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MICRO-ELECTROPHORETIC MOBILITY STUDY OF THE INFLUENCE OF CHLORPROMAZINE HYDROCHLORIDE ON DIMYRSTOYLPHOSPHATIDYLCHOLINE LIPOSOMES IN DIFFERENT MEDIA

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ABSTRACT: In this study, the possible influence of the model, cationic drug chlorpromazine hydrochloride (CPZ-HCl) concentration on the micro-electrophoretic mobility of neutral large multi-lamellar dimyrstoylphosphatidylcholine (DMPC) liposomes was investigated in various media at both 25°C and 37°C. In addition the effect CPZ-HCl concentration on the micro-electrophoretic mobility of both positively charged DMPC/stearyl amine (ST) liposomes and negatively charged DMPC/dicetyl phosphate (DCP) liposomes were also investigated. The effect of pH on the micro-electrophoretic mobility of neutral positively charged and negatively charged liposomes in the absence and presence of CPZ-HCl in water and in 0.1M KCl at 25°Cwere also studied. Lastly, the influence of CPZ-HCl at concentrations known to cause anesthesia, on the micro-electrophoretic mobility of neutral, positively charged and negatively charged liposomes in phosphate buffer (pH 7.4) at 37°C was also investigated. Present study indicates that DMPC liposomes in water exhibited zero electrophoretic mobility over a wide pH range. DMPC liposomes acquired negative charges in 0.1M KCl, phosphate buffer (pH 6.0 and 7.4) and in human plasma (pH 7.4). The addition of CPZ-HCl shifted the mobility of neutral, positive and negative charged DMPC liposomes towards positivity. Linear relationship were observed between the electrophoretic mobility of DMPC, DMPC /ST, and DMPC /DCP liposomes as a function of CPZ-HCl concentrations known to cause anesthesia.

INTRODUCTION: Liposomes has been extensively used as drug delivery systems [1-10]. In addition, a number of liposomal formulations have been investigated in preclinical and clinical trials [11]. Aqueous liposomal dispersions of phosphatidylcholines have been widely studied as model membranes because of their striking resemblance to biological membranes [12, 13]. The interaction of CPZ-HCl with phospholipid liposomes has been reported [14-20].

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CPZ-HCl was observed at anesthetic concentrations to protect human erythrocytes against hemolysis, increase the mean cellular volume and decrease the sedimentation rate of the erythrocytes [21]. The adsorption of ions onto the lipid membranes and liposomes has been reported [22–27].

The adsorption processor ion-membrane interactions not only induces physicochemical and electrical surface changes in the membrane, but also plays an important role in its overall functional behavior such as membrane fusion and transport [28]. Ion adsorption on the lipid membrane surface has been explored using various techniques, including micro-electrophoresis [29, 30], A nuclear magnetic resonance [31, 32], Langmuir method [33, 34], molecular dynamics simulations [35, 36], Doppler electrophoretic light scattering [37] and more recently using a

technique that combines on-chip micro-capillary electrophoresis with a low noise EM-CCD camera [38].

In particular, micro-electrophoresis can be used to determine membranes surface charge density which is an important parameter for characterizing equilibria in natural or artificial membranes. Membrane surface charge density was observed to strongly depend on pH, ionic strength and the lipid composition of the membrane [39]. The zeta potential as calculated using electrophoretic mobility, is considered an important physicochemical parameter of liposomal drug formulation, not only assessing in vitro physical stability, but also in vivo stability [40-42]. Zeta potential of liposomes has also been used to determine the variations of the degree of coverage of individual liposomes of different lipids and to calculate the dissociation constants and the stoichiometry of the binding [43].

Electrophoretic mobility study of phosphatidylserine liposomes, reflected that the binding of certain trypanocides to phospholipids correlate with their biological activity [44].

The effect of charge inducers such as stearylamine or dicetylphosphate as positive and negative charge inducers respectively on the size and encapsulation efficiency of soybean phosphatidylcholine/ cholesterol liposomal ciprofloxacin, showed that both liposomal size and drug encapsulation efficiency were increased; where positively charged liposomes showed superior entrapment efficiency over both negatively charged and neutral liposomes [45].

The present study investigates the possible influence of the model, cationic, drug CPZ-HCl on the micro-electrophoretic mobility of neutral, positively charged and negatively charged large multi-lamellar DMPC liposomes in different media. The influence of CPZ-HCl at concentrations known to cause anesthesia, on the micro-electrophoretic mobility of neutral, positively charged and negatively charged DMPC liposomes in 0.2M phosphate buffer (pH 7.4) at 37°C was also investigated.

MATERIALS AND METHODS:

Materials:

Synthetic dimyrstoylphosphatidylcholine (DMPC) (not less than 98% pure), chlorpromazine hydrochloride (CPZ-HCl), stearyl amine (ST) and dicetyl phosphate (DCP) were purchased from Sigma Co. Chloroform (Analar grade) was purchased from BDH.

Methods:

A Rank (II) micro-electrophoresis apparatus (Rank Bros., Cambridge) was used. The apparatus consists of a cylindrical glass cell placed in a thermo stated water bath kept at 25°C or 37°C. A platinum black electrodes, prepared by oxidation in platinum chloride for DMPC liposomes in water or low ionic media (< 0.1M) or Ag/AgCl reversible electrodes for DMPC liposomes in high ionic strength media, where placed at either end of the cell. The particle mobility was followed using the microscope attachment at a magnification of 400X.

Determination of the micro-electrophoretic mobility (EPM) (UE):

EPM (UE) has been determined using the following relationship

$$U_E = \frac{\text{Particle velocity } (\mu ms^{-1}) / \text{ voltage applied(v)}}{\text{Interelectrode distance (cm)}} \quad (1)$$

Hence U_E unit is $\mu ms^{-1}v^{-1}cm$.

The distance travelled by the particles was kept constant at 60 µm throughout the study. The voltage applied was adjusted at 40v. The inter electrode distance (L) was determined using 0.1 M KCl solution of known specific conductivity (K), from the following equation

$$K=L/A.R \quad (2)$$

Where A is the cross sectional area of the cell=πr^2 (r=the radius of the cell).

R=the resistance 0.1 M KCl solution which was calculated using a conductivity bridge (Wayne-Kerr B462) and by plotting the voltage (v) against current (I) where the gradient is equal to R. A value of 6.96 cm was obtained for the inter electrode distance (L). The apparatus was calibrated using human RBC in 1/15M phosphate buffer (pH 7.4) at 25°C. A value of -1.27 $\mu ms^{-1}v^{-1}cm$ for U_E was obtained compared with a literature value of -1.28 $\mu ms^{-1}v^{-1}cm$ [46].

Preparation of DMPC liposomes for electrophoresis experiments:

Accurately weighed DMPC was dissolved in chloroform (1mg.ml^{-1}) in around bottom flask. The chloroform was evaporated on a rotary evaporator (Rotavapor-R, Buchii) at 40^{o}C. Traces of chloroform were removed by introducing a jet of dry N_2. The dry lipid film is then dispersed indifferent media in the absence or presence of different CPZ-HCl concentrations to make a final lipid concentration of 0.015g.ml^{-1}. The dispersions were swirled using a vortex mixer at 40^{o}C to form large multilayer liposomes. The different liposomal dispersions were equilibrated in a water bath at 25^{o}C or 37^{o}C for 48 hours and were protected from light to prevent CPZ-HCl photolysis. Ionic lipid ST and DCP were incorporated at a concentration of 0.1mg.ml^{-1}. For pH studies, 0.1M NaOH or 0.1M HCl was used for pH adjustment. 5ml liposomal dispersions were used for determining U_E. The U_E was determined by timing twenty different particles in each direction and the mean taken.

Electrophoresis experimental:

The following experiments were carried out:

a) The effect of CPZ-HCl concentrations on the U_E of DMPC liposomes in water (pH 6.0), in 0.2M phosphate buffer (pH 6.0) and in 0.1 M KCl (pH 6.2) at 25^{o}C.

b) The effect of CPZ-HCl concentrations on the U_E of DMPC liposomes in water (pH7.4), in 0.2M phosphate buffer (pH 7.4) and in human plasma (pH 7.4) at 37^{o}C.

c) The effect of KCl concentrations on the U_E of DMPC liposomes pH (6.2) 25^{o}C.

d) The effect of CPZ-HCl concentrations on the U_E of both positively charged DMPC/stearyl amine (ST) liposomes and negatively charged DMPC/dicetyl phosphate (DCP) liposomes in 0.2M phosphate buffer (pH 6.0)at 37^{o}C.

e) The effect of pH on the U_E of DMPC, DMPC/ CPZ-HCl, DMPC/ST, DMPC/ST/CPZ-HCl, DMPC/DCP and DMPC/DCP/CPZ-HCl liposomes in water at 25^{o}C.

f) The effect of pH on U_E of DMPC and DMPC/CPZ-HCl liposomes in 0.1M KCl at 25^{o}C.

g) The effect of CPZ-HCl at concentrations known to cause anesthesia, on U_E of DMPC, DMPC/ST and DMPC/DCP liposomes in 0.2 M phosphate buffer (pH 7.4) at 37^{o}C.

RESULTS AND DISCUSSION: DMPC liposomes acquired negative charges in the presence of 0.2M phosphate buffer (pH 6.0) and in 0.1M KCl (pH 6.2) at 25^{o}C (**Fig. 1**) as well as in 0.2M phosphate buffer (pH 7.4) at 37^{o}C (**Fig.2**).

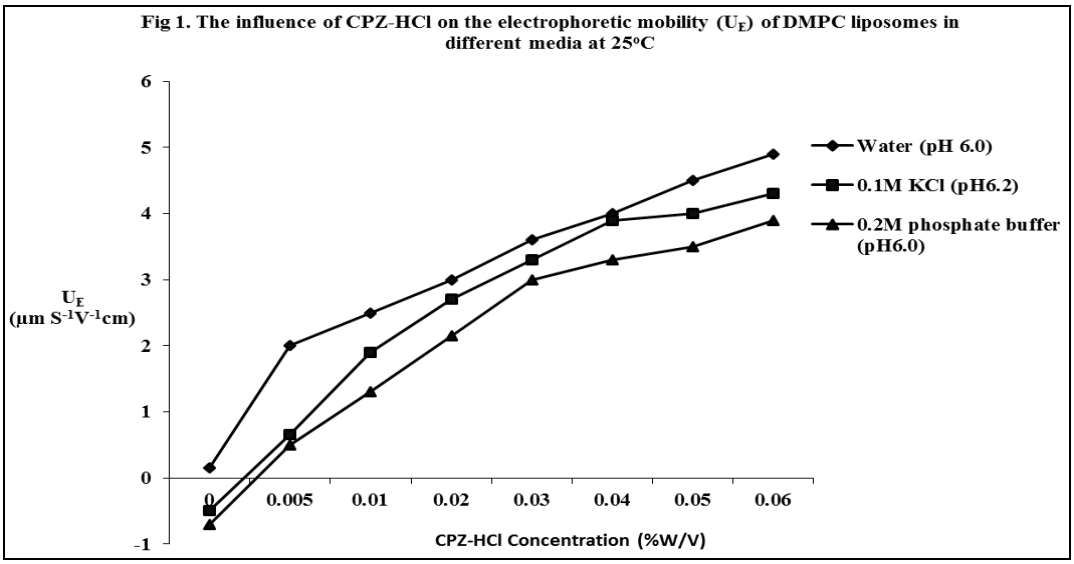

FIG.1: THE INFLUENCE OF CPZ-HCl ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC LIPOSOMES IN DIFFERENT MEDIA AT 25°C

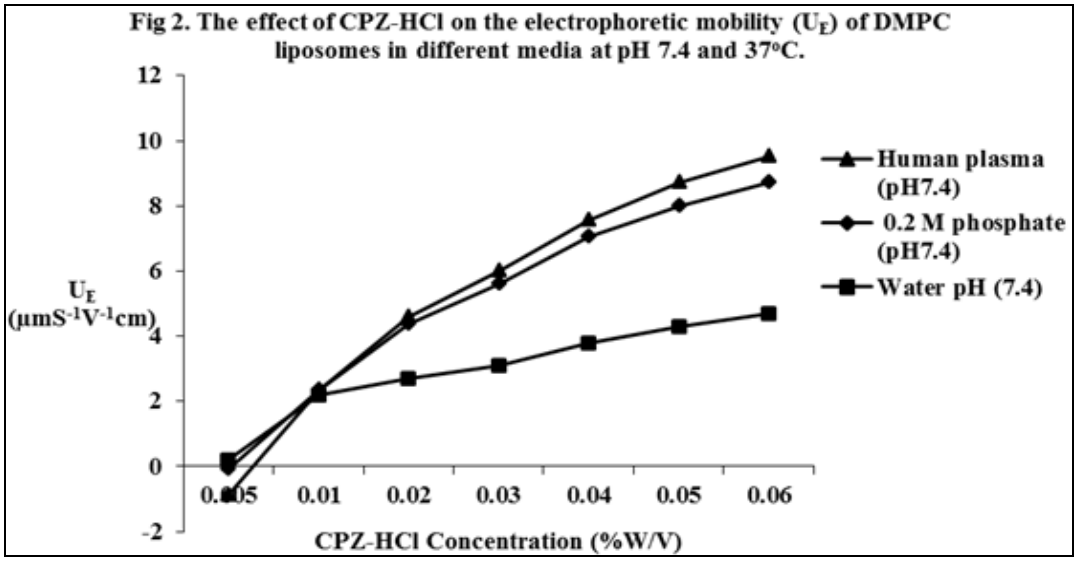

FIG.2: THE EFFECT OF CPZ-HCl ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC LIPOSOMES IN DIFFERENT MEDIA AT pH 7.4 and 37°C

This negative mobility of DMPC liposomes was observed to increase linearly with increasing KCl concentrations **(Fig.3**).

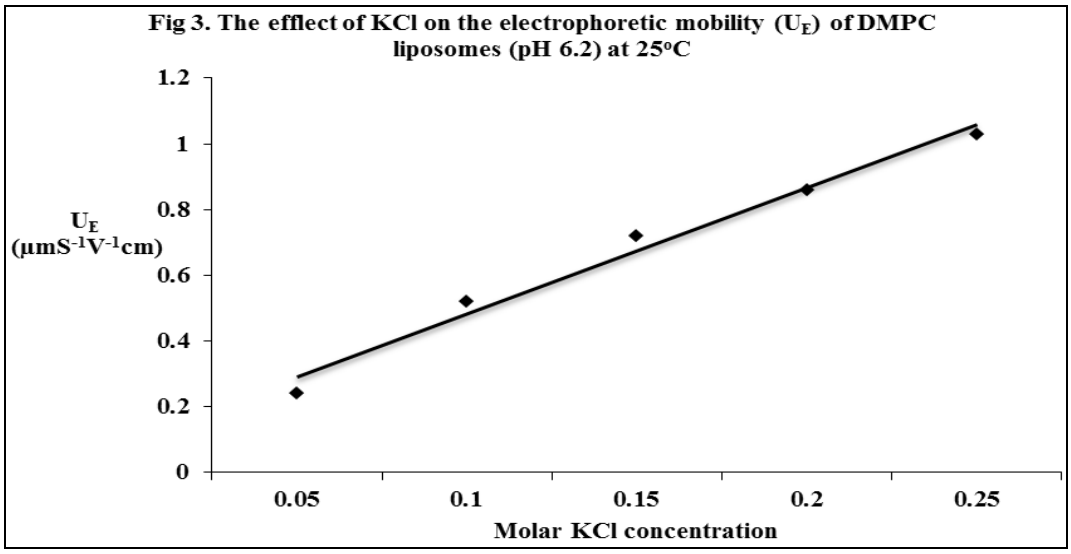

FIG.3: THE EFFECT OF KCl ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC LIPOSOMES (pH 6.2) AND 25°C

The mechanism of selective adsorption of Cl^- ions over K^+ in KCl and phosphate ions over Na^+ in the phosphate buffer can be attributed to the assumption that cations are generally more hydrated than anions and so they have greater tendency to reside in the bulk aqueous media whereas the smaller, less hydrated and more polarizing anions have the greater tendency to be preferentially adsorbed [47]. DMPC liposomes acquired a negative charge in human plasma (pH7.4) at 37°C (**Fig. 2**). Similar results were reported using phosphatidylcholine/cholesterol liposomes prepared in human plasma [48] and it was shown that the acquired negative charge is due to the adsorption of α_2-macroglobulin fraction of the plasma protein. It was observed that both neutral and ionic liposomes interact with α and β-globulin fraction of the plasma protein and acquired net negative charges [49].

The addition of increasing CPZ-HCl concentrations to DMPC liposomes in water (pH6.0), in phosphate buffer (pH 6.0) and in 0.1 M KCl (pH6.2) at 25°C (**Fig. 1**), as well as to DMPC liposomes in water (pH 7.4), in 0.2M phosphate buffer (pH 7.4) and in human plasma (pH7.4) at 37°C (**Fig. 2**), was observed to shift the electrophoretic mobility towards positivity. This indicates an increase in the

surface concentration of positively charged CPZ ions, where CPZ-HCl is predominantly at these pHs. The shift in electrophoretic mobility of DMPC liposomes in human plasma towards positive mobility was observed to be considerably reduced compared with other media (**Fig. 2**) and this may be attributed to the possible interaction of part of the positively charged CPZ ions with negatively charged α and β-globulin fraction of the plasma protein. The effect of ionic lipids on the electrophoretic mobility of DMPC liposomes in the absence and present of CPZ-HCl in phosphate buffer (pH 6.0) at 25^{o}C was also investigated (**Fig. 4**).

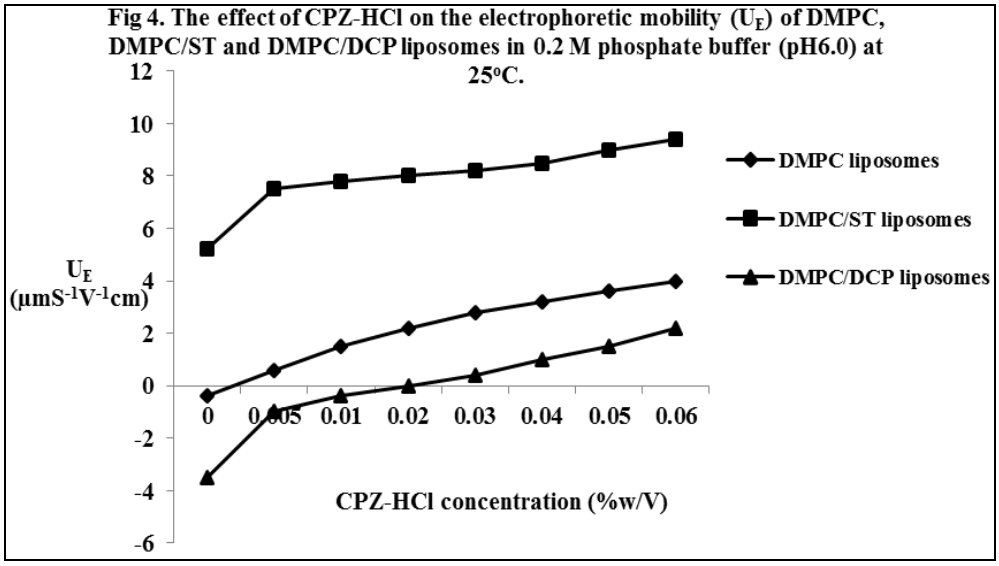

FIG.4: THE EFFECT OF CPZ- HCl ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC, DMPC/ST AND DMPC /DCP LIPOSOMES IN 0.2 M PHOSHPHATE BUFFER (pH 6.o) AT 25°C

The addition of the positively charged lipid ST to DMPC, resulted in highly positively charged liposomes (**Fig. 4**). This is due to the ionization of the amine group at the surface of the bilayer. The addition of increasing CPZ-HCl concentrations to these positively charged liposomes, increases further their positive mobilities (**Fig. 4**). The addition of anionic lipid DCP to DMPC, resulted in negatively charged liposomes (**Fig. 4**). The addition of CPZ-HCl to negatively charged DMPC /DCP liposomes also shifted mobility towards positivity (**Fig. 4**). Similar results that were reported in the literature, where it was observed that the addition of organic cations such as acetylcholine and tetraethylammonium chloride to negatively charged phosphatidylserine liposomes increases their mobilities towards positivity [50]. Similarly cetyltrimethylammonium bromide was observed to shift the mobility of negatively charged lecithin/dicetylphosphoric acid liposomes towards positivity [51].

DMPC liposomes in water over a pH range (2-12) showed negligible electrophoretic mobility (**Fig. 5**). This agrees with similar studies reported in literature [52]. Since the phosphatidylcholine molecule contains both a negative phosphate residue and a positive $-N^{+}(CH_3)_3$ group on the choline moiety, the net charge effect is zero. Hence phosphatidylcholine molecule is known to be isoelectric over a wide pH range.

The mobility of the positively charged DMPC/ST liposomes remains almost constant throughout the pH range studied (**Fig. 5**). The addition of CPZ-HCl to both DMPC and DMPC/ST liposomes, increases the mobility towards positivity (**Fig. 5**). At low pH values, higher mobilities were observed and the mobility started to decrease when the pH values approached the pK_a of CPZ-HCl of 9.2 (**Fig 5**). This decrease in the electrophoretic mobility at pH values higher than the pK_a of the drug is due to the fact that the unionized form of CPZ predominates over the ionized form.

DMPC liposomes in 0.1M KCl at 25^{o}C, exhibited negative mobilities which remain almost constant throughout the pH range 2-12 (**Fig. 6**).

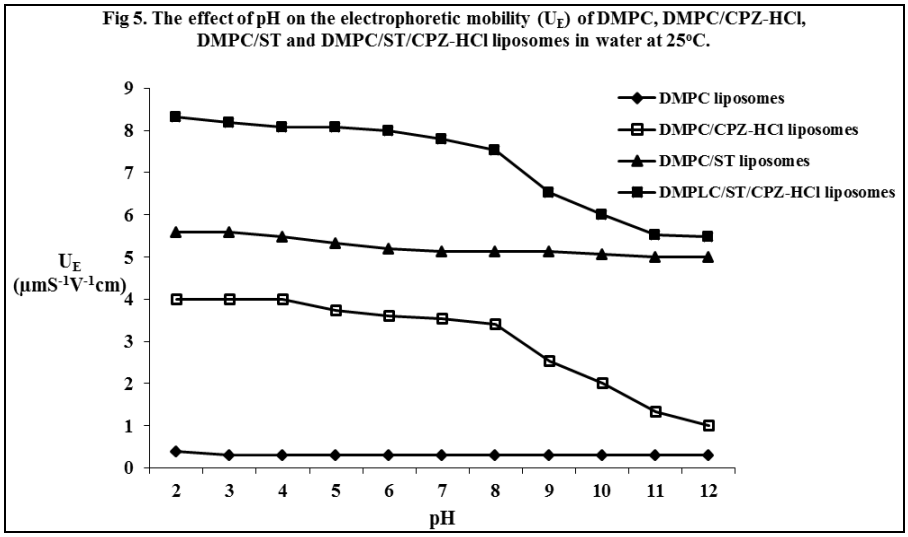

FIG.5: THE EFFECT OF pH ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC, DMPC/CPZ-HCl, DMPC/ST AND DMPC /ST/CPZ-HCl LIPOSOMES IN WATER AT 25°C

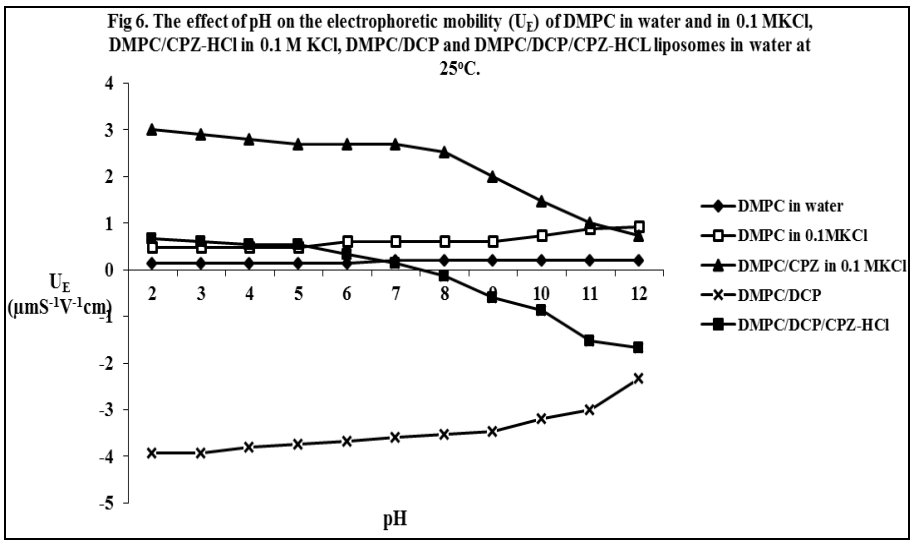

FIG.6: THE EFFECT OF pH ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC IN WATER AND IN 0.1 M KCl, DMPC/CPZ-HCl, IN 0.1M KCl DMPC/DCP AND DMPC/DCP/CPZ-HCl LIPOSOMES IN WATER AT 25°C

The addition of CPZ-HCl, shifted the negative mobility towards positivity (**Fig. 6**). The mobility as a function of pH started to decrease at pH values equivalent to the pK_a of CPZ-HCl and continued to decrease at higher pH values (**Fig.6**). The negatively charged DMPC /DCP liposomes showed high negative mobilities at low pH values which decreased gradually with increasing pH (**Fig. 6**). Addition of CPZ-HCl, to these negatively charged liposomes shifted the mobility towards neutrality, in fact at low pH values a positive mobility was observed where CPZ-HCl is fully ionized and the mobility started to shift towards negativity at higher pH values where CPZ-HCl is mostly unionized (**Fig. 6**). The effect of CPZ-HCl at concentrations known to cause anesthesia on the mobility of DMPC liposomes in 0.2 M phosphate buffer (pH 7.4) at 37^{o}C, in the presence and absence of ionic lipid is shown in **Fig. 7.** The addition of CPZ-HCl to DMPC liposomes shifted the mobility from negativity towards positivity (**Fig. 7**). The mobility was observed to increase linearly as a function of log molar CPZ-HCl concentration. The additon of CPZ-HCl to negatively charged DMPC/DCP liposomes was observed to increase towards neutrality and the mobility also exhibited a linear relationship as a function of log molar CPZ-HCl concentration (**Fig. 7**). The addition of CPZ-HCl to positively charged DMPC/ST liposomes also increases the positive mobility and a linear relationship was also observed to exist between electrophoretic mobility log molar CPZ-HCl concentration (**Fig.7**).

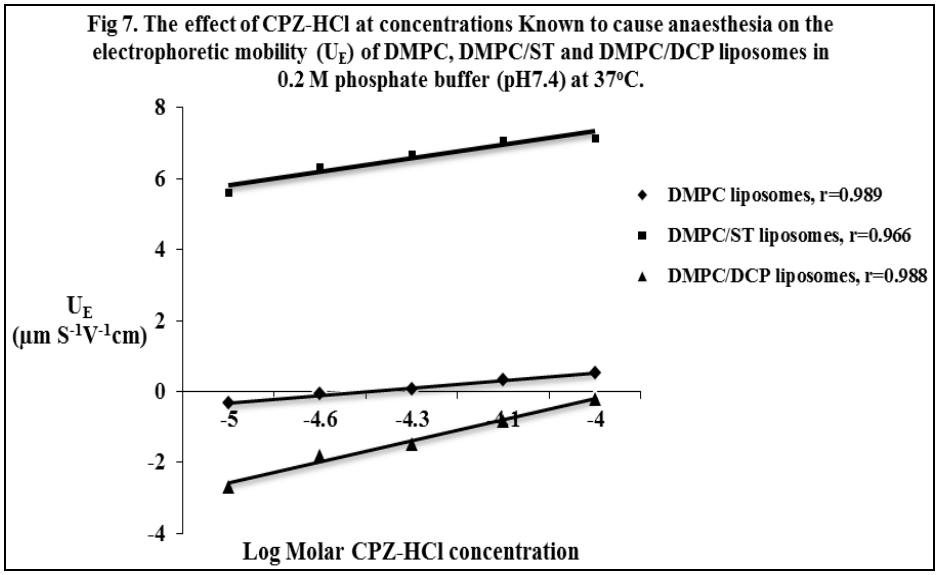

FIG.7: THE EFFECT OF CPZ-HCl AT CONCENTRATIONS KNOWN TO CAUSE ANAESTHESIA ON THE ELECTROPHORETIC MOBILITY (U_E) OF DMPC/ST and DMPC/DCP LIPOSOMES IN 0.2M PHOSPHATE BUFFER (pH 7.4) AT 37°C

CONCLUSION: Present study indicates that DMPC liposomes in water exhibited zero electrophoretic mobility over a wide pH range, showing no specific isoelectric point. DMPC liposomes acquired net negative charges in aqueous KCl; this negativity was observed to increase linearly as a function of KCl concentration. DMPC liposomes also acquired negative charges in phosphate buffer (pH 6.0 and 7.4) and in human plasma (pH7.4). The acquired negative charge acquired in human plasma is due to the adsorption of α_2-macroglobulin fraction of the plasma protein. The incorporation of cationic and anionic lipid produced additive-induced charges in the surface charge characteristics of the liposomes. The addition of CPZ-HCl shifted the mobility of neutral, positive and negative DMPC liposomes towards positive mobility.

At pH values equivalent or more than the pk_a of CPZ-HCl, the mobility of DMPC liposomes decreases which is due to the predominantly unionized form of the drug. Linear relationship were observed between the electrophoretic mobility of DMPC, DMPC /ST, and DMPC /DCP liposomes as a function of log molar CPZ-HCl concentrations known to cause anesthesia.

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