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THE EFFECT OF HYDRODYNAMIC CONDITIONS AND DELIVERY ORIFICE SIZE ON THE RATE OF DRUG RELEASE FROM THE ELEMENTARY OSMOTIC PUMP SYSTEM (EOP)

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ABSTRACT

The results obtained in this study indicate that the release of potassium chloride from EOP system is controlled by the agitation intensity and the nature of fluid flow. The size of delivery orifice has no effect on the delivery rate at low agitation speeds, but at higher agitation and under turbulent fluid flow, the orifice size has a significant effect. In the absence of delivery orifice in EOP system, the release of potassium chloride took place through the pores formed in the membrane with an initial lag period of about two hours.

INTRODUCTION

Research has been accelerating in recent years for developing new drug delivery systems. Different therapeutic systems using osmotic pressure as energy source have been introduced in the last years (1-5).

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The EOP is one of those new drug delivery systems. It consists of a solid core containing the drug, alone or with an osmotic agent, surrounded by a semi-permeable membrane which has a delivery port. The drug release rate from EOP has been described to be a) independent of the properties of the active material b) predictable and programmable c) independent of pH and agitation intensity d) independent of the delivery orifice within a specified range e) equal in vitro and in vivo (6,7,8). Indomethacin was recently introduced in Europe as EOP and was later recalled because of serious adverse reactions (9, and there is an increasing evidence that the wide range of characteristics claimed for the EOP delivery rate should be reexamined.

The present work tries only to assess the effect of agitation intensity, fluid flow pattern and delivery orifice size on the rate of release of potassium chloride from the EOP.

EXPERIMENTAL

1. Preparation of EOP

Potassium chloride was compressed into tablets using a rotary tablet machine with standard concave punches. No additives were used with potassium chloride. The tablets were coated using the air suspension method. Coating was provided by Merck-Frosst Research Laboratories in Montreal, according to the coating formulation described in the patent literature. The coated tablets were dried in an oven at $50^{o}C$ for one week, and drilled using a microdrill to make the delivery port. The actual orifice diameter was measured using microscopical method(A). The characteristics of the potassium chloride EOP used in this study are given in the following table. (Table I)

(A) Quantimet, 700 Leitz, West Germany

TABLE I

Characteristics of the potassium chloride EOP used in the study

Weight of potassium chloride tablet	403.43 mg	S.D. ± 7.595
The average of tablet diameter	10.44 mm	S.D. ± 0.0212
Tablet thickness	3.455 mm	S.D. ± 0.0599
Tablet hardness	7.0 kg	S.D. ± 0.32
Thickness of the membrane	156.1 µm	S.D. ± 10.04

(by Scanning Electron Microscope)(B)

2. Drug release as function of the agitation intensity

The delivery of potassium chloride from the EOP (orifice diameter 300 µm) was studied under different rotating speeds, and in different fluid flow conditions in a rotating basket (USP) and in the Turbula® shaker mixer(C). The Turubula - shaker is an agitating system based on the three dimensional movement of the release-cell around its axis. The release medium is bidistilled water (200 ml) at 37°C. Samples were taken at different intervals of time and analysed for K^+ using automatic flame spectrophotometer(D).

3. Drug release as function of orifice size: Different orifice sizes (70 - 500 µm) were drilled in the coated tablets using a microdrill. The delivery rate of potassium chloride was determined under the influence of different fluid motions.

(B) Joel ISM. 840, Tokyo, Japan

(C) Willy A. Bachofen, Basel, Switzerland

(D) Instrumental Laboratory, Lexington MA 02173

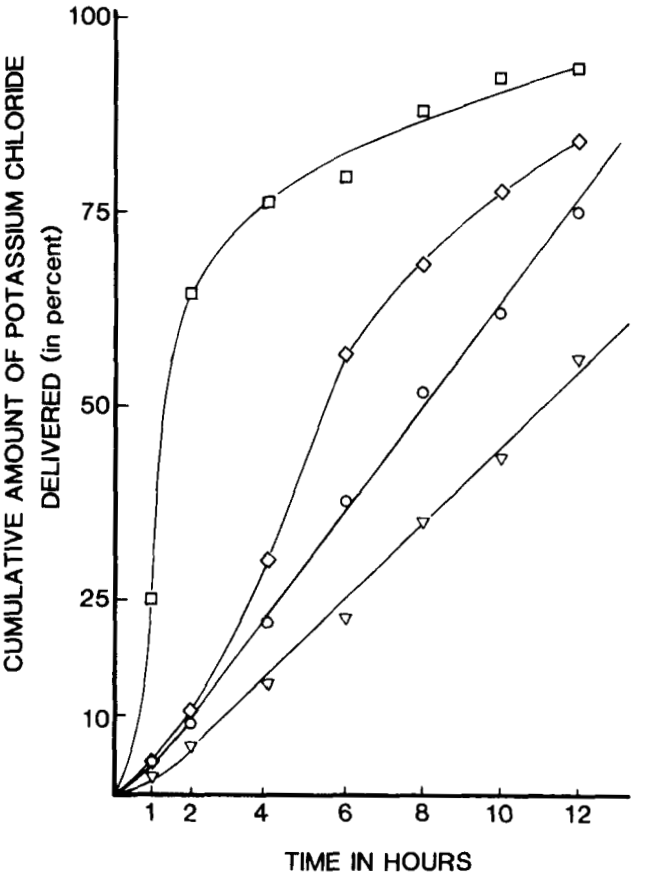

Fig. 1 : Release profiles of potassium chloride from the elementary osmotic pump (EOP) in bidistilled water at 37° C using the rotating basket apparatus at zero (▽), 50 (○), 100 (◇) and 250 rpm (□). (orifice diameter = 300 μm)

4. Drug release from systems without orifices: In order to simulate the complete blocking of the delivery port, the release of potassium chloride was studied under static and stirring conditions.

RESULTS AND DISCUSSION

Fig. 1 and Fig. 2 show the delivery profile of potassium chloride for the EOP's using the rotating basket method and Turbula-shaker under different rotating speeds. Using the rotating basket, the drug release

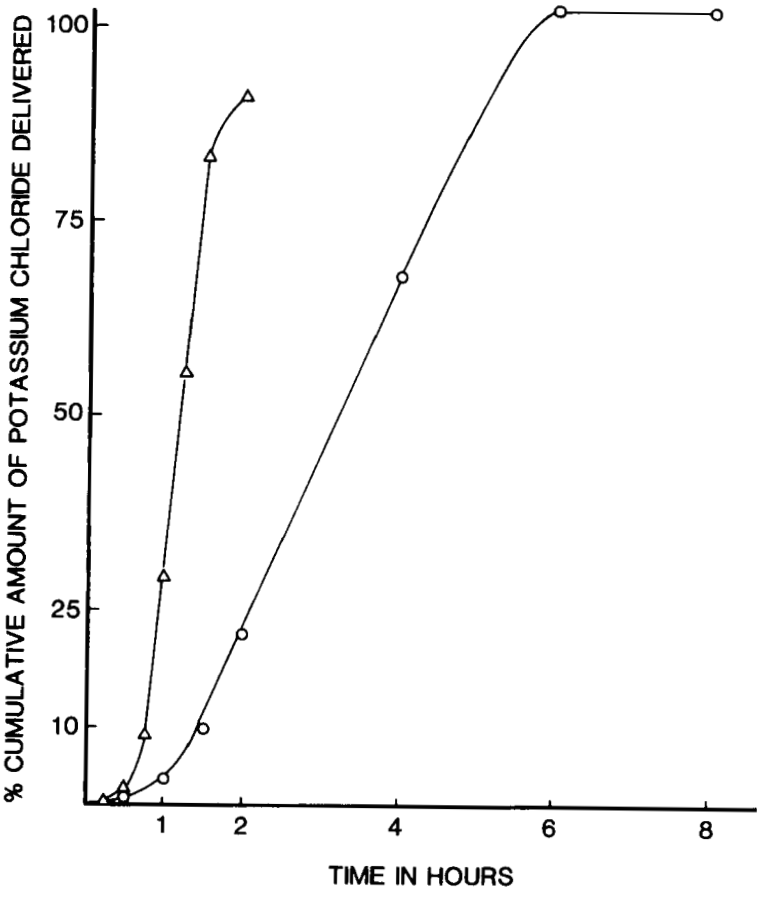

Fig. 2: Potassium chloride delivery profiles from the EOP in bidistilled water at 37° C using the Turbula mixer at 23 rpm (○) and 50 rpm (△), (orifice diameter = 300 μm).

follows a zero-order kinetic in static condition and at low stirring rates. 55-75% of the content, is delivered within 12 hours. At 100 and 250 rpm, the release rate deviates from a zero-order.

In the Turbula-shaker, the mass transfer of the potassium chloride increased with the increase of fluid velocity, and it was remarkably higher (for the same rpm) than the rotating basket. The increase in drug delivery as a function of fluid velocity, in both cases, could be explained by the fact that agitation increased water influx into

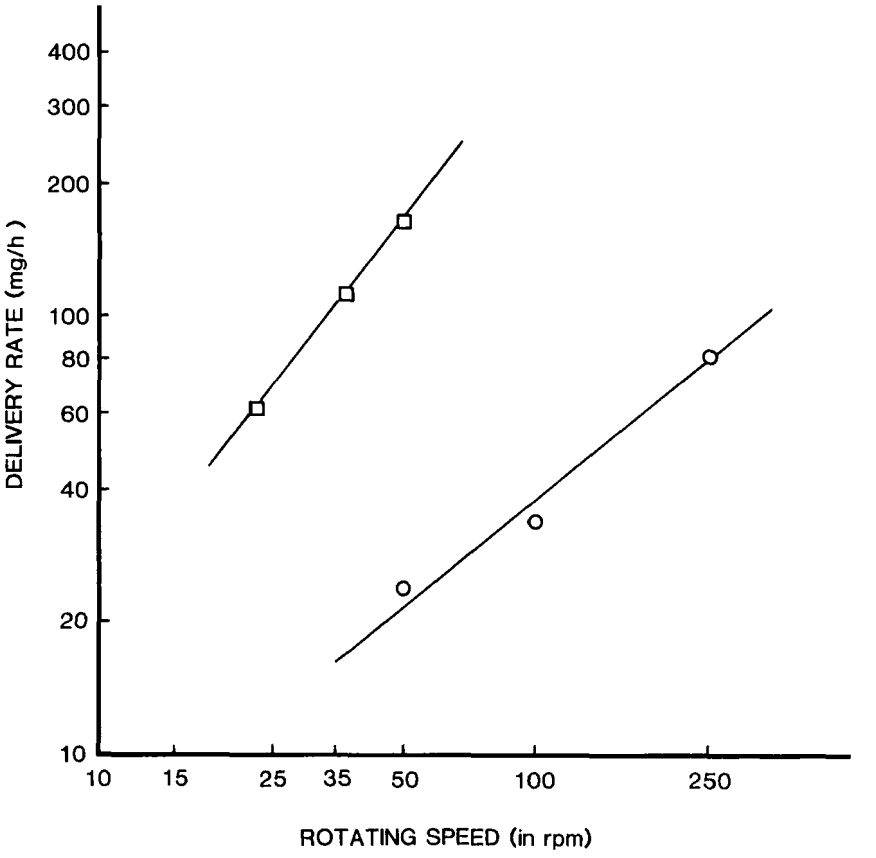

Fig. 3 : The effect of speed of rotation on the delivery rate using the rotating basket apparatus (○) and the Turbula mixer (□).

the core of EOP by forcing water through the pores of the membrane and/or through the delivery orifice. The improvement of the mixing conditions by the energetic movement and random agitation in the Turbula[10] accelerated the transport of potassium chloride and provided higher release rates (at lower rpm) than in the rotating basket.

Fig. 3 shows clearly the effect of the speed of rotation on the delivery rate of potassium chloride and illustrate the difference between the two methods. The log of delivery rate was plotted against the speed of rotation for the two processes. The slopes of the two curves were

calculated and the values obtained correspond to the exponent of the angular velocity ε in the following general equation (11, 12).

$$R = KC_s D^{\alpha} V^{\beta} \mu^{\varepsilon} A$$

when R = the flux rate of potassium chloride

K = proportionality factor

C_s = solubility

D = diffusion coefficient

V = kinematic viscosity

μ = flow velocity

A = geometric factor

α, β, ε, are exponents.

A value of 0,84 was calculated for the rotating basket curve and 1.28 for the Turbula-shaker. The remarkable difference of drug transport in the two agitating systems can be attributed to the transition of the flow from laminar to turbulent (10). At 50 rpm, the delivery rate of potassium chloride from EOP in the Turbula-shaker, is about 7 times the delivery rate in the rotating basket.

The effect of orifice size

The study of the release profile of potassium chloride from EOP, over a range of 70 - 500 μm orifice diameter reflects the role of hydrodynamic conditions. In static condition and at low agitation, there is no significant difference in the average release rates. However, at higher agitation speeds, and particularly in turbulent flow, the difference in release rates started to be evident. Fig. 4 and Fig. 5 show the delivery rate of potassium chloride from 150 μm and 300 μm delivery port at different fluid velocity. In turbulent flow conditions and under high rotating speeds, the difference becomes significant.

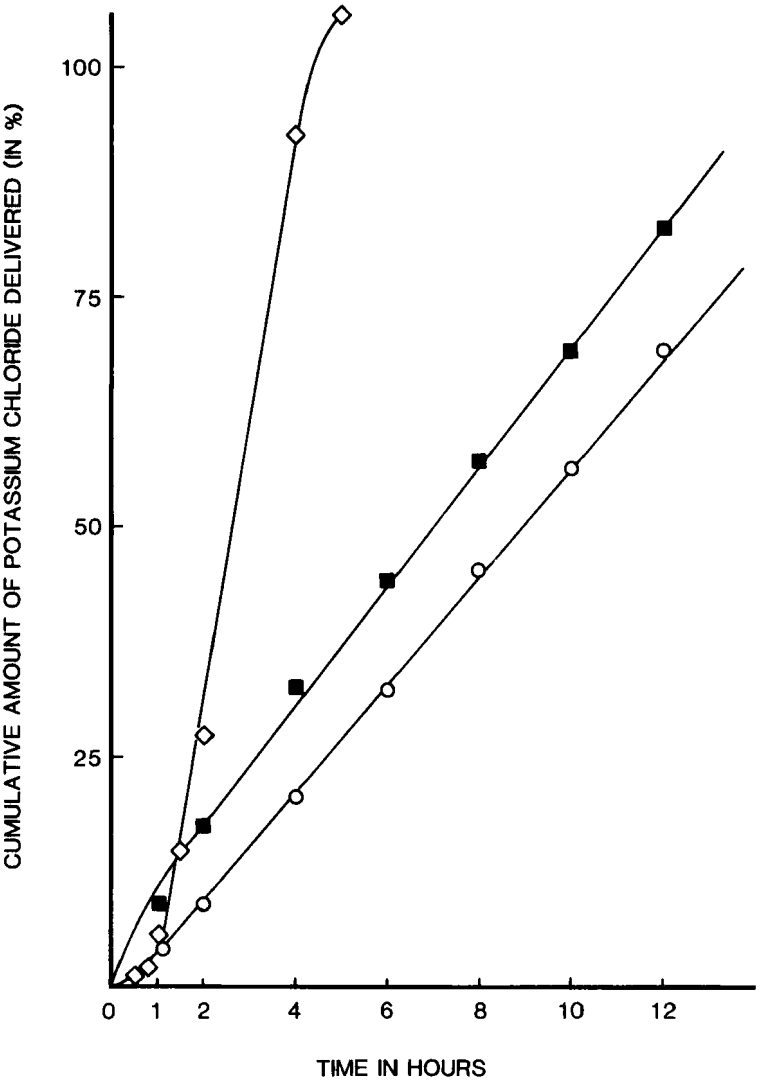

Fig. 4 : The release profile of potassium chloride from the EOP (orifice diameter = 150 μm) at 50 rpm (○) and 250 rpm (■) using the rotating basket apparatus, and 50 rpm using the Turbula mixer (◇).

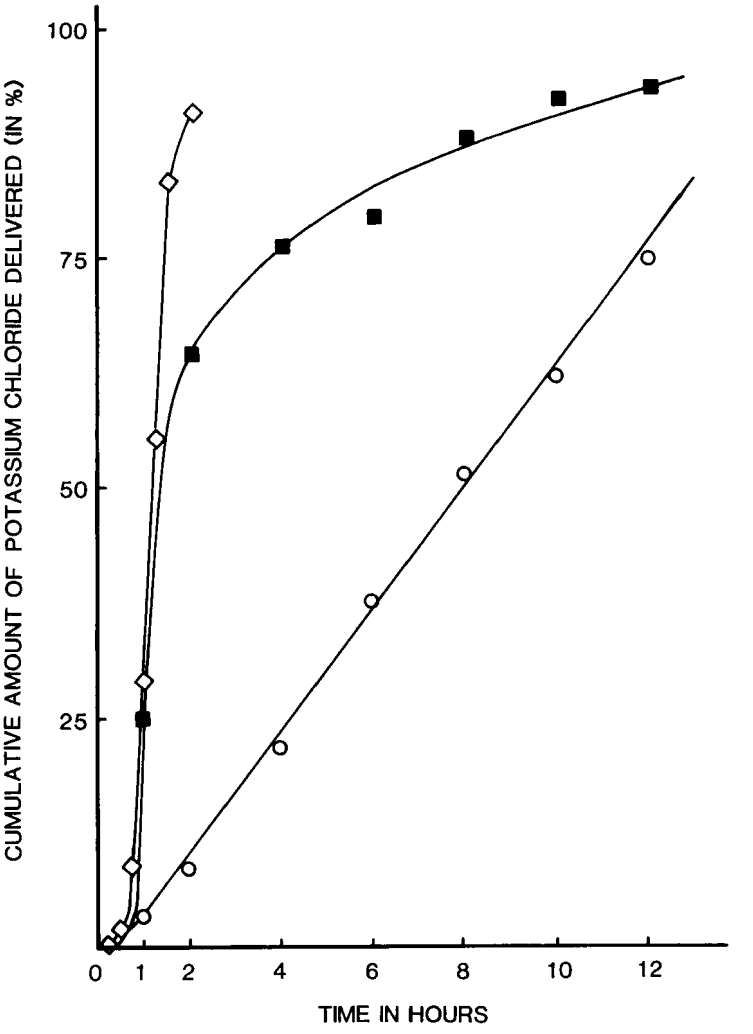

Fig. 5 : The release profile of potassium chloride from the EOP (delivery orifice diameter = 300 μm) at 50 rpm (○), and 250 rpm (■) using the rotating basket apparatus, and 50 rpm using the Turbula mixer (◇).

This finding could be attributed mainly to the increase of water influx through the delivery orifice.

Drug delivery from systems without orifices

It was interesting to notice that during the drug release studies, the volume of the coated tablet (system without delivery orifice) has increased and the shape changed when the tablet was kept for 2 hours in bidistilled water. The EOP did not change under these conditions. The release profile of potassium chloride from coated tablets (systems without orifices) and EOPs (orifice diameter = 300 μm) under static condition is given in Figure 6. An initial lag period of about 2 hours is noticed which can be attributed to the period required for the system to wet, absorb water or attract water, solubilize drug and to build osmotic pressure. The drug release from the coated tablet unlike the EOP, deviates from zero-order kinetics and contrary to what has been expected the drug delivery rate from the coated tablet after the lag period is higher than that from the EOP. To explain this phenomenon, we believe that the continuous water influx into the system produced an increase in the volume of drug solution inside the coated tablet, and this lead to increase in the hydrostatic pressure inside the tablet. The pressure generated caused the expansion or disruption of the membrane which in turn, lead to the formation of pore(s) on the membrane or increased in the size of the micropores. The permeability of the membrane was just enough to reduce the hydrostatic pressure within the system and to make the rate of water influx into the system equal to that of drug delivery. The high pressure formed inside the coated tablet accelerated the delivery of the contents (in solution form) through the formed pore(s) on the membrane. The delivery rate becomes controlled by the osmotic pressure and the permeability of the membrane (which depends on the formation of pores on the membrane and the size of these pores).

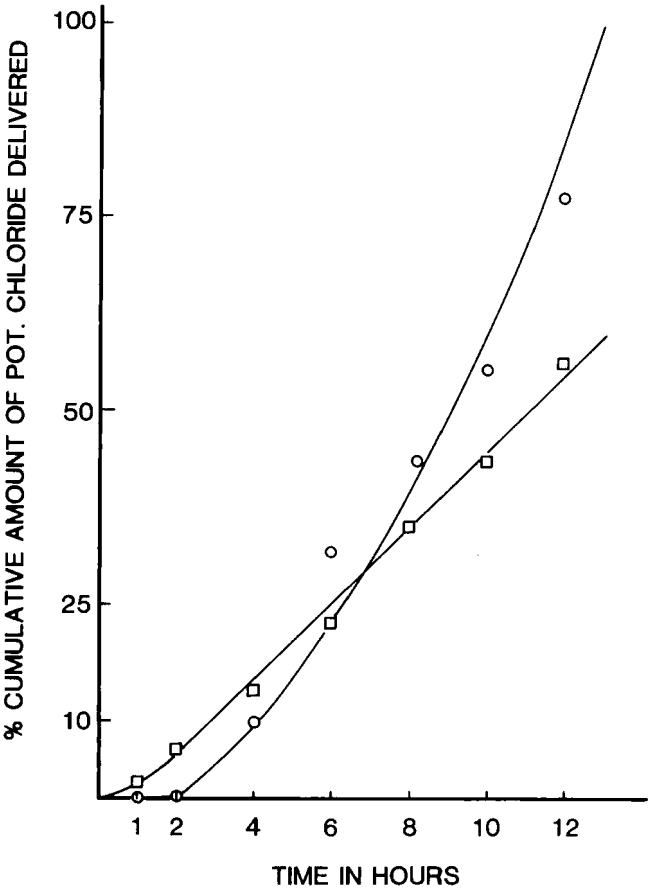

Fig. 6 : The release profiles of potassium chloride from the coated tablet without orifice (○) and from the EOP (orifice diameter = 300 μm) (◇) under static conditions.

Under high fluid motion (Fig. 7) the rate of delivery of potassium chloride becomes more significant. It follows a zero-order kinetics in both systems. In coated tablet there is an initial lag period of about 2 hours. The EOP however, delivers the drug at a higher rate than the coated tablets. This can be explained by the increase of water influx into the core of EOP by forcing water through pores of the membrane and through the orifice of the system. Since the volume of EOP remain constant (no swelling as in the case of coated tablets), therefore,

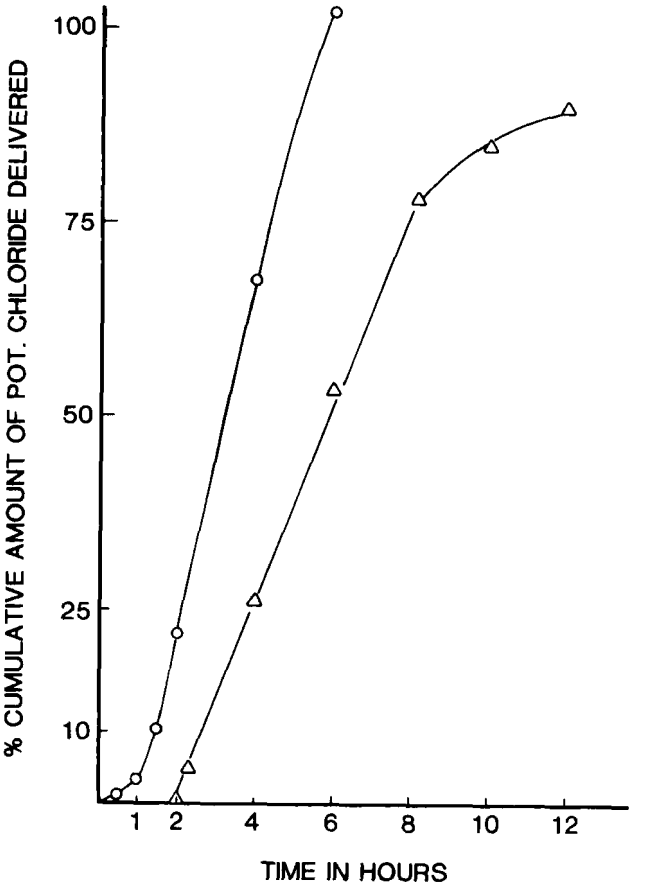

Fig. 7 : The release profiles of potassium chloride from the coated tablet without orifice (Δ) and from the EOP (orifice diameter. = 300 μm) (O) using the Turbula mixer at 23 rpm.

the total drug delivery through the orifice and pores of the membrane will be higher than in system without a delivery port.

CONCLUSION

Fluid dynamics have an effect on the delivery rate of ionic agents, such as potassium chloride, from the EOP and could have a similar effect on drugs of low molecular weight. The delivery rate increases as a function of the fluid flow. The fluid flow pattern has an effect on the

release and it is higher under turbulent than laminar flow. There was no significant difference between the delivery of potassium chloride from EOP systems with orifice diameter between 70 and 500 μm at low rotating speeds. However, under turbulent flow conditions and under high rotating speeds, the difference becomes significant. In the absence of delivery orifice or complete blocking of delivery port in the EOP system, the delivery of potassium chloride takes place through the pores formed in the membrane. There is an initial lag period of about two hours in drug release from systems without delivery orifices.

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