Formulation and Evaluation Sustained Release of Lomefloxacin Hydrochloride from In-Situ Gel for Treatment of Periodontal Diseases

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Abstract

Periodontal diseases is a world wide prevalent chronic infection, which is caused by accumulation of specific microorganism or group of microorganisms in dental plaque, which results in the progressive loss of bone around teeth leading to loss of teeth. The present study was developed and evaluated in situ gelling system of Lomefloxacin hydrochloride by using different concentrations of Carbopol 934 for treatment of periodontitis. The drug-polymer compatibility were study using DSC. The seven formulation (L1 to L7) were prepared and their appearance, pH, viscosity, gelling capacity, %drug content, syringeability and in vitro drug release were investigated. The findings of compatibility study indicates that the drug was compatible with polymer. The developed formulations showed satisfactory results for pH, viscosity, gelling capacity, %drug content, syringeability and in vitro drug release. Based on maximum desirability and cost effectiveness formulation L7 with 1.0 % of polymer Carbopol 940, showed a sustained release of drug for 16 hrs.

Keywords:
Lomefloxacin hydrochloride, Carbopol, Periodontal

1 Introduction

Periodontal illness is a term that includes a few obsessive conditions influencing the tooth supporting structures. Periodontal ailments are one of the basic microbial contaminations in the grown-ups. They are of two types namely gingivitis and periodontitis. Periodontitis is an inflammatory disease of supporting tissue of the teeth caused by gatherings of microorganisms. Elimination or adequate suppression of putative periodontopathic microorganisms in the subgingival microbiota is fundamental for periodontal healing. Antibacterial agents have been utilized successfully in the administration of periodontal infection.

The adequacy of mechanical debridement of plaque and rehashed topical and fundamental organization of antibacterial agents are restricted because of the absence of accessibility to periodontopathic organisms forms in the periodontal pocket. The advancement of in situ gel system has gotten significant consideration in the course of the last few years¹⁻³. This intrigue has been started by focal points appeared by in situ forming delivery system for example, ease of administration and diminished recurrence of administration, improved patient compliance and solace. The formation of gels relies upon factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner. Controlled drug delivery systems represents one of the most one of the most quickly propelling zones of science and various favorable circumstances incorporate improved viability, reduced toxicity and improved patients compliance and convinence. Many advanced drug delivery systems are being presented for the intrapocket delivery of drugs at the diseased site⁴⁻⁵. The objective in utilizing an intrapocket device for the delivery of an antibacterial agent is the accomplishment and upkeep of remedial levels of the drug for the necessary timeframe. In situ forming polymeric formulations are drug delivery systems that are in sol form before administration in the body, but once administered, undergo gelation in situ, to form a gel. The gel posses a higher biocompatibility and bioadhesivity allowing adhesion to the dental pocket and lastly they can be quickly dispensed through typical catabolic
pathways, diminishing the danger of anaphylactic responses at
the application site 4.

Lomefloxacin hydrochloride belongs to third generation fluoroquinolone category drug with a broad spectrum antibacterial activity. Fluoroquinolone are a class of synthetic antibacterial agents approved for periodontal treatment and display higher antimicrobial activity compared to amino glycosides and cephalothin. Lomefloxacin hydrochloride employed for the ailment of giardiasis, trichomoniasis of urogenital tract, dental infection, ocular infection etc. Consequently, it is used by dental practitioners for the control of the plaque and for the treatment of gingival inflammation6,7. The elimination half life of Lomefloxacin hydrochloride is 8 hrs, and was selected in order to provide extended release of the anti microbial agent that results in the efficient elimination of the microorganisms in the periodontal pockets. Hence it was planned to formulate in situ gel of Lomefloxacin hydrochloride by using different concentration of Carbopol 940. It has documented that Carbopol stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. Due to thickening property it can adhere on oral mucosa for prolong period of time and sustain the drug release from formulation in the treatment of periodontal disease.

2 Materials and Methods

2.1 Materials

Lomefloxacin hydrochloride (Dr. Reddy's Laboratory, Hyderabad), Carbopol 940 (Corel Pharmaceutical, Ahmedabad), Sodium Citrate (Qualigens Fine Chemicals, Mumbai), Methyl Paraben and Propyl Paraben (Molychem, Mumbai).

2.2 Preformulation study

The preformulation studies were performed for the obtained sample of the drug for identification by melting point estimation for the drug and compatibility study by Differential scanning calorimetry.

2.2.1 Melting point determination

Melting point of the drug was determined by capillary method and compared with the reported value

2.2.2 Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) technique has been used to study the physical and chemical interaction between drug and excipients. First, DSC of the drug Lomefloxacin hydrochloride was taken and the DSC of the mixture of drug and Polymer Carbopol 940 in the ratio of 1:1 was performed using a Shimadzu DSC -60. Samples were taken, sealed in aluminium pans and analysed in an atmosphere of air at flow rate of 25 ml/min. A temperature range of 50° C to 200° C was used and the heating rate is 20° C/min.

2.3 Preparation of in situ gel

For the preparation of Carbopol 940 containing in situ gelling system, Sodium citrate was first added to distilled water with continuous stirring and clear solution was obtained. Carbopol 940 was then sprinkled over this solution and allowed to hydrate overnight. Lomefloxacin hydrochloride was dissolved in required quantity of distilled water separately and then added to polymer solution under constant stirring until a uniform solution was obtained. Finally methyl paraben and propyl paraben were added to the formulation under constant stirring until a uniform solution was obtained.

2.4 Evaluation of formulations

2.4.1 Appearance

All the developed formulations were evaluated for the clarity from the visual inspection.

2.4.2 In vitro gelling capacity

All the formulations were evaluated for gelling capacity in order to identify the compositions suitable for use as in situ gelling systems. The gelling capacity were determined by placing a drop of the system in a vial containing 2ml of freshly prepared phosphate buffer pH 6.8 equilibrated at 37° C and visually assessing gel formation and noting the time for gelation and the time taken for the gel to dissolve. The in vitro gelling capacity was graded in 3 categories based on the gelation time and the time period for which the formed gel remains.

(+) – Gels after few minutes dispersed rapidly.

(++) – Gelation immediately remains after 12 hours.

(+++) – Gelation immediately remains for more than 12 hours.

2.4.3 pH

pH of all the formulations were measured using the calibrated digital pH meter at 27° C.

2.4.4 Viscosity

The viscosity of all prepared formulations was measured by using Digital Brookfield viscometer. The measurements were carried out using spindle no. 02 at the speed of a 10 rpm in the sample and the results are tabulated in table.

2.4.5 Drug content

The drug content of the formulations (L1 – L7), were analyzed by taking 1 ml of the gel in 100 ml volumetric flask, dissolved and the volume was made up to 100 ml with 6.8 phosphate buffers. From the above solution 4 ml was pipette out into a 10 ml volumetric flask and the volume was adjusted with 6.8 phosphate buffer. The absorbance of the sample solution was determined at 281 nm against pH 6.8 Phosphate buffer by using UV – Visible Spectrophotometer.
2.4.6 Syringeability

All the prepared formulations were transferred into an identical 5 ml syringe placed with 20 gauge needle to a constant volume (1ml). The solutions which were easily passed from the syringe was termed as pass and difficult to pass were termed as fail. The results are tabulated in table.

2.4.7 In vitro drug release studies

The in vitro release of Lomefloxacin hydrochloride from the formulations was studied through cellophane membrane using a modified USP II dissolution testing apparatus. The dissolution medium was phosphate buffer (pH – 6.8). Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both the ends of 5 cm diameter). A selected volume of the formulation was accurately pipette in to this assembly. The cylinder was attached to the metallic driveshaft and suspended in 50 ml of the dissolution medium maintained at 37±0.5 ºC so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at 50 rpm using magnetic stirrer. Aliquots of the sample were withdrawn at regular intervals and equal volume of receptor medium was replaced. The aliquots were diluted with the receptor medium and were analysed by using UV - VIS spectrophotometer at 281 nm8-11.

3 Results and Discussions

3.1 Determination of melting point

The melting point of given sample of Lomefloxacin hydrochloride was found to be 291 -294 ºC as compared with the standard value 290-300 ºC.

3.2 Differential scanning calorometry

The compatibility of Lomefloxacin hydrochloride with different ratio of Carbopol 940 was studied by using DSC. The thermal curves of Lomefloxacin and Lomefloxacin-polymer physical mixture (1:1) are shown in Figure 1 and 2, respectively.

The thermal curve of Lomefloxacin and lomefloxacin-carbopol 940 physical mixtures showed an endothermic peak at 199.26 ºC and 198.33 ºC, respectively. Moreover, the enthalpy of the endotherm was also calculated and it was -1.27J/g and 1.19J/g for Lomefloxacin and Lomefloxacin-carbopol 940 physical mixtures, respectively. From the graph, it
was cleared that Lomefloxacin alone has a high enthalpy value while that value decreased after the addition of Carbopol 940 polymer. This result confirms that there is no mutual interaction between for Lomefloxacin and polymer Carbopol 940.

3.3 Appearance
All the formulations were found to be clear except L6 and L7 containing 0.9% and 1.0% of Carbopol 940 which were found to be cloudy (Table 1).

3.4 In vitro gelling capacity
The two main requirements for the in situ gelling system are viscosity and gelling capacity. To inject at the affected site the formulation must possess optimum viscosity. And it should undergo rapid sol to gel transition upon contact at the affected site. All the formulations (L1 – L7) were found to have good gelling capacity (Table 2). The formulations L1 and L2 with less percentage of Carbopol 940 showed less gelation property after 15 min and the formulations L3 to L7 exhibited gelation immediately after 2 to 3 min and the in situ gel produced was stiff and exhibited action for an extended period of time, the reason might be due to the higher percentage of the gelling polymer Carbopol 940.

3.5 pH
The pH of the formulations were measured by using digital pH meter and the pH range of all the formulations were found to be within 5.8 to 6.9 which is the required range for the dental formulation. Further the gelling capacity of Carbopol 940 was found to be satisfactory at a pH of 4.0 to 7.4 (Table 2). So, all the formulations had a pH within the satisfactory level.

3.6 Viscosity
The viscosities of the formulations were found in the range of 320.6 to 621.5 cps (Table 1), and were found to be satisfactory. Viscosity increases as the polymer concentration increases.

3.7 Drug content
Drug content of the formulations was found in the range between 97.34% to 99.78% (Table 2). The drug content was found to be in acceptable range for all the formulations. This indicates that the process employed to prepare gels in this study was capable of producing gels with uniform drug content.

Table 1: Composition of the in situ gel formulations

| Ingredients                      | L1 | L2 | L3 | L4 | L5 | L6 | L7 |
|----------------------------------|----|----|----|----|----|----|----|
| Lomefloxacin Hydrochloride (% w/v)| 4  | 4  | 4  | 4  | 4  | 4  | 4  |
| Carbopol 940 (% w/v)             | 0.4| 0.5| 0.6| 0.7| 0.8| 0.9| 1.0|
| Sodium Citrate (% w/v)           | 0.1| 0.1| 0.1| 0.1| 0.1| 0.1| 0.1|
| Methyl Paraben (% w/v)           | 0.15| 0.15| 0.15| 0.15| 0.15| 0.15| 0.15|
| Propyl Paraben (% w/v)           | 0.02| 0.02| 0.02| 0.02| 0.02| 0.02| 0.02|
| Distilled Water                  | q.s| q.s| q.s| q.s| q.s| q.s| q.s|

Table 2: Evaluation parameter of in-situ gel of Lomefloxacin hydrochloride

| Batch Code | Clarity  | Gelling Capacity | pH       | Viscosity in cps at 37 °C | Drug Content (%) | Syringeability |
|------------|----------|------------------|----------|---------------------------|-----------------|---------------|
| L1         | Clear    | +                | 5.80±0.14| 320.6±1.35                | 97.34±0.45      | Pass          |
| L2         | Clear    | +                | 6.50±0.56| 345.1±1.87                | 98.13±0.32      | Pass          |
| L3         | Clear    | ++               | 6.68±0.23| 423.2±2.41                | 99.26±0.76      | Pass          |
| L4         | Clear    | ++               | 6.80±0.68| 567.9±1.41                | 98.89±0.85      | Pass          |
| L5         | Clear    | ++               | 6.26±0.91| 580.4±1.08                | 99.78±0.42      | Pass          |
| L6         | Cloudy   | +++              | 6.62±0.73| 584.3±2.51                | 97.81±0.19      | Pass          |
| L7         | Cloudy   | +++              | 6.90±0.55| 621.5±1.22                | 99.16±0.37      | Pass          |

Values represented mean ± SD

3.8 In vitro drug release studies
The in vitro dissolution profile of Lomefloxacin hydrochloride from the gels containing different concentration of polymer Carbopol...
940 (Fig 3). The Prepared gels are for the injection at the site of infection and the pH of the mouth saliva is 6.4 to 7.4. Hence in the present study, Phosphate buffer of pH 6.8 was used for in vitro release studies of the gel formulations. The result of cumulative percent release is depicted in Figure 3. From the figure 3 it is found that the formulation L7 with 1.0 % of polymer Carbopol 940, showed a sustained release for 16 hours and all other formulations (L1 – L6) had satisfactory release.

It was concluded that as the concentration of the polymer increased the release rate decreased and it produced sustained release of the drug. The mechanism for resistant barrier of Carbopol 940 gels to drug release may be due to reduction in the number and dimension of water channels. Further, it enhances in the number and size of micelles within the gel structure. The higher numbers of cross-links between neighboring micelles due to shorter intermicellar distance, it leads to higher viscosity and lower rate of drug release11.

Fig 3: In vitro drug release study of Lomefloxacin hydrochloride

4 Conclusion
Lomefloxacin hydrochloride is a broad spectrum antibacterial drug and used for the treatment of periodontitis. The findings suggest that the prepared in situ gel of Lomefloxacin hydrochloride retard the drug release from formulation, and extend the drug efficacy upto 16 hrs. The study concluded that non biodegradable polymer based dental film of Lomefloxacin hydrochloride is a potential local drug delivery device for the treatment of periodontitis

5 Conflict of Interest
Nil

6 Author’s contributions
BK and SK designed the protocol and performed experiments. JP and MK drafted the manuscript. All authors approved the manuscript for publication.

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