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Brief/Technical Note

Effect of Polacrilin Potassium as Disintegrant on Bioavailability of Diclofenac Potassium in Tablets : a Technical Note

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Abstract. Polacrilin potassium is an ion exchange resin used in oral pharmaceutical formulations as a tablet disintegrant. It is a weakly acidic cation exchange resin. Chemically, it is a partial potassium salt of a copolymer of methacrylic acid with divinyl benzene. It ionizes to an anionic polymer chain and potassium cations. It was hypothesized that polacrilin potassium may be able to improve the permeability of anionic drugs according to the Donnan membrane phenomenon. The effect of polacrilin potassium on the permeability of diclofenac potassium, used as a model anionic drug, was tested *in vitro* using diffusion cells and *in vivo* by monitoring serum levels in rats. The amount of drug permeated across a dialysis membrane *in vitro* was significantly more in the presence of polacrilin potassium. Significant improvement was found in the extent of drug absorption *in vivo*. It could be concluded that polacrilin potassium may be used as a high-functionality excipient for improving the bioavailability of anionic drugs having poor gastrointestinal permeability.

KEY WORDS: bioavailability improvement; disintegrants; permeability enhancement; polacrilin potassium.

INTRODUCTION

The International Pharmaceutical Excipients Council defines an excipient as any substance other than the drug or the prodrug that is included in the manufacturing process or in the finished pharmaceutical dosage form. In addition to their functional performance, the excipients should be ideally nonreactive with the drug and should be inert in the human body. However, some excipients may affect the bioavailability of drugs by altering drug dissolution or permeation.

Higuchi *et al.* (1) demonstrated the use of the polyelectrolyte sodium carboxymethyl cellulose for enhancing the absorption of drugs such as sodium salicylate and potassium benzyl penicillin. Farang *et al.* (2) described the increased permeation of salicylates in the presence of various carboxymethyl celluloses *in vitro*. Rege *et al.* (3) studied the effect of commonly used excipients on the permeability of some low-permeability drugs.

The increased absorption of drug substances in the presence of ionizable polymers may be explained with the help of the Donnan membrane phenomenon (4):

If sodium chloride is placed in solution on one side of a semipermeable membrane and a negatively charged colloid together with its counter ions R^-Na^+ is placed on the other side, the sodium and chloride ions can pass easily across the barrier but not the colloidal anionic particles. The system at equilibrium is represented by the following equation, in which R^- is the colloidal nondiffusible anion.

$$\frac{[Cl^-]o}{[Cl^-]i} = \sqrt{1 + \frac{[R^-]i}{[Cl^-]i}} \quad (1)$$

Equation 1 is the Donnan membrane equilibrium, and it gives the ratio of the concentration of the diffusible anion outside and inside the membrane at the equilibrium. The equation shows that a negatively charged polyelectrolyte inside a semipermeable sac would influence the equilibrium concentration ratio of a diffusible anion. It tends to drive the ion of like charge out through the membrane. When $[R^-]i$ is large compared with $[Cl^-]i$, the ratio roughly equals $[Cl^-]i$. If, on the other hand, $[Cl^-]i$ is quite large compared to $[R^-]i$, the ratio becomes equal to unity, and the concentration of the salt is thus equal on both sides of the membrane.

Polacrilin potassium is an ion exchange resin used in oral pharmaceutical formulations as a tablet disintegrant (5) (Fig. 1). It is a weakly acidic cation exchange resin. Chemically, it is a partial potassium salt of a copolymer of methacrylic acid with divenyl benzene. One can expect that the rate of an anionic drug absorption may be enhanced by the presence of an anionic nondiffusible polyelectrolyte like polacrilin potassium.

The objective of this work was to demonstrate the effect of polacrilin potassium added as disintegrant in tablets on the permeation of anionic drugs. Doshion P544 DS was chosen as a brand to represent polacrilin potassium. Diclofenac potassium was chosen as a model drug to study the effect of polacrilin potassium on its permeation *in vitro* and bioavailability *in vivo*.

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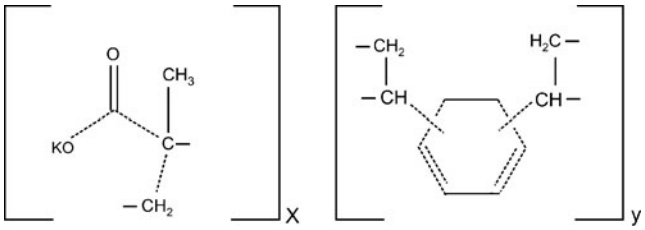

Fig. 1. Chemical structure of polacrilin potassium NF

EXPERIMENTAL

Materials

Doshion P544 DS was received as a gift sample from Doshion Ltd., Ahmedabad. Diclofenac potassium was received as a gift sample from GSK Ltd., Ambad, Nashik.

Methods

In Vitro Permeation

The effect of polacrilin potassium on the permeability of diclofenac potassium through dialysis membrane was determined using Franz diffusion cells. A 10-ml, 2% *w/v* solution of diclofenac potassium containing 36 mg Doshion P544DS in distilled water was placed in the donor compartment (test). A 10-ml, 2% *w/v* solution of diclofenac potassium containing 36 mg crospovidone in distilled water was used as a control (The diclofenac/disintegrant ratio was chosen in order to match the proportion used in the tablet dosage forms which were later tested *in vivo*). The solution in the receiving compartment was pH 6.8 phosphate buffer. The capacity of the receiver compartment was 22 ml. The diameter of the dialyzing membrane (which was equal to the inner diameter of the cell) was 1.34 cm and the area was 5.641 cm^2. Samples (5 ml) were withdrawn every 30 min from the sampling port and were replaced with the equal volume of the medium. The samples were analyzed on UV spectrophotometer at the wavelength of 273 nm.

The dialysis membrane (Type I, MWCA 3.5 K, Hi-Media) was chosen based on its molecular weight cutoff. The molecular weight of diclofenac potassium is 334.25. In order to allow passage of diclofenac potassium but to retain polacrilin potassium, the dialysis membrane with the smallest molecular weight cutoff, *i.e.*, 3,500, was used.

Table I. Formula for Direct Compression Tablet Formulations of Diclofenac Potassium Containing 3% Disintegrant

Ingredient	Quantity/tablet (mg)
Diclofenac potassium (active)	50
Spray dried lactose (filler)	238
Doshion P 544 DS/crospovidone	9
Magnesium stearate (lubricant)	3
Total tablet weight	300

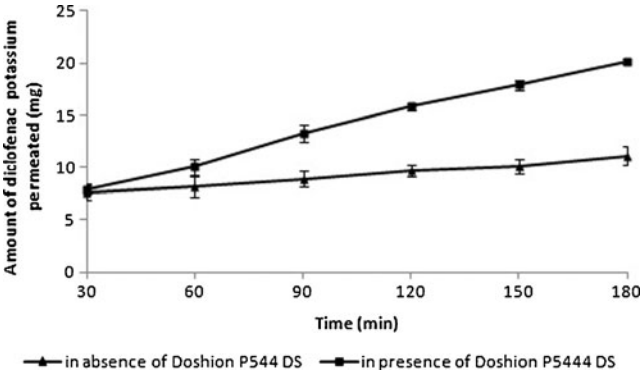

Fig. 2. *In vitro* permeation of diclofenac potassium alone and in the presence of polacrilin potassium *in vitro*

Calculation of Permeation Coefficient

Permeability coefficient is the velocity of drug passage through the membrane in centimeters per hour. The permeability coefficient (P) was calculated from the slope of the graph of percent of drug permeated *vs* time as (5):

$$P = \text{slope} \times \frac{V_d}{S} \tag{6}$$

where V_d = volume of donor solution, and S = surface area of tissue.

In Vivo Study in Rats

The protocol for the *in vivo* study in Wistar rats was approved by the animal ethics committee of MVP Samaj's College of Pharmacy, Nashik. Six healthy male and six healthy female Wistar rats were used in this study. The animals were fasted for 18 h. The animals of either sex were divided into two groups: a control group—1 (n=6) and the test group—2 (n=6). Diclofenac potassium (50 mg) tablets containing 3% polacrilin potassium/crospovidone as disintegrant were formulated (Table I). Rats in the control group were given crushed diclofenac tablets containing crospovidone. Rats in the test group were given crushed diclofenac tablets containing polacrilin potassium. Blood samples (0.5 ml) were withdrawn from the retro-orbital plexus with the help of a micro capillary from each animal at the intervals of 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, and 4 h after dosing.

Table II. *In Vitro* Permeation of Diclofenac Potassium in the Presence of Polacrilin Potassium and Crospovidone

Time (min)	Amount of diclofenac potassium permeated in the presence of crospovidone, average (±SD) (mg)	Amount of diclofenac potassium permeated in the presence of polacrilin potassium, average (±SD) (mg)
30	7.65 (0.08)	7.94 (0.09)
60	8.18 (0.06)	10.03 (0.12)
90	8.91 (0.09)	13.22 (0.16)
120	9.68 (0.11)	15.81 (0.08)
150	10.98 (0.23)	17.88 (0.06)
180	11.11 (0.21)	20.15 (0.24)

Table III. Dissolution of Diclofenac Potassium from Tablets Containing Polacrilin Potassium and Crospovidone

Formulation	% Dissolved in					
	5 min	10 min	15 min	20 min	25 min	30 min
Polacrilin potassium	77.78 (1.1)	84.23 (0.7)	87.78 (0.9)	89.61 (2.1)	92.80 (1.9)	95.86 (1.0)
Crospovidone	76.25 (1.2)	82.87 (1.1)	85.55 (1.0)	88.87 (0.7)	91.88 (1.3)	94.34 (1.5)

Dissolution Studies of Tablets

Dissolution studies were performed using USP 23 apparatus 2, *i.e.*, paddle method (Lab India 2000, Lab India Ltd., Thane, India) at 50 rpm. Six tablet samples were tested for each formulation, and an average of six tablets was reported. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer at 37°C.

Assay of Diclofenac Potassium in Plasma

The plasma concentration of diclofenac was determined by a modified high performance liquid chromatography (HPLC) assay method (6) using Shimadzu HPLC system (Kyoto, Japan) that is composed of a liquid chromatography pump (model LC-20A), a UV detector (model SPD-20A), a degasser (model DGU-20A), a communication bus module (model CBM-20A), and an auto sampler (model SIL-20A). The drug and internal standard were eluted from Nucleosil 5 μm C-18 column (150×4.6 mm, MACHEREY-NAGEL GmbH & Co. KG, Germany) at an ambient temperature using a mobile phase of acetonitrile and water (50:50% *v*/*v*, adjusted to pH 3.5 with orthophosphoric acid) at a flow rate of 1.5 ml/min with UV detection at 280 nm. To 0.5-ml rat plasma samples, an aliquot of 20 μl internal standard (0.1 μg/ml flufenamic acid) was added followed by shaking on a vortex mixer for 30 s. Precipitation of serum proteins was achieved by addition of 500 μl cold acetonitrile. The mixture was shaken again on a vortex mixer for 1 min and centrifuged for 5 min at 10,000 rpm. The supernatant was transferred to an autosampler vial for injection in HPLC.

Calculation of Pharmacokinetic Parameters

Maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were obtained from the plasma concentration–time curve.

Statistical Analysis

The significance of the differences between plasma concentrations of diclofenac at each sampling time and the pharmacokinetic parameters of treatment group *versus* control were evaluated using a one-way analysis of variance test. A p value ≤0.05 was taken as the criterion for statistically significant difference.

RESULTS AND DISCUSSION

In Vitro Permeation

Figure 2 and Table I indicate the amount of diclofenac potassium permeating alone and in the presence of polacrilin potassium *in vitro* using a dialyzing membrane. It can be seen that the amount of diclofenac potassium permeating through the dialyzing membrane in the presence of polacrilin potassium was significantly more at each time point than that in the presence of crospovidone ($p<0.005$) (Table II).

Polacrilin potassium is a cation exchange resin, and diclofenac potassium is a NSAID whose anionic form is effective after ionization in the GIT. The polymer ionizes in an aqueous medium giving an anionic polymer chain and potassium cations. The anionic polymer cannot permeate through the dialyzing membrane due to its large size. It was hypothesized that the charged potassium ions may be able to enhance the permeation of diclofenac anions through this membrane, according to the

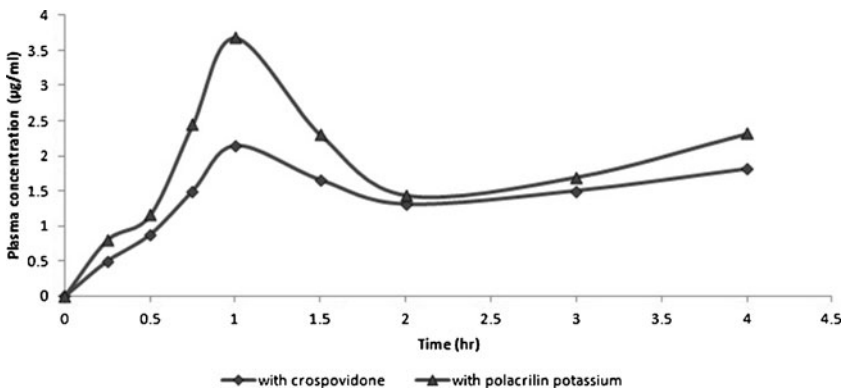

Fig. 3. Mean plasma concentrations (±SD) of diclofenac potassium in Wistar rats following oral administration of 50-mg diclofenac tablets containing crospovidone or Doshion P 544 DS

Table IV. Pharmacokinetic Parameters for the *In Vivo* Study of the Effect of Polacrilin Potassium on Diclofenac Potassium

Pharmacokinetic parameter	Control	Test
C_{max} (μg/ml)	2.14	3.68
t_{max} (h)	1	1
AUC (μg·h/ml)	5.73	7.57

C_{max} maximum plasma concentration, t_{max} time to reach maximum plasma concentration

Donnan membrane phenomenon. The increase in the amount of diclofenac permeating through the dialyzing membrane *in vitro*, in the presence of polacrilin potassium, confirmed this hypothesis. Crospovidone does not have ionizable groups and hence did not affect the permeability of diclofenac.

Dissolution Study

No significant differences were observed in percent diclofenac potassium dissolved from the tablets containing polacrilin potassium and crospovidone ($p>0.05$) (Table III).

In Vivo Bioavailability Study in Rats

Figure 3 shows the plasma concentration of diclofenac in Wistar rats followed by oral administration of a 50-mg tablet containing crospovidone (control) or polacrilin potassium (test) as disintegrant. The extent of absorption of diclofenac potassium was significantly increased in the presence of polacrilin potassium ($p<0.005$). This was accompanied by a significant increase in the AUC. However, there was no significant increase in the rate of absorption as indicated by no change in t_{max} (Table IV).

No significant differences were observed in the dissolution profiles of tablets containing polacrilin potassium and crospovidone. The results of the *in vivo* bioavailability study were in line with the *in vitro* permeation studies. Hence, it could be indirectly concluded that the difference in the bioavailability of diclofenac potassium from the two formulations could be attributed to the difference in the permeabilities of the drug and not to its dissolution. This further confirmed our hypothesis that presence of polacrilin potassium improves *in vivo* bioavailability of anionic drugs *in vivo* due to permeation enhancement.

CONCLUSIONS

The *in vitro* permeation and *in vivo* bioavailability of anionic drugs are enhanced by the presence of polacrilin potassium, which proved our hypothesis. It can be concluded that polacrilin potassium may be used as a high-functionality excipient for improving the permeability of anionic drugs. This could be particularly useful in improving the bioavailability of low-permeability drugs (BCS class III and IV). However, further studies need to be carried out to determine the effect of the concentration of polacrilin potassium on the permeability. Also, more improved methods to measure the permeability *in vitro* may be tried like the rat everted sac method or caco-2 cell permeability studies.

Declaration of Interests The authors report no declaration of interest.

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