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Original Article

ESTIMATION OF THE DRUG-DRUG AND DRUG-POLYMER OPHTHALMIC COMPLEX AT STOICHIOMETRY BY TERNARY PHASE BEHAVIOUR

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ABSTRACT

Objective: The study focus on the drug-drug and drug-polymer interaction and their estimation at stoichiometry when such systems were formed. In this discovery we tried to make use of the latest research and novel concepts to explore the drug-polymer-polymer Ionic ternary Interaction

Methods: Partial ternary phase diagrams were constructed and the stoichiometry of the ciprofloxacin/anionic polymer interaction was assessed in distilled water by means of dialysis equilibrium. The polymers were completely hydrated in distilled water by gentle stirring at room temperature and studied for viscosity and turbidimetric measurements.

Results: Comparing the partial ternary phase diagrams of the different anionic to each other. PAA exhibited the largest gel area even with low polymer content. The anionic polymers HA and PAA showed good capability to interact with the drug giving soluble drug/polymer complexes; moreover they were able to form polymer/polymer complexes with Poloxamer and HCS, with a stoichiometry depending on the polymers involved.

Conclusion: From the results of the present study, it can be concluded that formulations were made isotonic and favours corneal permeation of both the drug. Ocular Irritancy denotes formulations were quite stable & useful in novel format of sol-gel transformations.

Keywords: Cationic, Anionic, Cul-de-sac, Poloxamer.

INTRODUCTION

The ophthalmic products should always been considered for the critical bioavailability and ocular retention. The critical parameters in ocular dosage form depend upon the interaction between drug and polymer. Extensive literature is available on drug-drug-polymer interaction [1]. Yet most data were not capable of describing things efficiently. In the present study, we tried to elaborate drug-drug-polymer interaction at stoichiometric concentration by ternary phase behaviour study. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye [2, 3]. To enhance the amount of active substance reaching the target tissue or exerting a local effect in the cul-de-sac, the residence time of the drug in the tear film should be lengthened. The use of a water-soluble polymer to enhance the contact time and possibly also the penetration of the drug was previously proposed by different authors. Where very promising results and improved bioavailability were observed in animal studies, only a small increase in precorneal residence time was obtained in humans [4]. The most useful an alternative approach has been the application of in situ gelling systems or phase transition systems, which are instilled in a liquid form and shift to a gel or solid phase in the cul-de-sac. The phase transition is triggered by the pH of the tears, the temperature at the eye surface or the electrolytes present in the tear film. A further approach to optimize the ocular dosage form was the implementation of the mucoadhesive concept. Interactions of suitable natural and synthetic polymers with mucin were evaluated. Due to interactions with the mucus layer or the eye tissues, an increase in the precorneal residence time of the preparation was observed [5]. The present study will focus on development of the formulation of Ophthalmic Gel and Solution. In this discovery, we tried to make use of the latest research and novel concepts to explore the drug-polymer-polymer Ionic ternary Interaction.

MATERIALS AND METHODS

Poloxamer P407 was obtained from BASF Corp. (Ludwigshafen, Germany); Ciprofloxacin HCl was kindly gifted from Inventia healthcare Pvt. Ltd. (INDIA). Chitosan and PVA were purchased from MERK. Triethanolamine, Benzalkonium chlorides were obtained from Research lab fine chem. industries (INDIA). Poloxamer (P), Polyacrylic acid (PAA), Polyvinyl alcohol (PVA) was obtained from laboratory UDPS, Nagpur University.

Effect of ionic interaction on phase behaviour

Constructions of ternary phase diagrams

Partial ternary phase diagrams were constructed for (≤2% (w/v) of polymeric solution, anion and cation. The effect of cationic and anionic interaction that is feasible for the sol to gel transition was investigated. Polymers were dissolved in water & then, the appropriate amount of a 1% cationic & anionic solution was added in stoichiometry and left overnight to equilibrate. Formulations were assessed the following day in terms of their visual appearance and flow (by tilting the vial to an angle of 90ñ), and were classified as solutions, viscous solutions or gels.

Estimation of the drug–polymer complex

The stoichiometry of the ciprofloxacin/anionic polymer interaction was assessed in distilled water by means of dialysis equilibrium. Dialysis bags were filled with 10 ml of a 0.5% w/v anionic polymer solution. The bags were closed and put in 40 ml of ciprofloxacin solution where they were maintained under agitation at 37 °C until equilibrium was reached (24h). The dialysis membrane did not allow the polymer to get out but allowed the ciprofloxacin to diffuse into and eventually to interact with the polymer. Different initial ciprofloxacin concentrations outside the dialysis bags were tested ranging between 0.5 and 5 µM. After the equilibrium was attained, the final ciprofloxacin concentration outside the dialysis bag was assayed by means of a spectrophotometrically detection at 274.2 nm specific wavelengths. The data were interpreted & the procedures were reproduced with ketorolac tromethamine [6, 7].

Estimation of the polymer–polymer complex

viscosimetric measurements

The polymers were completely hydrated in distilled water by gentle stirring at room temperature. Mixtures (30 ml) containing a fixed amount of HCS (0.5% w/w) and increasing amounts of the anionic polymers (HA and PAA) were also prepared at different ratios ranging from 1/0.25 to 1/2. The interaction products were removed by means of the centrifugation at 2000 rpm for 10 min and the viscosity of the supernatants was measured. The polymer/polymer ratio where a minimum of viscosity was observed could be considered the

stoichiometric composition of the complex. Viscosity measurements were performed by means of a Brookfield rheometer [8].

turbidimetric measurements

turbidimetric measurements were effected employing a spectrophotometer UV/VIS specified wavelength. The turbidity of 0.1% w/v HCS polymer solutions (30 ml) prepared in distilled water was evaluated after successive additions of fixed amounts (1 ml) of each anionic polymer (HA and PAA) hydrated in the same media at the same concentration [9]. A maximum turbidity value corresponded to the stoichiometric polymer/polymer ratio.

RESULTS AND DISCUSSION

Effect of ionic interaction on phase behaviour

Constructions of ternary phase diagrams

Partial ternary phase diagrams for poloxamer solution, polycationic & polycationic polymer solution were shown in fig. 1 to 4. Systems based on poloxamer was much more susceptible to cationic polymerization at stoichiometry. While PAA was needed to transform chitosan formulation into a gel, same phase transition was achieved with 10 fold & 20 fold increase in polyanionic polymer composition with difference in poloxamer solution content. This was in accordance with previous study [10], who found that divalent cations give rise to much stronger double helical interactions at the junctional zones than two monovalent cations and gels of similar apparent viscosities can be formed with divalent cations at much lower concentrations of the polymer than are required for gelation with monovalent cations [11].

In the case of HA, gel formation was solely dependent on the polymer concentration, with almost no difference between the addition poloxamer solutions. The higher chitosan concentration required may partly be explained by the branched nature of the polymer backbone, with trisaccharide side chains preventing helix formation at low concentrations. The units that impart a strong anionic character to the polymer backbone resulting in high cation sensitivity. HA used in this study seemed to be more susceptible to chitosan than PAA as seen by the slightly bigger gel area in Figure.1 compared to fig. 2. While addition of poloxamer base solution having specific cationic & anionic interaction would found to enhance the gelling behaviour of the formulation. The need to achieve sol-to-gel phase transition was found to satisfy with 20 folds anionic solution to cationic solution. Previously it has been reported increasing the borax-PVA ration also hardens the gelling property & so the redistribution more specifically the sol-gel transformation was found to be difficult. Comparing the partial ternary phase diagrams of the different anionic to each other, PAA exhibited the largest gel area even with low polymer content [5].

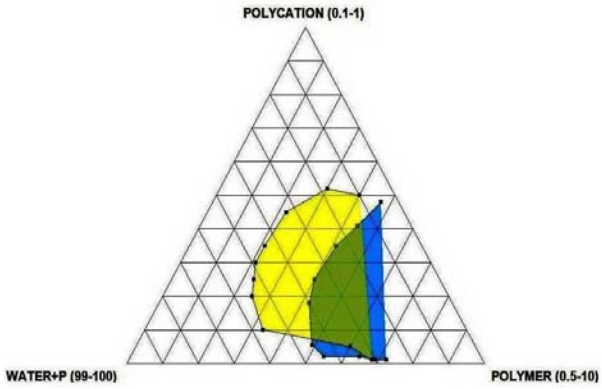

Fig. 1: The phase diagram showing formulation A, HCS as polycation, PAA as anionic polymer and poloxamer solution as Water+P. HCS was used in concentration range of 0.1 to 1 %. At stoichiometry, PAA in concentration range of 0.5 to 10 % and poloxamer solution of 18% was used for the preparation of pseudo ternary phase diagram

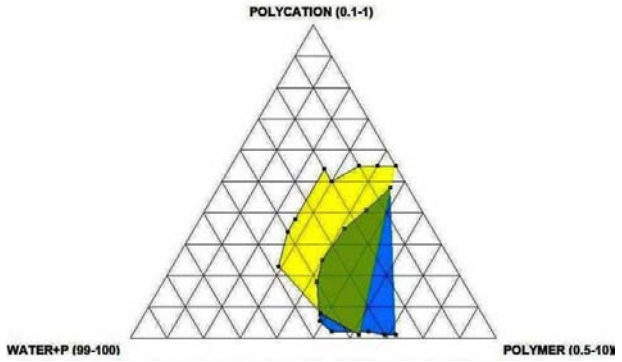

Fig. 2: The phase diagram showing formulation B, HCS as polycation, PAA as anionic polymer and poloxamer solution as Water+P. HCS were used in concentration range of 0.1 to 1 %. Where 20 fold excess PAA in concentration range of 0.5 to 10 % and poloxamer solution of 18% was used for the preparation of pseudo ternary phase diagram

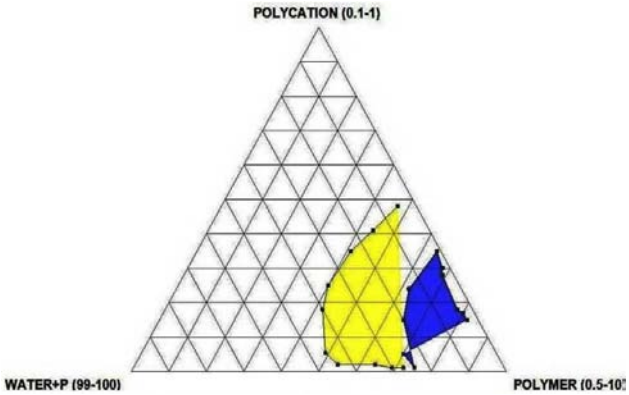

Fig. 3: The phase diagram showing formulation C, HCS as polycation, PAA as anionic polymer and poloxamer solution as Water+P. HCS were used in concentration range of 0.1 to 1 %. Where 20 fold excess HA in concentration range of 0.5 to 10 % and poloxamer solution of 18% was used for the preparation of pseudo ternary phase diagram

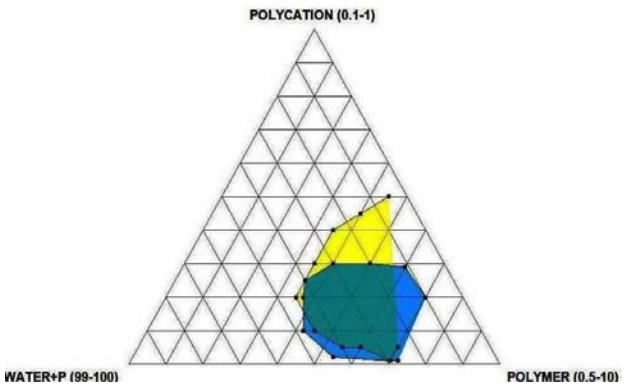

Fig. 4: The phase diagram showing formulation D, HCS as polycation, PAA as anionic polymer and poloxamer solution as Water+P. HCS were used in concentration range of 0.1 to 1 %. Whereas polyanionic combination of HAA and PAA was used in concentration range of 0.5 to 10 %

Estimation of the drug–polymer complex stoichiometry

Table 1 reports the values of maximum binding capacity n (μMol of drug bound per milligram of polymer) and Kd (constant of dissociation of the polymer–drug complex) obtained for the

interaction of the drug with anionic polymers HA and PAA. The values of the parameters confirm that an interaction between Cipro and the anionic polymers (HA and PAA) occurs resulting in an ionic complex. In particular, HA shows a higher binding capacity for Cipro with respect to PAA. Binding capacity values shows lower results with ketorolac tromethamin formulation [9]. The effect of cations on rheological and textural properties of the gels was in accordance with the results obtained for the partial ternary phase diagrams. In general, pseudoplastic systems showing an increase in the flow index upon increase in the cation concentration are preferred, as they would exhibit an increase in viscosity once in contact with the ions in the tear fluid [1, 5].

Table 1: Estimation of the drug–polymer complex stoichiometry

Formulation	n (µmol/mg polymer)	K_d (µM)
Cipro/HA	13.740	87.274
Keto/HA	11.411	82.142
Cipro/PAA	09.154	27.618
Keto/PAA	10.245	39.812

Estimation of the polymer–polymer complex stoichiometry

Table 2 reports the weight ratios corresponding to the stoichiometry of interaction obtained between oppositely charged polymers, by means of the viscosimetric and the turbidimetric methods. By means of viscosimetric measurements it was not possible to detect a minimum in the range of the weight ratios tested. The stoichiometric weight ratio is therefore below 1/0.25 for both P/HA and P/PAA. This was confirmed by means of the turbidimetric evaluations that determined the stoichiometry of P/HA and P/PAA interaction products as equal to 1/0.18 and 1/0.08. HCS interacts much more strongly with both the anionic polymers [9]. The stoichiometry of the HCS/HA interaction products is 1/1 weight ratio as evidenced by both the viscosimetric and the turbidimetric measurements. For HCS/PAA the stoichiometry for the interaction product as determined with the viscosimetric measurements, quite close to the value obtained with the turbidimetric ones[12]. Almost similar results were obtained with ketorolac formulations.

Table 2: Estimation of the polymer–polymer complex

Composition	Stoichiometric weight ratio	
	viscosimetric method	turbidimetric method
Cipro/HA	<1/0.25	<1/0.16
Keto/HA	<1/0.25	<1/0.16
Cipro/PAA	<1/0.25	<1/0.10
Keto/HA	<1/0.25	<1/0.10
HCS/HA	1/1	1/1
HCS/PAA	1/0.60	1/0.40

CONCLUSION

All systems exhibited physically entangled polymer networks, which renders them favourable for ocular use as they can easily disentangle upon shear stress associated with blinking. Formulations based on PVA and chitosan with Poloxamer solution as vehicle exhibited the most favourable characteristics in terms of phase transition, rheological and textural properties, as their viscosity remarkably increased upon contact with cations of the tear fluid, thus prolonging corneal residence time and reducing nasolacrimal drainage.

These systems should therefore be further investigated and compared for their *in vivo* performance. This study investigated a pseudo ternary phase diagram of Poloxamer solution and fixed combinations of cation and anionic ingredients.

An area could be identified containing formulations (gel-and creamlike) for appropriate ophthalmic application, whereas other systems were either too hard or liquid and thus inappropriate for this purpose. Some of the liquid in homogeneous systems could also gel around body temperature and could thus be used as vehicles for ophthalmic application of active pharmaceutical ingredients. The majority of the semisolid systems exhibited ringing gel characteristics.

The anionic polymers HA and PAA showed good capability to interact with the drug giving soluble drug/polymer complexes; moreover they were able to form polymer/polymer complexes with Poloxamer and HCS, with a stoichiometry depending on the polymers involved. Poloxamer mildly interacted with both HA and PAA resulting in just a slight turbidity, while HCS interaction with the anionic polymers was stronger with a marked opalescence.

CONFLICT OF INTERESTS

Declared None

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