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IONTOPHORETIC IN VITRO RELEASE OF ANTIMYCOTICS FROM HYDROGELS

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ABSTRACT

A new in vitro model for iontophoretic release from hydrogels was developed. It represents a modification of the rotary disk cell developed by Moll/Bender and can be used in a normal dissolution tester. The iontophoretic release from antimycotic hydrogels through an artificial membrane was investigated and different types of antimycotics were tested. The influence of current density, drug concentration and vehicle was determined.

INTRODUCTION

Iontophoretic drug delivery is known as the migration of ionic drugs into tissue by the use of electric current. Since Leduc and his famous experiment about iontophoretic transdermal application of strychnine and cyanide ions into rabbits in the beginning of the 20th century [1,2] numerous in vitro and in vivo studies on iontophoretic drug delivery were reported.

Most of the in vitro studies describe iontophoresis in drug solutions. Different types of modified diffusion cells were used [3]. The drug migrates from the donor compartment through a membrane into the acceptor compartment. One electrode each is placed in donor and acceptor compartment. These arrangements are suitable for mechanistic studies about iontophoretic migration. Normally not drug solutions but drug containing hydrogels are iontophoretically applied. For example indometacin, hirudin and heparin have been iontophoretically applied as hydrogels [4]. Despite a few studies there is little information available about iontophoretic in vitro delivery rates from hydrogels [5-11]. These investigations can't be carried out with normal types of diffusion cells.

Three passive and three iontophoretic drug release experiments from hydrogels can be realized parallely by our model. It represents a modification of the rotary disc cell developed by Moll/Bender [12].

Iontophoretic drug delivery can be used for transdermal as well as for dermal application. Different types of mycosis do not only effect the surface of the skin but also effect deeper skin layers. Some trichophytosis reach down to subcutis. A conventional local therapy cannot cure this disease. A systemic treatmemt is necessary. But findings indicate aggravating side effects caused by systemically applied antimycotics. Mutagenous side effects were reported for flucytosin and griseofulvin. Different imidazol derivates have hepatotoxic and amphotericin nephrotoxic side effects [13]. With iontophoretic application it might be possible to let antimycotics penetrate into deep skin areas and decrease side effects of systemic delivery. The present study qualifies antimycotics for iontophoretic in vitro release from hydrogels.

MATERIALS AND METHODS

Materials

Hydroxyethylcellulose DAB 10 (Tylose "H 300", Kalle, Ch.B. 47659118, Caesar & Loretz; D-Hilden); methylhydroxyethylcellulose DAB 10 (Tylopur MH 300, Kalle, Ch.B. 46444076, Caesar & Loretz, D-Hilden); methylcellulose USP XXII (Methocel A 4C premium, Ch.B. MM86122701A, Synopharm GmbH, Barsbüttel); hydroxypropylcellulose DAB 10 (Aldrich Chemical Company, Inc., Milwaukee); lutrol F127 (Product No.: 583206, BASF); glycerin 85% DAB 10 (Caesar & Loretz); aqua purificata DAB 10; natriumdihydrogenphosphat monohydrat (Merck); di-natriumhydrogenphosphat-dihydrat (Merck); dequaliniumchlorid DAB 10 (Ch.B. 93144270; Caesar & Loretz, D-Hilden); naftifinhydrochlorid (Ctr.No. 910002 000; Sandoz AG; D-Nürnberg); chlormidazolhydrochlorid (Ch.B. 1A3154; Grünenthal; D-Stolberg); ciclopiroxolamin (Ch.B. HOU3; Cassella-Riedel Pharma GmbH; D-Frankfurt); cellulose membranes (Diachema, Fa. Dianorm, München).

In vitro Release Studies

The release tests were carried out in a Pharma Test-Drug-Release-Apparatus DAB 10/USP XXII (PTW S II; Pharma Test, D-Hainburg) using modified rotary disk cells [11]. As acceptor medium served phosphate buffer or a mixture of phosphate buffer and methanol(1:1) both pH 7,4 with a decrease of freezing-point of 0,1°K to minimize iontophoretic side effects by buffer ions. The volume of the dissolution medium was 600 ml, the temperatur 34°C and a stirring rate of 100 rpm was used. Round platinum disks were used as electrodes

(diameter: 38 mm, thickness: 0,1 mm, Heraeus, D-Hanau). The distance between anode and cathode was 2,2 cm. As current generator served the Duodynator 829 (Siemens), which is also used in medical practise for iontophoretic drug delivery. All experiments were carried out for 8 hours. The current flow was continuous and not interrupted. Samples were taken every 20 minutes for the first 5 hours and every 60 minutes for the last 3 hours. Sink conditions were maintained.

The new in vitro Model for testing the iontophoretic Release of Hydrogels

The dissolution tests were carried out with six rotary disk cells [12], each cell rotating in her own vessel. Three cells were unmodified to test the passive drug release from the hydrogels. The remaining three cells were modified (Figure 1) to enable a current flow from donor to acceptor. Each modified rotary disk cell is equipped with a platinum electrode on the bottom. The surface of the platinum electrode is identic with the diffusion surface (11,3 cm^2). A platinum wire is soldered with the electrodes and isolated. Each rotary disk cell is sticked on the end of a rotating metal bar. These metal bars have sliding copper/coal contacts, which connect the platinum wires of the electrode with the Duodynator. The metal bars are isolated. The second electrode is located on the bottom of the vessel on top of a spherical teflon segment and is connected with the Duodynator by a platinum wire. Spherical teflon segments without platinum electrodes are also placed in the three vessels with unmodified rotary disk cells. The rotary disk cells can be filled with drug containing hydrogels and covered with a

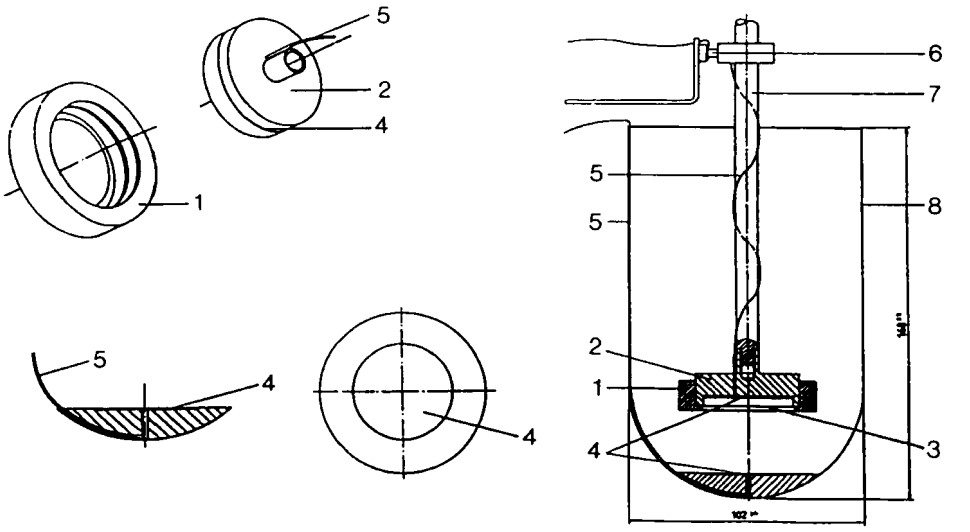

FIGURE 1

Modified rotary Disk Cell: 1 = Snap Ring; 2 = Donator; 3 = Membrane; 4 = Platinum Electrode; 5 = Platinum Wire; 6 = Sliding Contact; 7 = Metal Bar; 8 = Vessel

membrane. The membrane is fixed with a snap ring. During release test the rotary disk cell is rotating with the metal bar in the dissolution medium. So the rotary disk cell works as donor compartment and the dissolution medium as acceptor compartment. All three modified rotary disk cells are connected in series and current is divided in three equal intensity parts. For testing positively charged drugs the electrode on the bottom of the vessel is connected as cathode, for testing negatively charged drugs the electrode on the bottom of the vessel is connected as anode.

Assay Procedure

The amount of drug released was detected by UV/VIS Photometer (Beckmann DU-70 Spectrophotometer).

TABLE 1

Composition of Hydrogels

Hydrogel	Gelling substance [%]	Gycerin [%]
HEC-hydrogel	5	10
MC-hydrogel	5	10
	3	10
MHEC-hydrogel	5	10
Lutrol F127-hydrogel	25	/
HPC-hydrogel	5	10

The following absorption maxima were used:

dequaliniumchlorid: 327,0 nm
chlormidazolhydrochlorid: 247,5 nm
naftifinhydrochlorid: 255,0 nm
ciclopiroxolamin: 300,5 nm

Preparation of Hydrogels and Drug loading

Cellulose hydrogels (Table 1) were prepared by mixing the gelling substance with glycerin and drug and carefully adding the water while stirring. Methylcellulose (M) and hydroxypropylcellulose (HPC) hydrogels were prepared with hot water. Hydrogels were formed under ice cooling and mixing. Methylhydroxethylcellulose (MHEC) and hydroxyethyl-cellulose (HEC) hydrogels were prepared with freshly distilled and cooled water. Lutrol hydrogel was prepared corresponding to the hot method [14]. The drug was mixed with hot water and the gelling substance was

TABLE 2

Current Intensity and resulting Current Density

Current intensity [mA]	Current density at the electrodes [$mA \cdot cm^{-2}$]
7	0,206
10	0,295
14	0,413
17	0,501

added. Hydrogels were formed under cooling down to room temperature. All hydrogels were stored between 12 and 60 hours in the refrigerator at 8°C.

Variation of Current Density

Iontophoretic release with different current densities and passive release was tested with dequaliniumchlorid (0,4%) containing hydroxyethylcellulose hydrogel. Release experiments were carried out in phosphate buffer pH 7,4. Different current intensities were chosen at the Duodynator and resulted in the following current densities at the electrodes (Table 2).

Variation of Drug Concentration

Four hydroxyethylcellulose hydrogels with different dequaliniumchlorid contents (0,2%, 0,4%, 0,8%, 1,6%) were tested at constant current density (0,4 $mA \cdot cm^{-2}$).

Every iontophoretic release was compared with the according passive release. Release experiments were carried out in phosphate buffer pH 7,4.

Variation of Vehicle

Nonionic hydrogels (hydroxyethylcellulose hydrogel (HEC 5%), methylcellulose hydrogel (MC 3%, 5%), methylhydroxyethylcellulose hydrogel (MHC 5%), hydroxypropylcellulose hydrogel (HPC 5%) and lutrol F127 hydrogel (Lu 25%)) were tested regarding their effect upon the iontophoretic enhancement. Dequaliumchlorid content was 0,4% and current density was 0,4 $mA \cdot cm^{-2}$. Release experiments were carried out in phosphate buffer pH 7,4.

Variation of Drug

Four antimycotics (dequaliniumchlorid (0,4%), naftifinhydrochlorid (1%), chlormidazolhydrochlorid (5%), ciclopiroxolamin (1%)) were investigated. The release experiments were carried out in a mixture of phosphate buffer pH 6,2 and methanol (ratio 1+1). The resulting pH was 7,4. This dissolution medium was chosen to obtain sink conditions for all drugs. Ciclopiroxolamin is negatively charged at pH 7,4. The remaining three antimycotics are positively charged at pH 7,4. Current density was 0,4 $mA \cdot cm^{-2}$. As vehicle served hydroxyethylcellulose hydrogel.

RESULTS AND DISCUSSION

1. Effect of Current Density

To investigate the influence of current density upon drug release from hydrogels a curve fitting was done.

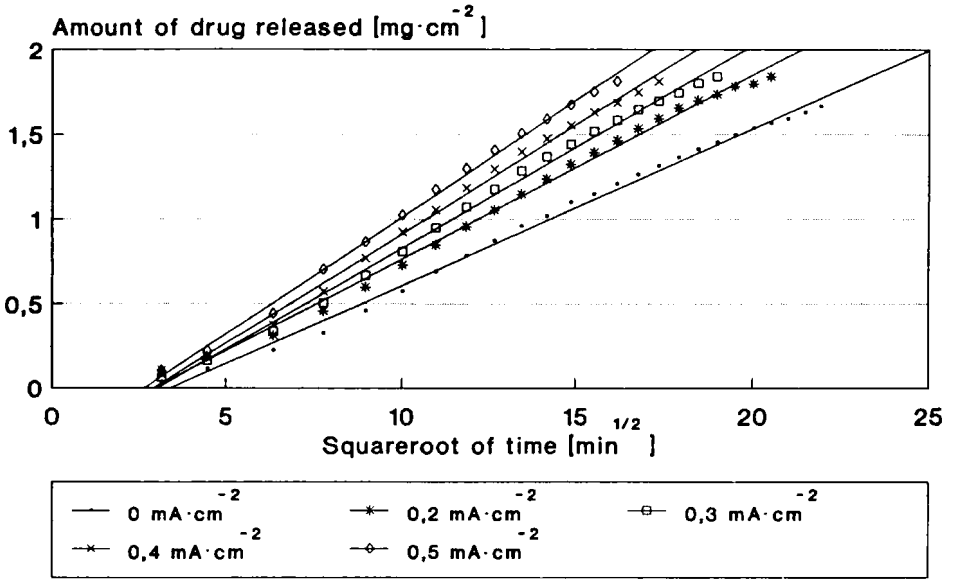

FIGURE 2

Iontophoretic and passive Release of Dequaliniumchlorid from Hydroxyethylcellulose Hydrogel depending on Current Density

Straight lines resulted by plotting the amount of drug released per square centimeter against the square root of time (Higuchi Plot) (Figure 2). Both passive and electrically assisted drug delivery showed matrix controlled delivery. This is also proved by the correlation coefficients.

The slopes K [$mg \cdot cm^{-2} \cdot min^{-1/2}$] (regression coefficient) of the regression lines were used to compare the release curves (Table 3, Figure 3).

The following relation is defined as percent iontophoretic enhancement (IE):

$$IE = [K_{active} \cdot (K_{passive})^{-1} \cdot 100] - 100.$$

$K_{passive}$ is the regression coefficient for passive

TABLE 3

Correlation Coefficient for Higuchi-Plot r, Regression Coefficient K, Iontophoretic Enhancement IE at different Current Densities.

Current density [mg·cm^{-2}]	r	K [mg·cm^{-2}·min$^{-1/2}$]	IE [%]
0	0,995	0,093	/
0,206	0,995	0,108	16,1
0,295	0,996	0,119	28,0
0,413	0,996	0,129	38,7
0,501	0,997	0,138	48,4

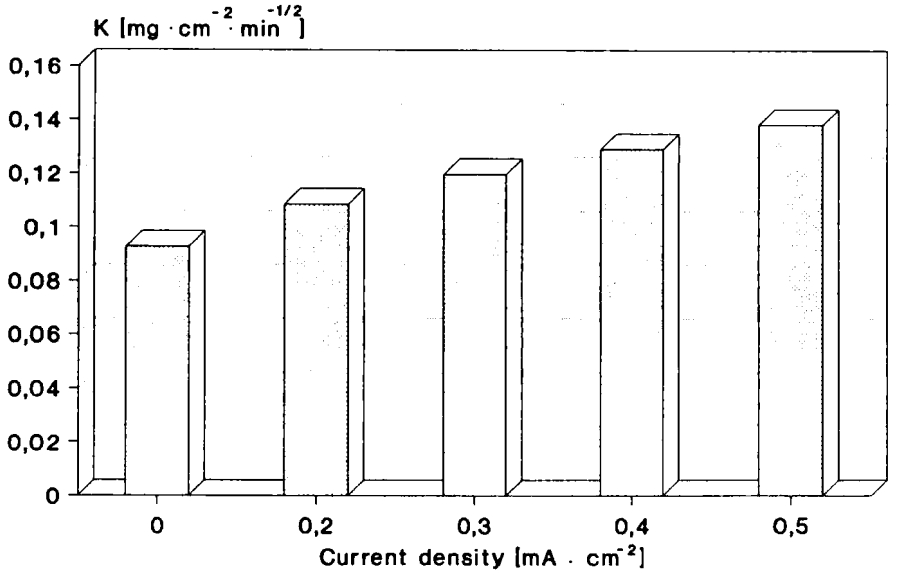

FIGURE 3

Effect of Current Density on Regression Coefficient K.

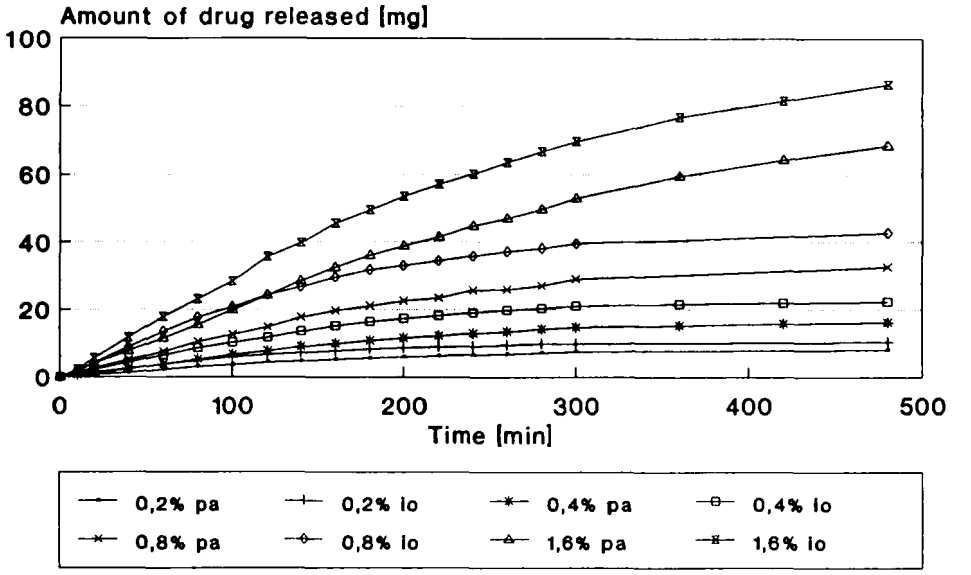

FIGURE 4

Iontophoretic (io) and passive (pa) Release of Hydroxyethylcellulose Hydrogel containing different Amounts of Dequaliniumchlorid

release and K_{active} is the regression coefficient for iontophoretic release.

The correlation coefficient for linear dependence between current density and K is 0,9974. So linear dependence was proved for current density between 0,2 and 0,5 $mA \cdot cm^{-2}$.

2. Effect of Drug Concentration

The absolute amount of dequaliniumchlorid released from hydrogel increases with increasing drug content. This is valid for passive and iontophoretic release (Figure 4).

Table 4

Correlation Coefficient for Higuchi Plot r, Regression Coefficient K and Iontophoretic Enhancement IE for different Concentrations of Dequaliniumchlorid in the Hydrogels

Concentration of drug [%]	r		K [mg·cm^{-2}·min$^{-1/2}$]		IE [%]
	passive	active	passive	active	
0,2	0,991	0,977	0,045	0,060	33,3
0,4	0,992	0,996	0,090	0,129	43,3
0,8	0,993	0,993	0,180	0,248	37,8
1,6	0,990	0,993	0,344	0,442	28,5

There is a linear relationship between drug concentration and both passive and iontophoretic release up to a drug concentration of 0,8%. From 0,8% to 1,6% the percentage of passive and iontophoretic release decreases. Maximal iontophoretic enhancement is shown by a 0,4% dequaliniumchlorid concentration (Table 4).

3. Effect of Vehicle

Iontophoretic release with the same current density from different vehicles doesn't comprise the same release rate. Not only the passive release of dequaliniumchlorid varies with different vehicles but also iontophoretic release is substantially influenced by the vehicle. More over the iontophoretic enhancement varies with different vehicles. The iontophoretic enhancement is high for hydrogels which show a low passive release, for example hydroxypropylcellulose

TABLE 5

Correlation Coefficient for Higuchi Plot r, Regression Coefficient K and Iontophoretic Enhancement IE for different Vehicles

Hydrogel	r		K [mg·cm^{-2}·min$^{-1/2}$]		IE [%]
	passive	active	passive	active	
HEC 5%	0,992	0,996	0,090	0,129	43,3
HPC5%	0,999	0,989	0,059	0,112	89,8
MHC 5%	0,995	0,979	0,054	0,095	75,9
Lu 25%	0,959	0,994	0,064	0,108	68,8
MC 3%	0,992	0,982	0,062	0,117	88,7
MC 5%	1,000	0,990	0,055	0,106	92,7

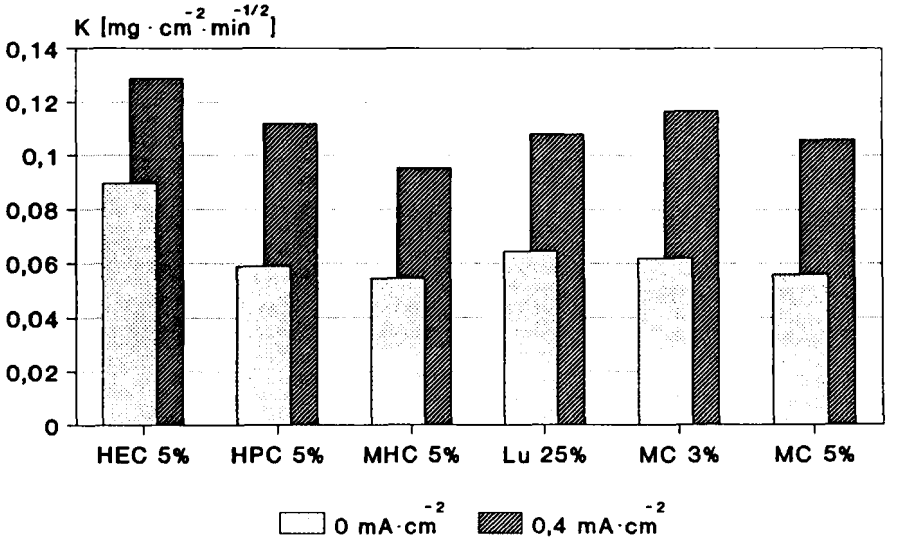

FIGURE 5

Effect of Vehicle on Regression Coefficient K HEC=Hydroxyethylcellulose, HPC=Hydroxypropylcellulose, MHC=Methylhydroxyethylcellulose, MC=Methylcellulose, Lu=Lutrol

Table 6

Correlation Coefficient for Higuchi Plot r, Regression Coefficient K′ and Iontophoretic Enhancement IE for different Drugs

Drug	r		K' [%·min$^{-1/2}$]		IE [%]
	passive	active	passive	active	
Cic	0,996	0,997	4,055	5,356	32,1
Chl	0,983	0,992	4,007	5,376	34,2
Deq	0,992	0,997	3,176	6,228	96,1
Naf	0,997	0,981	2,430	6,395	163,2

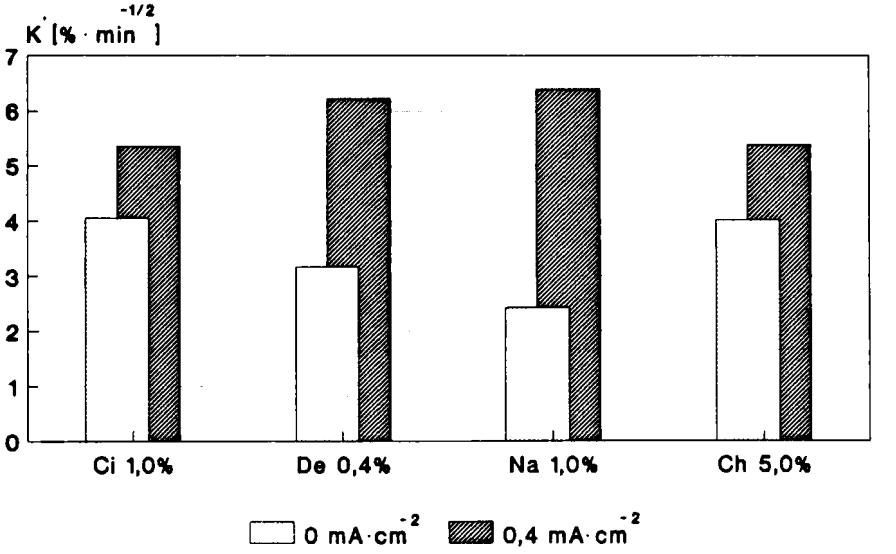

FIGURE 6

Comparison of iontophoretic and passive Release of different Antimycotics on the Basis of Regression Coefficient K′ [%·min$^{-1/2}$]
Ch=Chlormidazolhydrochlorid, Na=Naftifinhydrochlorid, Ci=Ciclopiroxolamin, De=Dequaliniumchlorid

(HPC) and methylcellulose hydrogel (MC). Besides that iontophoretic enhancement changes with different concentration of gelling substance. Methylcellulose hydrogel 5% shows a higher iontophoretic enhancement as methylcellulose hydrogel 3% (Table 5, Figure 5).

Variation of Drug

Different iontophoretic enhancement resulted from release of hydrogels loaded with different drugs. Corresponding to the influence of different vehicles on iontophoretic enhancement low passive release (Naftifinhydrochlorid, Dequaliniumchlorid) resulted in a high iontophoretic enhancement and high passive release resulted in a low iontophoretic enhancement (Table 6, Figure 6).

CONCLUSION

In conclusion the modified rotary disk cell is a new approach to study the iontophoretic in vitro release from hydrogel vehicles. Different types of antimycotics showed in vitro a substantial iontophoretic enhancement. Current density, drug concentration and type of vehicle influenced passive and iontophoretic release.

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REFERENCES

1. S. Leduc, Ann. d'Electrobiol., 3, 545, (1900)

2. S. Leduc, Electric Ions and their Uses in Medicine, Rebman, London, (1908)
3. M. Clemessy, G. Couarraze, C. Herrenknecht, S.T.P. Pharma Sciences , 1(1), 24, (1991)
4. H.G. Pratzel, "Iontophorese", Berlin Heidelberg New York, 1987
5. J. Corish, O.I. Corrigan, D. Foley, in "Prediction of percutaneous penetration", R.C. Scott, R.H. Guy, J. Hadgraft, IBC Technical Services Ltd, 1990, p. 302
6. P. Maury, B. Bévan, E. Teillaud, C. Herrenknecht, F. Falson-Rieg, G. Couarraze, in "5th International Conference on Pharmaceutical Technology", Vol. III, Papers 31, 1989, p. 304
7. J. De Meirsman, N. Rosselle, Ars medici, 35, 263, (1980)
8. R. Gröning, International Journal of Pharmaceutics, 36, 37, (1987)
9. Y.B. Bannon, J. Corish, O.I. Corrigan, Drug Dev. Ind. Pharm., 13(14), 2617, (1987)
10. Y.B. Bannon, J. Corish, O.I. Corrigan, J.G. Masterson, Drug Dev. Ind. Pharm., 14(15-17), 2151, (1988)
11. Y.B. Bannon, J. Corish, O.I. Corrigan, in "Proceedings of the third European Congress of Biopharmaceutics and Pharmacokinetics", Volume 1, Biopharmaceutics, Freiburg, West Germany, 1987, p. 301
12. F. Moll, H. Bender, Pharm. Ind., 8(52), 1006, (1990)
13. E. Mutschler, Arzneimittelwirkungen, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 5, 1986, p. 618-624
14. BASF, Technisches Merkblatt, Lutrol F 127