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CONTROLLED PULSATILE DUTY CYCLE FOR MASS TRANSFER USING IONTOPHORETIC POWER SUPPLY AND DATA ACQUISITION SYSTEM

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ABSTRACT

In the transdermal drug delivery, Drug transport across biomembrane is increased using Iontophoresis by applying electric pulse to the biomembrane. The objective of the present study was to investigate the effects of pulsed current for different duty cycles of time on iontophoretic transport. Drug transport across biomembrane is enhanced using iontophoresis is by three mechanisms: (a) the ionic and electric field interaction; (b) flow of electric current; (c) electroosmosis. The ionic-electric field interaction provides an additional force which drives ions through the biomembrane. Flow of electric current increases permeability of biomembrane. Electroosmosis produces bulk movement of ionic solvent itself that caries ions. The relative selection of suitable duty cycle of time and importance of duty cycle in iontophoretic Power Supply has been studied. Theoretical Concepts with this respect are reviewed and Experimental observations are explored to clarify the nature of duty cycle for drug transport and also to define the conditions under which duty cycle drug transport is optimal in iontophoresis. The Egg membrane is used as biomembrane for the study. NaCl dissolved in the de-ionized water is used for transport study across biomembrane. For the study Vertical Franz cell with two side arms is used. The mass transported across the biomembrane with Iontophoresis power Supply by changing the different duty cycles are compared with the mass transport without iontophoresis.

KEY WORD: *Iontophoresis, Duty cycle, Data Acquisition system, biomembrane.*

INTRODUCTION:

Iontophoresis is the application of an electric current pulses which enhances the delivery of the ionized or deionized drug through any biological or synthetic membrane like skin [1]. By the application of iontophoresis the trandermal drug deliverded range is enhanced [2]. In transdermal drug delivery through the skin, the pharmacetical research study requires the flexible iontophoresis power supply with maximum current density of 0.5 mA/cm2 and with different duty cycles [3,4]. The work till date done was with continuous current and with the duty cycle of 50.00 % with ON time of one second and OFF time of one second [5-7]. The flexible the iontophoresis power supply with capable of delivering controlled electrical pulses using AVR microcontroller was constructed and tested. Pulse duration, duty cycle can be controlled from the panel of the power supply that has three buttons and will be displayed on Liquid Crystal Display (LCD). The on time and off time can be individually set to the desired value from 0 to 10 second, and this range can be suitably adapted by in the firmware of the microcontroller based power supply. Two terminals are provided on the main panel for

taking the output, a LED on the main panel shows the ON or OFF state of the output.

Also data acquisition system is developed to save the readings automatically. The experiments found that with continuous current application reduce the efficiency drug transport of drug transportation through membrane. As the drug transport can be enhanced with duty cycles. The transfer of mass diffused through the membrane is studied for different duty cycles using iontophoresis power supply and compared with the mass diffused without power supply.

EXPERIMENTAL

The work presented relates to the study of transport of a chemical substance across a bio-membrane [8-11]. It is known and established that in the field of medicine drug administration through skin or other bio-membranes is of interest and brisk research and developmental activity [12-13]. Additionally the assisted transport through bio-membranes using external stimuli is also at focus and drug patches administering drug through skin are being successfully employed in areas that were not explored so far [14-15]. There is limited literature in the field of iontophoresis assisted drug transport [16-18]. Because of lack of availability of resources and technical instrumentation required this area is still in the stage of infancy as technology from different disciplines is involved [19-20]. The experiments demand mulidisciplinary activity in groups with resources and the issue being health related there is more of concern and needs careful experiments [11-23].

There is no systematic study that provides an insight into the role of the external stimulus like iontophoresis pulses and their effect on the drug transport. With this in view we designed and constructed an iontophoresis power supply that is capable of providing pulse for ionotophoresis in the range where others made attempts and showed that the drug transport is enhanced using iontophoresis. The iontophoresis power supply has the facility to control the output current as most of the experiments recommend that the current through the bio-membrane should not exceed 0.5 – 1 mA per square centimeter of the bio-membrane [24]. It is also shown that higher the current through the biomembrane faster and larger is the amount of drug transport, however our present experiments strictly use a current of less than 0.5 mA/cm2. The power supply is flexible in the sense that the ON time of the pulse and the OFF time of the pulse can be selected using the control panel of the power supply using thumb wheel switch of the push button control. In other words the duty cycle of the square wave pulses being applied to the bio-membrane can be altered according to the need and requirement using the contorl panel of the iontophoresis power supply.

To study the drug transport across a biomembrane there is tradition to use a standard Franz cell which consists of two compartments separated apart by a bio-membrane. On one side of the bio-membrane a chemical solution of known concentration is kept and on the other side of the membrane pure solvant is used. As a result of diffusion through the membrane as more and more drug comes out of the membrane the concentration of the drug in the second compartment increases. The present work aims at establishing the role of iontophoresis assisted drug transport through bio-membrane we used a simple chemical, Sodium chloride (NaCl). For sodium chloride solution lot of information is available and in the region of interest, the concentration and conductivity of the solution have a linear relationship as shown in following figure1.

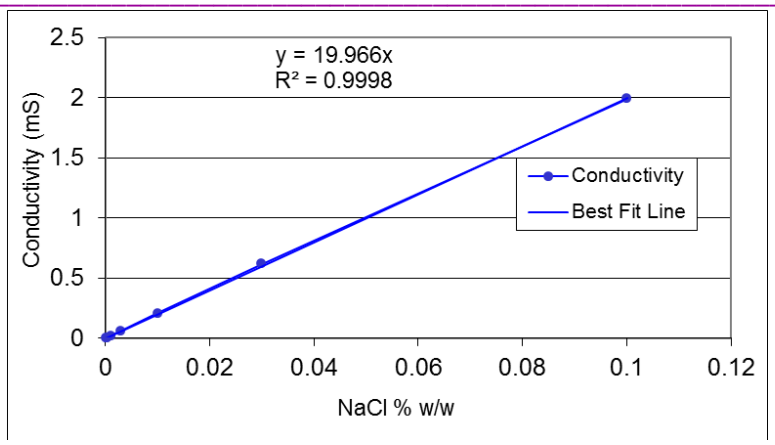

Figure 1: Linear relationship plot for NaCl Conductivity virsus NaCl % w/w

The study is limited to the transport of NaCl across bio-membrane taking it as a case study to indicated the factors on which the drug transport depends and the relative importance of different working conditions could be established. The advantage of selecting a chemical substance like NaCl includes the ease of estimation of the concentration of the solute in the solvant using the relation between the conductivity and concentration [25]. The effort simplifies to the measurement of resistance of the cell, resistivity of the solution of the conductivity of the solution. Thus for the measurement of the resistance of the cell a special conductivity cell is designed and constructed with a active silver are of cell constant of 1 per cm. The iontophoresis power supply was designed to accommodate this measurement of resistance of the cell. For certain experiments we used this resistance measuring cell along with the built in data acquisition system of the iontophoresis power supply in conjunction with the computer side controlling program developed in VB. A typical screenshot of the working of the data acquisition system of the iontophoresis is shown in following Figure 2.

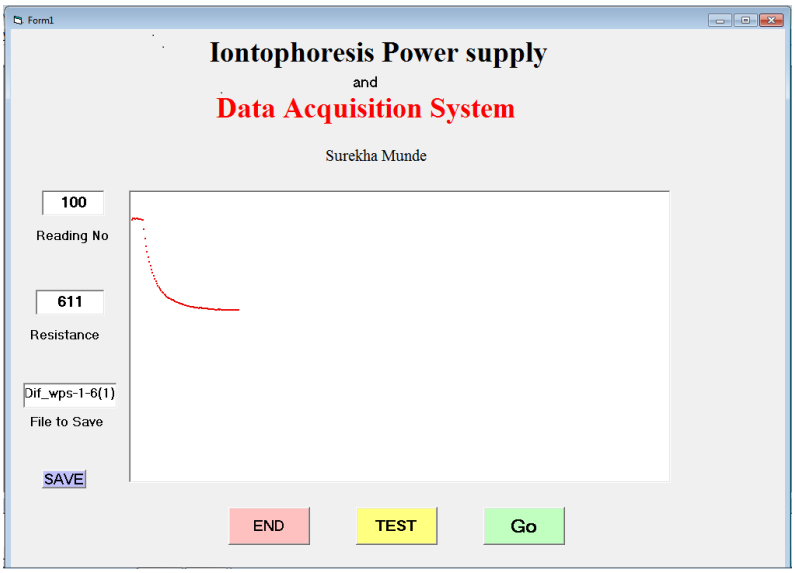

Figure 2: Screen shot for Data Acquisition system.

For several other experiments we used an external calibrated conductivity meter where continuous monitoring of the conductivity in relative to time was not a primary interest.

In an experiment we used 1 M sodium chloride solution in the upper compartment of the Franz cell filled with an egg membrane and on the other side of the membrane i.e. in the lower comparment, deionised water was used. The two electrodes used for application of the iontophoresis pulse were made

from silver and coated with silver chloride, these electrodes were fed with the selected type of electrical pulses from the iontophoresis power supply and the current was set to remain within the limits discussed earlier (0.5 mA/cm2). With the help of thumb wheel switch ON time and OFF time was set. When power supply is switched on, the drug is diffused through the membrane in the acceptor compartment of the Franz cell. As drug diffuses in the lower compartment the resistivity decreases. Initially the ON time used was one second and the OFF time used was one second making the duty cycle = 50.00 %. Figure 3 shows the plot of resistance of the cell measured using the microcontroller based data acquisition system of the iontophoresis power supply interfaced with a computer where the readings are saved in a computer file.

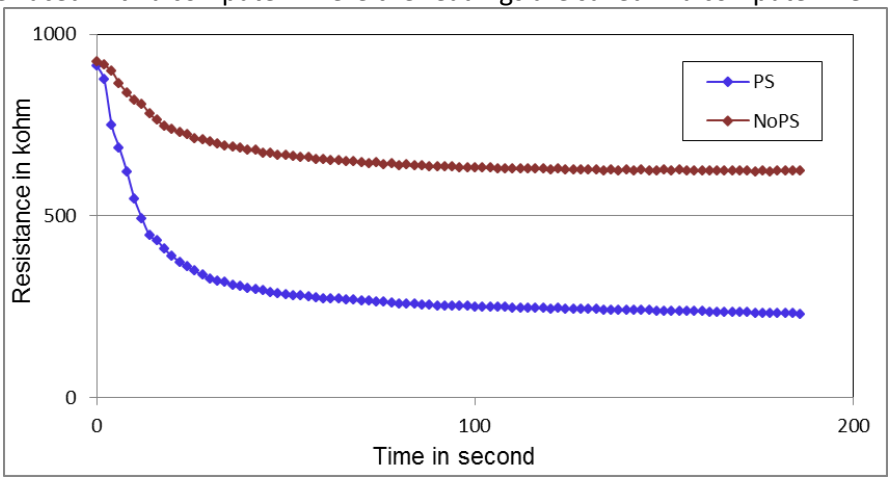

Figure 3: Plot of resistance of the solution in the second compartment versus time with Duty Cycle of 50 % with ON time = 1 sec OFF time = 1 sec.

There are two plots in Figure 3, the upper curve is the resistance measured in the lower compartment of the Franz cell without iontophoresis power supply and the next curve is the resistance measured in the lower compartment of the Franz cell using power supply. As discussed above the drug transport is enhanced using iontophoresis power supply when the pulses are given to the bio-membrane. It is seen from the graph that the resistance of the cell falls down rapidly during the initial stages and the change in resistance of the cell becomes slower with time and exhibits a tendency to reach a steady state. The reason for this type of behavior is attributed to the fatigue of the pores of the bio-membrane where the pores become immune to the external stimulus after repeated exposure to the electrical impulses in addition to the behavior showing a sort of saturation effect. This saturation effect comes from the transport of the chemical across the cell wall as a result of osmosis [26]. The data saved in the computer file is serial number and resistance. The data is given in the table below. In the table 1 the first column is time in second in the second column resistance without power supply and in the third column the resistance with power supply. The experiment was observed for about three hours by the time duration of two second.

Table – 1: Summary of data from the data acquisition system

Resistance of Cell in Kohms						
Time (s)	With Power supply	Without Power supply		Time (s)	With Power supply	Without Power supply
0	914	925		94	253	635
2	875	915		96	251	634
4	750	899		98	251	633
6	688	865		100	250	633
8	622	840		102	250	632

10	547	820	104	248	632
12	493	808	106	248	631
14	447	782	108	248	631
16	432	763	110	246	630
18	408	748	112	246	629
20	389	739	114	246	630
22	373	729	116	245	629
24	360	724	118	245	629
26	348	712	120	244	626
28	337	710	122	245	629
30	327	703	124	243	628
32	320	698	126	244	628
34	317	694	128	242	628
36	310	689	130	242	627
38	305	686	132	242	627
40	300	680	134	241	625
42	298	680	136	241	626
44	294	674	138	240	624
46	290	673	140	240	627
48	286	668	142	240	624
50	284	666	144	239	626
52	281	665	146	240	625
54	280	662	148	238	625
56	277	661	150	238	626
58	275	657	152	238	625
60	273	657	154	238	626
62	273	652	156	237	623
64	272	653	158	237	625
66	269	650	160	237	623
68	268	649	162	235	625
70	267	648	164	236	623
72	265	645	166	235	624
74	262	646	168	234	624
76	263	642	170	235	624
78	260	643	172	234	623
80	259	639	174	232	622
82	258	640	176	232	624
84	258	637	178	232	621
86	255	638	180	232	625
88	255	636	182	231	623
90	253	636	184	231	625
92	253	635	186	230	623

Table – 1 show the data plotted in figure 3 that is obtained from the data acquisition system with the iontophoresis power supply, this data is used along with the cell constant to convert the resistance measured into the conductivity of the solution. Figure 4 shows the plot of the conductivity of the solution in the lower compartment of the Franz cell estimated using the data from Table 1.

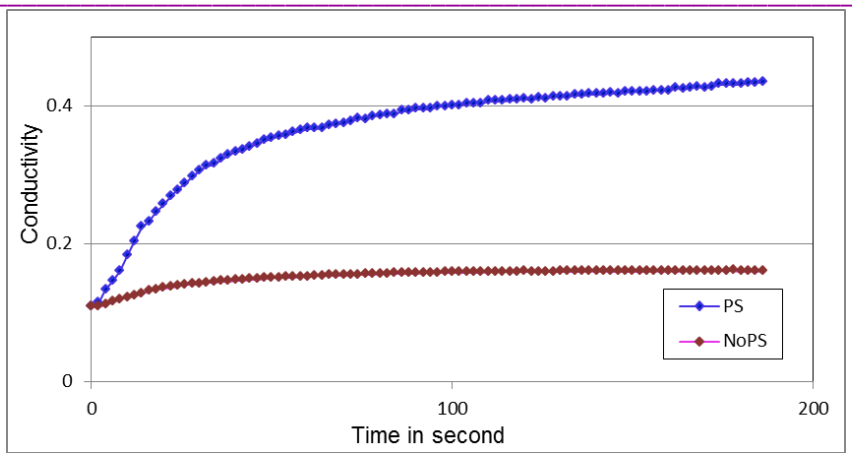

Figure 4: Plot of conductivity of the solution in the second compartment versus time with duty cycle of 50.00 % with ON time = 1 sec OFF time = 1 sec.

The duty cycle of the pulses applied to the iontophoresis cell was 50.00 % with ON time equal to one second and OFF time equal to one second and it is seen that that conductivity obtained with power supply is maximum when compared with the conductivity without power supply.

A similar experiment was conducted using the same experimental setup with the same power supply and data acquisition system using the Franz cell mounted with the egg membrane but the duty cycle of the iontophoresis pulses was changed to 33.33% of duty cycle with ON time equal to one seconds and OFF time equal to two seconds. The results are presented in the form of graph in figure 5. Figure 5 is the plot of resistance and conductivity measured as a function of time of the solution in the second compartment. The next set makes use of ON time = One seconds and OFF time = Two seconds.

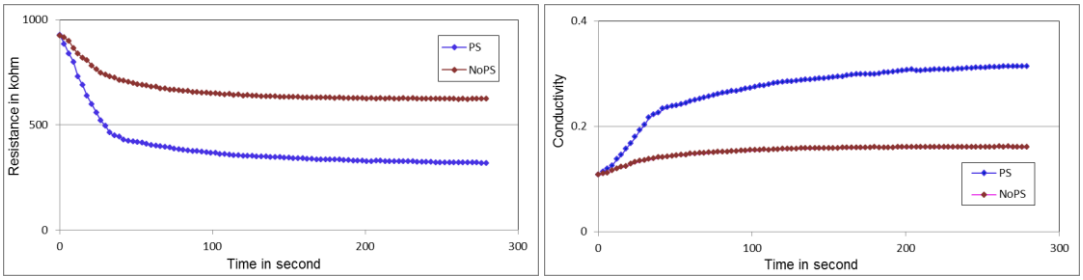

Figure 5: Plot of resistance and conductivity of the solution in the second compartment versus time with Duty Cycle of 33.33 %

If we compare the graphs of figure 5, the curves with iontophoresis power supply the resistivity for the duty cycle of 33.33% is maximum i.e. mass transport is enhanced for the duty cycle 33.33 % compared with mass transport without iontophoresis power supply.

Along similar lines when the ON time was set to One seconds and off time was set to Four seconds, with duty cycle of 20% the resulting resistance and conductivity versus time plot is shown in figure 6.

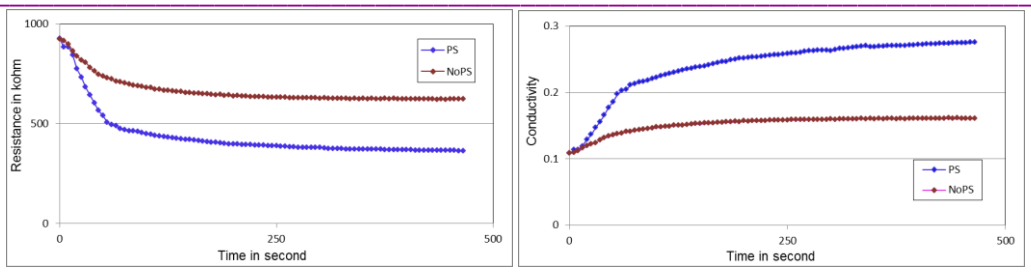

Figure 6: Plot of resistance and conductivity of the solution in the second compartment versus time Duty Cycle of 20.00 %

The duty cycle for next set kept is 11.11% with ON time of One second and OFF time of Eight seconds. The plot of graph for resistance and conductivity versus time is given in figure 7. It is seen that though the duty cycle changed is small it affect the drug transport through the membrane as the curves in the figures 7 are very close.

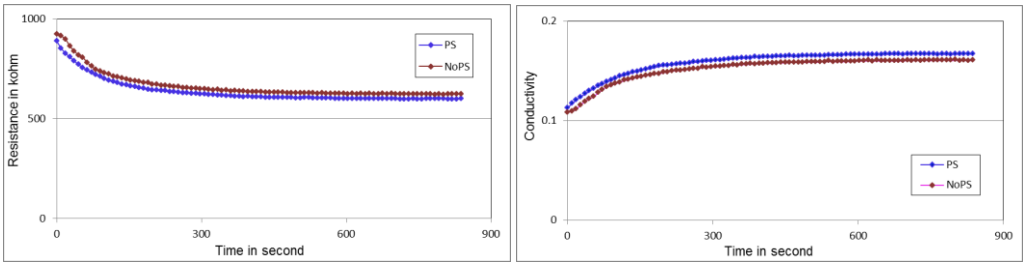

Figure 7: Plot of resistance of the solution in the second compartment versus time Duty Cycle of 11.11 %

Figure 8 shows the comparison between the all duty cycles i.e. 50.00%, 33.33%, 20%, 11.11% discussed in above figures with different ON and OFF timings.

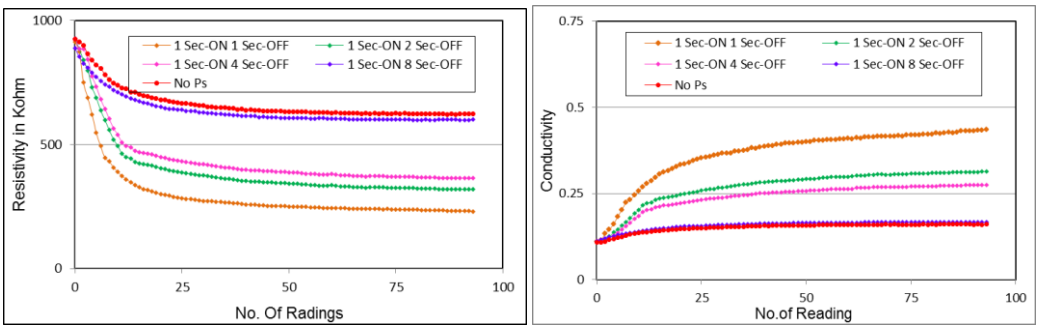

Figure 8: Plot of Resistance in Kohm of the solution in the second compartment for all duty cycles (50%, 33.33%, 20%, 11.11%) discussed in above figures

In figure 8 all the data taken with different duty cycles with different On and OFF timings are compared with the plot of resistivity without iontophoresis power supply. From the graph it is found that permeation for duty cycle 50.00 % was higher in comparision with other pulse ratios and minimum for the duty cycle of 11.11%.

CONCLUSION

This paper presents in vitro studies when the cumulative amount is permeated through the membrane in acceptor compartment of Franz cell. The cumulative mass transferred for diffusion study using iontophoresis power supply for different duty cycles such as 50%, 33.33%, 20% and 11.11% for egg

membrane. For diffusion study the AVR Microcontroller based iontophoresis power supply with data acquisition system is used. Low cost iontophoresis power supply and data acquisition system was designed and tested is used for the study. The resistivity using computer interface with data acquisition is measured for different duty cycles for different ON and OFF timings and compared the data. The resistivity then converted into conductivity for diffusion study. The data is obtained with and without iontophoresis power supply and compared. Details are presented and results are discussed.

RESULT:

The Iontophoresis power supply capable of constant current (less than 0.5 mA/cm2) and of different duty cycles using microcontroller ATmega32 is designed, constructed and successfully tested along with the automatic data acquisition system. It is observed that significant modification in cumulative amount of mass transferred in the lower compartment of Franz cell using iontophoresis is observed. Further it is observed that for the time controlled pulsatile duty cycle keeping current constant the drug transportation is improved. For the duty cycle of 50 % the drug transportation is maximum compared for other duty cycles i.e. 33.33%, 20%, 11.11% .

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