence of two orifices especially for tablets with a 5% weight gain (F9, Figure 5B).

3.2. Influence of tablet core components

Tablets with various core compositions were prepared and coated with a microporous membrane consisting of PEG 400 dissolved in CA solution. Total tablet weight gain, representing membrane thickness, was kept at 10% (w/w). For the microporous membrane, once the tablet comes in contact with the aqueous environment, the water soluble component (PEG 400) dissolves, and therefore, drug release from these systems occurs from the surface rather than from a single orifice (33). Different core variables were studied as follows.

3.2.1. Effect of hydrophilic swellable polymers

Figures 6A and 6B show the effect of PEO (MW 300,000 and 900,000) and HPMC K15M, on the release rate of DS in the presence of either NaCl (F5, F11, and F14) or KCl (F6, F12, and F15) as osmotic agents, respectively (Table 1). The results revealed that the release rate of DS decreased as PEO molecular weight increased while HPMC K15M showed the slowest release rate. Figure 6A shows that for DS osmotic tablets containing NaCl, the amount of DS released was 58.4%, 55.45%, and 9.27% using PEO MW 300,000 (F5), 900,000 (F11), and HPMC K15M (F14), respectively. While, with DS osmotic tablets containing KCl, the amount of DS released were 55.5%, 25.6%, and 4.04% for F6, F12, and F15, respectively. The presence of KCl, as an osmotic agent, compared to NaCl, generally slowed the release rate of DS to a certain extent depending on the kind and

![Figure 5](https://www.ddtjournal.com)

Figure 5. Effect of membrane weight gain on DS release rate from osmotic pump tablets; (A) One delivery orifice; (B) Two delivery orifices. Bars represent ± SD (n = 3).
containing either lactose (F4) or NaCl (F5) compared to F3 which contains no osmotic agents. Figure 7 shows an initial lag time of about 1 h in all formulations which is the time taken by the system to hydrate and solubilize the contents of the core before generating sufficient osmotic pressure to start drug release (36). The study revealed that the presence of osmotic agents increased the release rate of DS from 26.29% to 39.41% and 58.40% in the absence of osmotic agent, presence of lactose and NaCl (F3, F4, and F5, respectively). The higher release rate of DS obtained in the case of NaCl could be attributed to the fact that NaCl possesses a higher osmotic pressure (356 atm) compared to lactose (150 atm pressure), upon imbibition of water, both solutes absorb water and dissolve, but NaCl produces a more distinct osmotic gradient, which in turn allows faster release of drug (32).

It is noteworthy to mention that the two osmotic agents, i.e. NaCl (F5) and KCl (F6), gave almost the same release rate for DS from the two formulations (58.04% and 55.50%, respectively), which in turn concluded that addition of NaCl or KCl [osmotic pressure 356 and 245 atm, respectively (33)] gave the same release rate. These results might be important, and should be considered when proposing a formulation of an osmotic system containing DS, especially for hypertensive patients, where it is not recommended to incorporate sodium salts in their regimen.

3.3. SEM studies

Figure 8 compares the cross-sectional SEM micrographs of both SPM containing TA as well as PM containing PEG 400. Before dissolution, both coating membranes appeared to be integral and smooth with no visible imperfections (Figures 8A and 8C), also the PM showed no evidence of pore formation. After dissolution (Figures 8B and 8D), the coating membranes lost their integrity, and the pores were

![Figure 6. Effect of different hydrophilic polymers on DS release rate from CPOP tablets containing (A) NaCl and (B) KCl. Bars represent ± SD (n = 3).](image1)

![Figure 7. Effect of different osmotic agents on DS release rate from CPOP tablets containing PEO 300,000; F3 (absence of osmotic agent); F4 (lactose); F5 (NaCl). Bars represent ± SD (n = 3).](image2)
clearly evident. More pores were observed in PM with PEG 400 as compared to SPM with TA, which was possibly a result of the more hydrophilic nature of PEG 400 compared to TA. The obtained micrographs of the SEM correlated well with DS release rate results, which proved that the formation of pores in the membrane controlled DS release rate from the proposed osmotic systems.

3.4. Kinetic analysis of the data

By applying the linear regression method, and subjecting the release rate data of the CPOP tablets to different release kinetics and mechanisms (zero-order, first-order, and Higuchi diffusion model), all the controlled porosity osmotic pump formulations were found to follow the zero-order release model.

4. Conclusion

DS can be formulated in an osmotic pump system. The optimum choice of polymer type, osmotic agent, type and amount of plasticizer as well as membrane thickness could provide a prolonged, zero-order release pattern and it can be expected that the osmotic pump system will perform therapeutically better with improved patient compliance. However, an elaborate in vivo study, in human subjects, of these systems is required.

References


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