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Effect of salt and urea on complexation behavior of pharmaceutical excipient gelatin with phenothiazine drug promazine hydrochloride

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ABSTRACT

An evaluation of the interactions of cationic phenothiazine drug promazine hydrochloride (PMZ) with gelatin in aqueous solution as well as in the presence of 50 mM NaCl and 100 mM urea, investigated through different physicochemical measurements is presented in the present study using conductometric method. PMZ is used for the control of mania and schizophrenia. The drug interacts with gelatin similar to the interaction of surfactants and polymers. The plots of specific conductivity versus concentration of the drug were nonlinear with three different linear regions with two clear breaks. The first break point, i.e., critical aggregation concentration (*cac*), appeared well below the typical critical micelle concentration (*cmc*). The second break point is considered as polymer saturation point (*psp*) that is akin to *cmc*. The *cac* value decreases on increasing the gelatin concentration, whereas the *psp* value increases for all fixed concentrations (%w/v) of gelatin which is a clear signal of the interaction of the drug with gelatin. As inorganic salts increase the ionic strength, the solubility of amphiphile (drug) is lowered by ionic screening effects, ensuing in a greater tendency to aggregates at lower concentration. As a result, both the *cac* and *psp*/*cmc* values decrease. By the addition of urea an increase in the surface charge of the micelles was observed followed by halt of the aggregation of the drug hence both the *cac* and *psp*/*cmc* values increase. Free energies of aggregation (ΔG_{agg}), micellization (ΔG_{mic}), polymer saturation (ΔG_{psp}) and transfer (ΔG_t) were also evaluated.

1. Introduction

Amphiphiles have been the focus of considerable research interest because of their characteristics, such as surfactant–macromolecule (protein) interaction, which make them suitable for a variety of applications including drug delivery, cosmetics and foods [1,2]. It has been well known in polymer science that a positively or negatively charged polyelectrolyte electrostatically interacts with an oppositely charged coworker to form a polyion complex and has been broadly explored for drug coating and encapsulation [3,4]. It appears unlikely that all of the ionic interactions between the two polyelectrolytes with many charged groups are dissociated at the same time. Therefore, contrary to low-molecular-weight electrolytes, stable bonding will take place between the oppositely charged polyelectrolytes, which will not be dissociated effortlessly. The application of this polyion complexation, which we will explain here, is "drug complexation with polymer carriers". This is a new test that will permit us to pharmaceutically modify a charged polymeric drug to increase its stability, targeting and sustained release, leading to improved therapeutic efficacy.

Gelatin, the denatured form of collagen, is one of the proteins used as surfactants in industry (Fig. 1(a)). Normally, gelatin is commercially made from skins and skeletons of bovine and porcine [5] and is used widely for industrial, pharmaceutical, and medical applications [6]. Moreover, it is suggested as one of the most used natural materials, extensively engaged due to its biocompatibility, biodegradation, nontoxicity and nonimmunogenicity [7,8]. Owing to the various potential uses of gelatin, it is useful to explore its amendment to build up new materials with enhanced properties [9]. Gelatin encloses many glycine (almost 1 in 3 residues, arranged every third residue), proline and 4-hydroxyproline residues. A distinctive structure is -Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro-. Gelatin contains the mixtures of these strands together with their oligomers and breakdown (and other) polypeptides. Gelatin is a denatured protein and does not interact with surfactants like the folded proteins do [10]. Gelatin may interact in a surfactant-like manner with the occurrence of both critical aggregation concentration (*cac*) as well as polymer saturation point (*psp*) [11–13] and hydrophobic and electrostatic forces play a significant role in the interaction.

Herein we have studied the effect of gelatin on the association phenomenon of promazine hydrochloride (PMZ, 10-(3-dimethylaminopropyl) phenothiazine hydrochloride), the most widely prescribed

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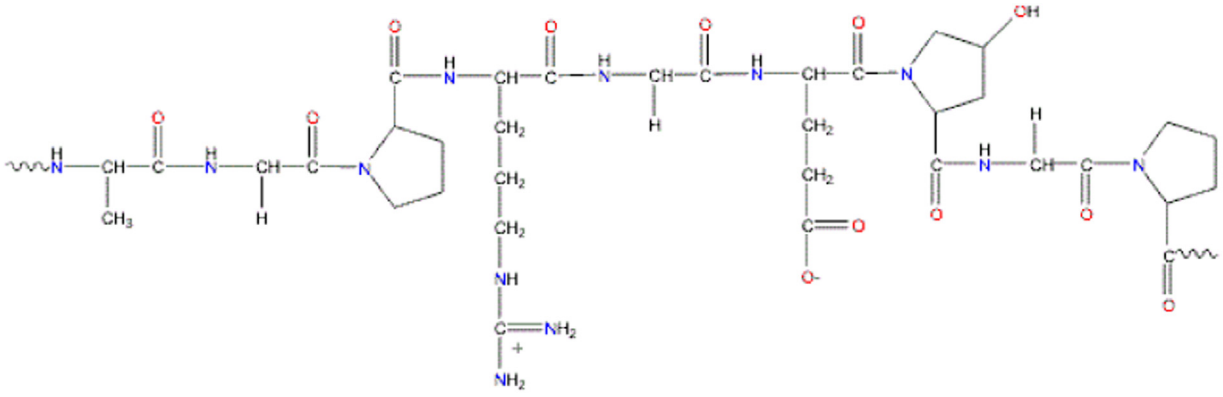
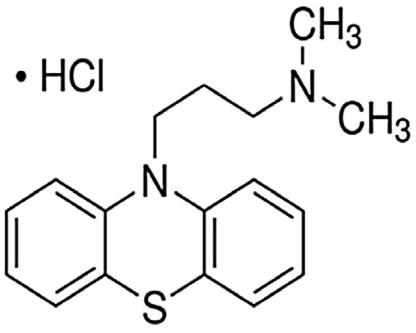


(a)



(b)

Fig. 1. Molecular model of (a) gelatin and (b) promazine hydrochloride (PMZ).

tricyclic phenothiazine drug (Fig. 1(b)) in the absence and presence of 50 mM NaCl and 100 mM urea. PMZ which consists of two phenyl rings joined by sulfur and nitrogen atoms along with an aminopropyl chain is used for the control of mania and schizophrenia. PMZ shows similar aggregation behavior to that of surfactant due to the presence of a tricyclic rigid ring part which behaves as a hydrophobic part and an aminopropyl part which acts as a hydrophilic head group. Its pKa value is 9.4 [14] and, under physiological conditions, it acquires a positive charge. The effect of inorganic salts is known to alter the properties of amphiphile solutions, like solubility, aggregation numbers (N_{agg}), shape, solute–solute and solute–solvent interaction parameters, etc. On the whole, since inorganic salts increase the ionic strength, the solubility of an ionic surfactant will be lowered by ionic screening effects, ensuing in a greater propensity to form aggregates at lower concentration, i.e., decreasing of the *cac* or *cmc*/*psp* value. Previously, the decrease was elucidated in terms of the dehydration of hydrophilic groups, that is the salting out [15]. However, it has been claimed that the salting out of the hydrocarbon chains also contributes considerably to the decrease in *cmc* [16]. Urea is found in the body and their effect on micellization will allow the better designing of effective therapeutic agents. Keeping all the above facts in mind, we have systematically studied the PMZ–gelatin interaction by conductometry in the absence and presence of salt and urea.

2. Materials and method

2.1. Materials

The amphiphilic drug PMZ (≥98%, Sigma, USA) was used as received. Sodium chloride, NaCl (97%, BDH, England), urea, NH_2–CO–NH_2 (99%, Sigma, Germany) and gelatin from bovine skin (Sigma, USA, 225 bloom, type B) were used as received. Double-distilled water with conductivity lower than $1–6 \times 10^{-6}$ S cm^{-1} was used to prepare the solutions. A stock solution of 0.40% gelatin was prepared by weight for which 0.40 g of gelatin was dissolved in 100 ml distilled water/50 mM NaCl/100 mM urea solution, the gelatin was stirred with the spoon or glass rod and left to swell for at least an hour, or overnight. On the second day, the stock solution was slightly heated, cooled to room temperature, warmed, and cooled again until it is fully dissolved. This gelatin solution was diluted with distilled water/50 mM NaCl/100 mM urea solution to obtain other different concentrations (0.05%, 0.10%, 0.15%, 0.20% and 0.30%) of gelatin which were used as solvent for preparation of stock solution of drug–gelatin mixtures in the absence and presence of 50 mM NaCl/100 mM urea. The use of buffer was avoided due to the plausible phase separation of PMZ in the presence of electrolytes. On the other hand, the pH of the solution was recorded at the beginning and end of every measurement which was always found to be in the range of 6.85–6.20; this is well above the isoelectric point of type B gelatin (4.8) [17]. Hence, in the present case the gelatin has the domination of negative over the positive sites.

2.2. Conductivity measurements

The conductivity meter principle is a digital representation of solution conductivity with conduction current capacity. Application of a conductivity meter is required in laboratory for measurements of electrical conductivity of solution. A conductivity meter bridge (model 4510, Jenway, UK), using a cell constant of 1.0 cm^{-1} dip cell (glass electrode), was used for the collection of solution conductance. The temperature was kept constant by means of circulating water through a