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Research Article

Stability Prediction of Polymeric Suspensions of some Fluoroquinolones

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Abstract

Considering the importance of physical stability, zeta potential values, percentage volume of sedimentation and redispersibility of polymeric suspensions of some fluoroquinolones like Ciprofloxacin (Cipro) and Ofloxacin (Oflox) were measured. These formulations were prepared using two grades of Carbopol polymer such as C934 and C940; and Hydroxypropyl methylcellulose (HPMC). Above mentioned values of each suspension was determined by following standard methods. The results of those experiments suggested that Cipro with HPMC and Oflox with C940 were probably more physically stable and flocculated than other suspensions.

Keywords: Polymeric suspension, Ciprofloxacin, Ofloxacin, Zeta potential

1.Introduction

Zeta potential is a scientific term for electrokinetic potential in colloidal systems. It is the potential difference between the dispersion medium and the stationary layer of fluid attached to the dispersed particles.[1] As we know, the particle charge is one of the factors determining the physical stability of suspensions.[2] Higher is the electrostatic repulsion between the particles, higher is the physical stability. Typically the particle charge is quantified as the so called zeta potential, which is measured *e.g. via* the electrophoretic mobility of the particles in an electrical field. [1] During the particle movement, the diffuse layer is shorn off; hence the particle obtains a charge due to the loss of the counter ions in the diffuse layer. This potential at the plane of shear is called the zeta potential.[3] The significance of zeta potential is that its value can be related to the physical stability of colloidal dispersions. Actually, the physical stability of the colloid is a balance between the attractive Van der Waals' forces and the electrical repulsion due to the surface charge. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in a dispersion. If the zeta potential falls below a certain level, the force of attraction between particles exceeds the force of repulsion, and the dispersion will break and flocculate. This phenomenon is referred to as flocculation. In other words, the colloid will aggregate due to the attractive forces. Conversely, a high zeta potential maintains a stable system (mentioned earlier). That is why molecules and particles that are small enough, having a high zeta potential, will confer stability, *i.e.* the solution or dispersion will resist aggregation. So, colloids with high zeta potential (negative or positive) are electrically stabilized, while colloids with low zeta potentials tend to coagulate or flocculate.[4]

Generally, redispersible suspensions have a high sedimentation volume, because a low sedimentation volume usually indicates the occurrence of caking. On the other hand, high sedimentation volume suggests flocculation, rather than caking. Generally, the aim is to make suspensions in which the ingredients have high pourability and those suspensions must possess high sedimentation volume and good redispersibility properties. This is done because a suspension having a high sedimentation volume and good redispersibility forms a physically stable suspension.[5,6]

Considering the importance of obtaining stable suspensions, the values of zeta potential, percentage volume of sedimentation and redispersibility of different polymeric suspensions containing two fluoroquinolone antibacterial agents such as Ciprofloxacin (Cipro) and Ofloxacin (Oflox) were determined. For the study, three polymers, Hydroxypropyl methylcellulose (HPMC) and two grades of Carbopol polymer (C934 and C940), were selected.

2. Materials and Methods

2.1. Materials

The following materials were used for the study: Ciprofloxacin (Cipro) and Ofloxacin (Oflox) were obtained from Dr. Reddy's Lab, Hyderabad, India, as gift samples. Hydroxypropyl methylcellulose (HPMC E15 LV Premium) was supplied by Loba Chemie Pvt. Ltd., Mumbai, India. It was having methoxy group (23.8%) and hydroxypropoxy group (8.3%). Pluronic F 68 and Soya lecithin were purchased from Himedia Laboratories Pvt. Ltd., India. C934, C940, Glycerol, Citric acid, Sodium citrate, Methyl praraben sodium, Propyl paraben sodium, Sorbitol solution I.P. and Sucrose were supplied by Cosmo Chem. Laboratory, Pune, India. Tri-sodium citrate dehydrate purified was obtained from Merck Specialities Private Limited, Mumbai, India. Ultra pure water was obtained from a Millipore Milli-Q UV water filtration system.

2.2. Preparation of Formulations

Preparation of Bulk A: In a beaker, 6 ml of distilled water was heated up to 80°C. Sucrose (10 g) was added to the hot water under continuous stirring. The temperature was monitored in such a way so that it should not fall below 70°C, till the sucrose was completely dissolved. The prepared syrup was cooled properly at room temperature and kept overnight. Syrup was filtered using 120 mesh nylon cloth.

Preparation of Bulk B: Five milliliters of distilled water was taken in a beaker to which 1.8 ml of sorbitol solution and 0.2 ml glycerin were added. The mixture was stirred properly. To this solution, pluronic F 68 (5%), soya lecithin (1%) and 5% of each polymer in w/w of drug were added with continuous stirring.

Preparation of Polymeric Suspension and Ultrasonication: Five millilitre of distilled water was taken in another beaker to which a drug (1.25 g of Cipro/250 mg of Oflox) was added. To the drug suspension, the bulk B and bulk A were added with continuous stirring. The volume was made up to 25 ml by Ultra pure water. The pH of both the formulations containing Cipro/Oflox was 5.5, only in case of Cipro formulations; pH was adjusted by citrate buffer. Homogenization was carried out for at least 20 min by ULTRASONIC HOMOZENIZER

LABSONIC® M (SARTORIUS), having operating frequency 30 KHz and line voltage 230 V/50 Hz, using the probe made up of Titanium of diameter 7 mm and length 80 mm. The setting knob "cycle" was adjusted to 0.8, indicating sound was emitted for 0.8s and paused for 0.2s. In this manner, we could expose our sample with 100% amplitude, while reducing the heating effect to 80%. This LABSONICRM generates longitudinal mechanical vibrations with a frequency of 30,000 oscillations / s (30 KHz). The probes bolted to the sound transducer were made of high-strength Titanium alloys, built as λ/2 oscillators. It amplified the vertical oscillation and transferred the ultrasonic energy *via* its front surface with extremely high power density into the sample that was to be subjected to ultrasonic waves. In the present study, stress applied was sound wave and, in addition, mild rise in temperature of the sample occurred during ultrasonication, which helped in the homogenization of the suspensions.

The results of optimization study (performed earlier in our laboratory) suggested the optimized formula for the preparation of polymeric suspensions. The composition of the optimized formula was as follows (percentage with respect to ciprofloxacin/ofloxacin):

Polymer (HPMC/C934/C940): 5%; Pluronic F68: 5%; Soya lecithin: 1%; Sorbitol Solution (80%): 7.2%; Glycerin: 0.8%; Simple Syrup IP: 40%; Distilled water q.s. up to 100 ml.

The concentration of ciprofloxacin used in the formulation was 1.25 g/25 ml of distilled water and the same for ofloxacin was 250 mg/25 ml of distilled water.

2.3. Measurement of Zeta Potential

The zeta potential value of each formulation was determined by a Malvern Zetasizer (Malvern Instruments, UK). The analysis was performed using a clear disposable zeta cell in distilled water at 25 °C. The zeta potential distribution values were obtained from the graph between zeta potential and total counts.[7]

2.4. Volume of Sedimentation

Ten milliliter of each suspension was taken in a glass stoppered measuring cylinder. The final volume of sediment was measured after 24h. The percentage volume of sedimentation of each formulation was determined using the following formula[8-10]

$$Vs = (H_u / H_0) \times 100$$

where, V_s = sedimentation volume, H_u = ultimate settled height of suspension, H_0 = original height of the suspension before settling.

2.5. Ease of Redispersibility

Each suspension was allowed to settle in a measuring cylinder. The mouth of the cylinder was closed, and it was inverted through 180°. The number of inversions necessary to restore a homogeneous suspension was determined. When the homogeneity of the suspension was attained in one inversion, the suspension was considered as 100% easily redispersible. Every additional inversion decreased the percentage of ease of redispersibility by 5%.[8-10]

3. Results and Discussion

In the present study, the values of zeta potential of Ciprofloxacin formulations were found from +0.332 to +0.571 mV, while they were between -0.205 and -0.431 mV in cases of Ofloxacin suspensions (Table 1). So, this study suggests that all formulations of both the drugs showed good flocculation and maximum/strong agglomeration properties, as the value of zeta potential of each formulation (suspension) was between -5 mV and +5 mV.[3,11] For C934, C940 and HPMC containing formulations of Cipro, the values of percentage volume of sedimentation and redispersibility were 45 and 85; 85.50 and 80; 90.40 and 90, respectively. On the other hand those values were 55.10 and 80; 64.90 and 90; and 50.10 and 80, respectively, in cases of C934, C940 and HPMC containing formulations of Oflox (Table 1).

Table 1. Stability behavior of polymeric suspensions

Polymeric suspensions	Zeta potential (mV)	Percentage Volume of sedimentation	Redispersibility	Stability behavior of polymeric suspensions
Cipro with C934	+0.409	45.00	85	Flocculation, Maximum agglomeration
Cipro with C940	+0.332	85.50	80	Flocculation, Maximum agglomeration
Cipro with HPMC	+0.571	90.40	90	Flocculation, Maximum agglomeration
Oflox with C934	-0.339	55.10	80	Flocculation, Strong agglomeration
Oflox with C940	-0.431	64.90	90	Flocculation, Strong agglomeration
Oflox with HPMC	-0.205	50.10	80	Flocculation, Strong agglomeration

Among the formulations of Ciprofloxacin used in the present investigation, the formulation containing HPMC was relatively more stable than other formulations because its zeta potential value was maximal. On the other hand, out of the three samples containing Ofloxacin, the formulation containing C940 was found to possess strong hydrogen bonding[12] and most electrochemical stability (considering its maximum zeta potential value) (Table 1). Like zeta potential values, the percentage volume of sedimentation and redispersibility values were also maximum in case of Cipro with HPMC amongst Cipro containing formulations, whereas those values were the highest for Oflox with C940 when Oflox containing formulations were taken into account (Table 1). Considering the values of those two studies, it may be mentioned that Cipro with HPMC/Oflox with C940 were more flocculated and easily redispersible than other formulations of Cipro/Oflox.[6] Due to these reasons, it suggests that those formulations were probably more stable and pharmaceutically acceptable than others.[5] In addition, zeta potential values (mentioned earlier) also indicate that those formulations were more stable. Considering all the above-mentioned information, it might be predicted that Cipro with HPMC and Oflox with C940 suspensions were more physically stable than other formulations used in the present study.

4. Conclusion

As mentioned earlier, the tests like measurement of Zeta potential, volume of sedimentation and ease of redispersibility were performed to get an idea about the physical stability of the formulations used in this investigation. The results of the present study indicate that Cipro with HPMC and Oflox with C940 were probably more stable and flocculated than other suspensions. For confirmation regarding the stability of all suspensions, other investigations like FTIR and Raman spectroscopic analyses, DSC analysis, XRD and SEM studies, etc. may also be carried out.

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