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Formulation and Development of Implantable Drug Delivery System of Ciprofloxacin Hydrochloride

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Abstract:
In the present work an attempt was made to formulate and evaluate a sustained release implant of Ciprofloxacin HCl using biodegradable polymer Chitosan. *In vitro* drug release of Ciprofloxacin was studied. The effect of different proportion of Chitosan and effect of drug loading on the drug release kinetics has been studied. *In vitro* study suggests that C4 formulation having drug: polymer ratio (1:1.5) retards the drug release for more than a month. The proportion of Chitosan has significant effect on rate of drug release. Stability study implants was also performed and had shown drug is stable over a studied range of period and there is no degradation taking place of the implant formulation.
Key words: Ciprofloxacin Hydrochloride, Implant, Osteomyelitis.

INTRODUCTION

Osteomyelitis is one of the oldest diseases which is still in existence and difficult to treat. Osteomyelitis is now a days becoming more common because of increased use of prosthetic devices and increased number of accidents resulting in traumatic injuries. Therefore osteomyelitis is a major health problem for both developed countries and developing counties. The treatment of osteomyelitis requires large doses of antibiotics administered by systemic routes a period of four to five weeks. Some of the disadvantages of prolonged parenteral therapy include; Patient discomfort, High cost of treatment, Development of systemic toxicity, Patient compliance problems. Bacteria adhere to bone matrix developing a slimy film or acquires a very slow metabolic rate therefore escapes from host defenses and antibiotics. Osteomyelitis results in bone necrosis and destruction of bone resulting in limited vascularity to the site of infection, systemic therapy may fail to produce therapeutic tissue concentrations of the antibiotic at the particular site of infection.[1,2]

To overcome some of these problems with the treatment of osteomyelitis, localized drug therapy using non biodegradable polymethacrylate (PMMA) bone cement implants was introduced in the 1970s. The advantages of local therapy include high, local, tissue, while simultaneously minimizing high, potentially toxic, systemic drug levels. However, previous studies on the nonbiodegradable carriers have shown that the in vitro release of antibiotics from PMMA beads is incomplete and poorly controlled. Another disadvantage of the nonbiodegradable carriers is that a second surgery is required for removal of implants. As, the treatment of osteomyelitis requires continuous parenteral administration of antibiotics for four to five weeks or even more depending on the severity of infection. Also such a long parenteral therapy may develop systemic toxicity. Therefore, to avoid the systemic toxicity and to produce effective drug concentration at the infected site subcutaneous implantable drug delivery of Ciprofloxacin HCl is developed from which drug slowly releases from implant and high local tissue concentration can be achieved at the infected site.

As, the minimum inhibitory concentration of Ciprofloxacin HCl is very low (0.25-2 µg/ml) for most of the pathogens that cause osteomyelitis, the growth of causative microorganism is easily inhibited.[3,4,5] An

implant of Ciprofloxacin HCl in combination with the naturally occurring biodegradable polymer i.e. Chitosan is formulated. Logic behind the use of Chitosan in the implant formulation is to achieve the controlled drug release and to avoid the occurrence of the peaks and troughs in the drug release form the implant.[3, 4 6, 7]

MATERIALS AND METHODS

Ciprofloxacin HCl, Chitosan, 0.2 M Sodium hydroxide, Potassium dihydrogen phosphate, Sodium azide, 0.1 N HCL, Citric acid, and Sodium citrate All the materials used for the study were of analytical grade.

Preparation of Implants

Formulations were developed in order to establish a controlled release implantable dosage form. The active ingredient (Ciprofloxacin HCl) and polymer (Chitosan) were weighed accurately and passed through 60# sieve. Mixing of powders was done by spatulation. Weight of implant tablet was kept constant in all the formulations (100 mg). The formulation code and Drug: Polymer ratio used is as shown in Table I.

Evaluation of Implants

The compressed implant matrix tablet was evaluated for thickness, hardness, weight variation test and drug content.

Drug Content

One milled implant was placed in 100 ml of HCl (0.1N) and kept under magnetic stirring (50 rpm) at room temperature for 24 h. After filtration, the drug content was determined spectrophotometrically at 277 nm in 0.1N HCl.

Water Uptake Study[8, 9, 10]

Initially weighed implants placed in the 20 ml release medium (Phosphate buffer 7.4 pH), withdrawn at appropriate intervals blotting away excess water and weighed again (wet weight). Water uptake was determined using following equation,

$$\text{Water Uptake } (\%) = \frac{W_w - W_i}{W_i} \times 100$$

Where, Ww is the wet weight, Wi is the initial weight.

Percent Erosion

% erosion was determined using following equation,

$$\% \text{ Erosion} = \frac{(W_i - W_{CFX\ Released}) - W_d}{W_i} \times 100$$

Where, W_i is the initial weight, W_d is the dry weight, $W_{CFX\ Released}$ is the weight of ciprofloxacin HCl released after 5 weeks.

In vitro drug release study

Drug release from the prepared formulations was studied by Vial method. In this method, the drug release study was performed in 30.0 ml screw capped glass vials (diameter =25 mm) containing 20.0 ml dissolution medium. The implants were immersed with USP phosphate buffer (0.1 M, pH 7.4) containing 0.05 % w/v benzalkonium chloride and 0.1 % w/v sodium azide as antibacterial agents. Samples from each of formulations were incubated in an oven at 37^0C for 5 weeks without agitation and were only shaken for 5.0 minutes before sampling time. At defined time points, 4.0 ml of the release medium was withdrawn and replaced with fresh buffer and absorbance was measured at 270.8 nm. [11]

Data treatment

The dissolution data was subjected to different model dependent viz. Zero Order Kinetics, First order Kinetics, Higuchi model,Korsmeyer-Peppas model and independent methods viz. Pair-wise procedure, Difference factor (f1), Similarity Factor (f2). [12, 13, 14]

Stability study

The selected formulation was subjected to 40 ± 2 °C, 50 ± 2 °C, 60 ± 2 °C temperature for one month. The formulation was studied for organoleptic characteristics, hardness, dissolution and Similarity factor f_2 also calculated. Three tablets were subjected to this study. [15]

Table I: Formulation Development Experiment

Sr. No.	Formulation Code	Ciprofloxacin HCl (%)	Chitosan (%)	Drug: Polymer	Weight of Implant (mg)
1	C1	10	90	1 :9	100
2	C2	20	80	1:4	100
3	C3	30	70	1:2.33	100
4	C4	40	60	1:1.5	100
5	C5	50	50	1:1	100

Table II: Evaluation of different formulation of Ciprofloxacin HCl

Parameters	C1	C2	C3	C4	C5
Diameter (mm)	7.25 (±0.162)	7.28 (±0.066)	7.26 (±0.098)	7.20 (±0.0876)	7.20 (±0.106)
Thickness (mm)	2.79 (±0.095)	2.74 (±0.136)	2.74 (±0.121)	2.70 (±0.092)	2.76 (±0.098)
Hardness (Kg/cm2)	4.8 (±0.241)	4.7 (±0.567)	4.8 (±0.430)	4.9 (±0.574)	4.7 (±0.536)
Drug Content (%)	98.82	98.24	99.15	98.96	99.21
% Erosion (w/w)	3.83	5.87	7.73	10.21	13.89

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Table III: Significant value calculation

Source of Variation	P value summary	Significant
Proportion of Chitosan	* (P<0.05)	Yes

Table IV: Comparison of Different proportions of Chitosan on water uptake study

Source of Variation	Degrees of Freedom	Sum-of-squares	Mean square
Treatment Between Column)	4	14480	3620
Residual (Within columns)	20	8800	440

Statistical treatments

Means and standard deviations were calculated using Prism 5. Dissolution data was fitted in various kinetic models described above and best fit was determined using linear regression. Value of R^2 was considered to determine the best fit kinetic model.

RESULT AND DISCUSSION

All the formulations show uniform hardness, thickness and diameter, drug content. (Table II) Percent water uptake of C1 to C5 formulation is as shown in (Figure II). Percent Erosion of C1 to C5 formulation is as shown in (Table II). The percent erosion of C4 and C5 formulation is comparatively

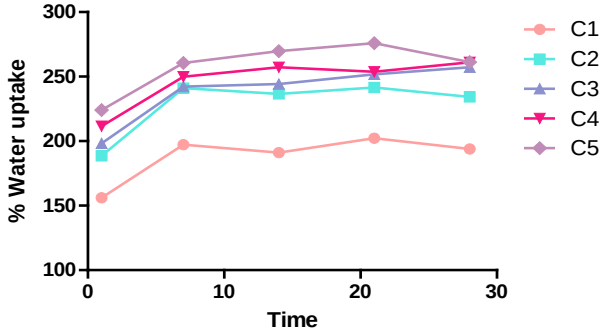

Figure I: Water uptake study of C1 to C5 formulations

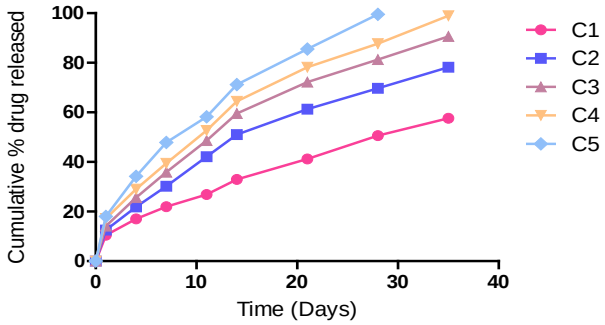

Figure II: Dug release profile of all formulations

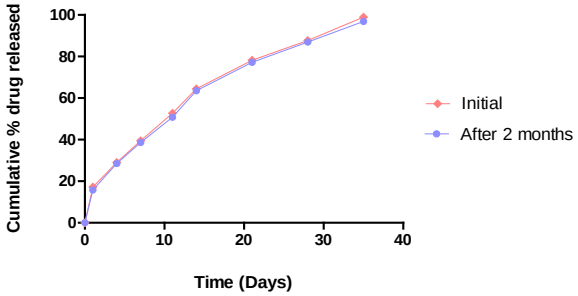

Figure III: Effect of temperature on drug release profile of implant

more than C1 formulation. Cumulative percent drug release from all formulations is presented in (Figure III). The cumulative percent release from implants is mainly depends on drug: polymer ratio. The implants with various drug: polymer ratios retarded the drug release for different time period. The C1 formulation shows only 57.59% release whereas C4 formulation shows 98.97% release in five weeks. This effect may be attributed to proportion of Chitosan in different formulation. In C1 formulation proportion of Chitosan is very high (drug: polymer ratios 1:9) which results in more retardation of drug release. In C4 proportion of Chitosan is low (drug: polymer ratio 1:1.5) which results in comparatively less retardation of drug release therefore cumulative percent release from C4 formulation is increased. In case of C2 and C3 formulation drug: polymer ratio is also high than C4 formulation (1**:**4 and 1**:**2.33 respectively) therefore shows only 78.23% and 90.58% release in five weeks respectively. In case of C5 formulation 99.54% drug is released is observed in 28 days, this can be attributed to less proportion of Chitosan (drug: polymer ratio (1:1)). From this study, drug release from chitosan matrices was found to be decreasing with increasing proportion of Chitosan. Also the solubility of the drug is very low which is playing a crucial role in release of drug from implants.

Similarity factor (f_2) tests were applied to study the effect of drug loading on percent cumulative CFX release from C1 and C4 formulations. The cumulative percent release from implants made with 10% CFX is significantly lower than from implants with 40% CFX for the two formulations C1 vs. C4 (f_2 < 50). This indicates that the cumulative percent release of Ciprofloxacin HCl increased with increasing drug loading.

For C1 to C4 formulation the R values were high for Higuchi equation, indicating that the drug release from these formulations follows Higuchi kinetics of drug release, whereas C5 formulation R values were high for Korsmayer- Peppas equations indicating that the drug release from these formulations follows Korsmayer-Peppas kinetics of drug release. The value of Release Exponent 'n' is also determined for each formulation. The value of 'n' in Korsmeyer's Peppas equation indicates the drug release mechanism. With respect to C1, the value of 'n' is less than

0.50, indicting that drug release from the implant is controlled by diffusion process only (Fickian diffusion). And with respect to C2 to C5 formulations, the value of 'n' is in the range of 0.50 to 1.0 indicting that drug release from these formulations is controlled by diffusion of drug as well as erosion of polymer chains (non-Fickian diffusion or anomalous diffusion).

Stability study of selected formulation was carried out for one month at 40 ± 2 °C, 50 ± 2 °C, 60 ± 2 °C temperatures. After two months Implant was found to be intact and showed the characteristics similar to those of the selected formulation. The similarity factor between dissolution data of implant before and after two months was found to be 86.928. From this study we can conclude that there is no degradation taking place of the implant formulation. Release profile of formulation after two month is shown in following Figure III.

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CONCLUSION

It is possible to develop Implantable drug delivery system of Ciprofloxacin Hydrochloride for the treatment of Osteomyelitis. The proportion of Chitosan has significant effect on rate of drug release. *In vitro* study suggests that C4 formulation having drug: polymer ratio (1:1.5) retards the drug release for more than a month. Stability study of the implant formulation indicates that the drug is stable over a studied range of period and there is no degradation taking place of the implant formulation. This type of implantable drug delivery system using Chitosan can be a cost effective alternative to the presently available drug delivery systems of Ciprofloxacin Hydrochloride.

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