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# SUSTAINED RELEASE OF CALCITRIOL FOR PREVENTION OF BONE RESORPTION IN ORTHODONTICS

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**ABSTRACT:**
Sustained release dosage form is useful especially for achieving controlled plasma level of drug as well as improving bio-availability.An oral sustained release formulation can reduce fluctuation in plasma concentration and allow longer dosing interval[1]. In this present study *in situ* gel of Calcitriol for the treatment of Orthodontics was successfully formulated using carbopol as gel base. This *in situ* gel formulation possesses muco-adhesive properties, results of which prolong residence time at the site of application, which in turn exhibited better therapeutic effects.

**Key words:** *in situ* gel**,** Sustained release ,Carbopol, Calcitriol.

**INTRODUCTION**:

Sustained release drug delivery system is designed to release a drug at a predetermined rate by maintaining a constant drug level for specific period of time with minimum side effect.[2] There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum utilization of the drug, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, reduction in healthcare costs through improved therapy and shorter treatment period. Wide varieties of polymers are available for retarding the release rate of drugs hence sustains the action of drugs.[3]

*In-situ* gel is a Latin word which means "In its original or in position"[4]. These *in situ* gels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH and temperature. Prolonged and sustained release of the drug, reproducible, excellent stability, biocompatibility, and accurate quantities of administration make the in situ gel reliable.[5]

Local drug delivery is frequently utilized for the treatment of several localized disorders. The main advantages of this route of drug administration is that it can deliver the active agents directly to the site of action at bactericidal concentration and it can facilitate prolong drug delivery[6].

The role of vitamin D in the maintenance of calcium homeostasis in human beings has been well documented. It is a steroid hormone that has specific receptors in many target organs and tissues. It exerts its action by activating DNA and RNA within the target cell to produce proteins and enzymes that can be used in the bone resorption process[7].

## MATERIALS AND METHODS

Calcitriol was obtained as a gift samples from Yarrow Chem Products, Mumbai, India. Carbopol and sodium chloride were procured from S.D. Fine chemical, Mumbai. All other ingredients used were of analytical grade.

### Pre-formulation studies[8]:

The pre-formulation studies like melting point determination and compatibility studies were done as per the procedure. Melting point of pure drug was determined by capillary method and obtained data were compared with the reported value. Compatibility study by FT-IR was carried out to identify possible interaction between drug and polymer used as per the standard procedure.

### Selection of Carbopol concentration:[9]

Solution of different concentration ranging from 0.6-1.0w/v % of Carbopol was prepared by cold process. Required amount of polymer was accurately weighed and dispersed in distilled water with continuous mild stirring for 5 m. The beaker containing partially dissolved Carbopol was sealed with aluminum foil and solution was kept aside till the entire polymer was completely dissolved (about 24 h.). The proper concentrations of Carbopol were selected on the basis of gelation temperature and gelation time.

### Preparation of *in situ* gel:[10]

For the preparation of *in situ* gel formulations, required quantity of sodium chloride was dissolved in 50 ml of distilled water. Carbopol 934 was sprinkled over this solution and allowed to hydrate over night. The solution was again stirred with magnetic stirrer after 24 hrs. Calcitriol was dissolved in 5 ml distilled water, benzalkonium chloride (BKC) was then added and the solution was filtered through 0.2 µm cellulose acetate membrane filter. The drug solution was added to the Carbopol. Distilled water was then added to make up the volume to 100 ml. The developed formulation were filled in 5 ml capacity ambered glass vials, closed with gray butyl rubber closures and sealed with aluminium caps. The formulations in their final pack were subjected to terminal sterilisation by autoclaving at 121ºc at 15 psi for 20 minutes.

Table 1: Composition design of various Calcitriol *in situ* gel formulations

| Name Of Ingredient | Quantity in 100 ml (%W/V) | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Calcitriol %W/V | 0.075 µg | 0.075µg | 0.075µg |
| Carbopol 934 %W/V | 0.4 | 0.6 | 0.8 |
| Sodium Chloride % W/V | 0.9 | 0.9 | 0.9 |
| Benzalkonium chloride %W/V | 0.01 | 0.01 | 0.01 |
| Distilled water | q.s | q.s | q.s |

The *in situ* gel contains strength of 750 pg/ml calcitriol (1.25 dihydroxycholecalciferol), from which a dose of 150 pg/ml calcitriol (i.e 0.2 ml) will be given for the complete treatment.

### Evaluation parameters.[6]

### Characterization of *in situ* gel formulation:

**Appearance:** All prepared formulations were evaluated from the visual inspection.

**Gelling Capacity:**

All formulations were evaluated for gelling capacity in order to identify the compositions suitable for use as *in situ* gelling systems. The gelling capacity was determined by visual method in which coloured solution of prepared formulations were prepared. Gelling capacity was estimated by placing 2 ml 1.2 pH buffer in a 10 ml test tube and maintained at 37±1°C temperature. One millilitre of coloured formulation solution was added to the buffer solution. As the formulation comes into contact with 1.2 pH buffer it was immediately converted into a stiff gel-like structure. The gelling capacity of formulation was evaluated on the basis of stiffness of formed gel and time period for which formed gel remains as such. The *in vitro* gelling capacity was graded in two categories on the basis of gelation time and the time taken for the gel formed to dissolve.

**pH measurement:**

pH is one of the most important parameter involved in the *in situ* gel formulation and it is measured directly with the help of digital pH meter.

**Gelation temperature:**

A magnetic bead and 10 ml of the sample solution were put into a 30 ml transparent vial placed in a low temperature digital water bath. A thermometer was placed in the sample solution. The solution was heated at the rate of 1ºc/m with the continuous stirring. The temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature.

**Gelation time:**

Gelation time of prepared *in situ* gel formulation was measured by placing 2 ml of the gel in 15 ml borosilicate glass test tube. This test tube was placed in water-bath (37±2ºC) and gelation time was noted when there was no flow of the gel when test tube was inverted.

**Drug content analysis:**

Accurately weighed amount of gel equivalent to 0.049 mg of drug was taken into a 100ml volumetric flask. They were lysed with 25 ml of medium (1.2 pH buffer) for 15 m. The clear solution was diluted to 100 ml of medium. Then 1ml of this solution was diluted to 50 ml buffer and the absorbance was measured at 211 nm against 1.2 pH buffer by using UV-Visible Spectrophotometer-1800 (Shimadzu, Japan) and drug content was calculated from the calibration curve.

**Syringeability:**

All prepared formulations were transferred into a 5 ml syringe placed with 20 gauge needle to a constant volume (2 ml). The solutions which were easily passed from syringe was termed as pass and difficult to pass were termed as fail.

**In vitro drug release studies:**

In vitro drug release study of Calcitriol from the *in situ* gel formulations was conducted for the period of 8 hrs using cellophane membrane. The diffusion medium was 1.2 pH buffer. Cellophane membrane, previously soaked overnight in the diffusion medium, was tied to one end of a glass cylinder. Then 1ml of the prepared formulation was placed in cellophane membrane tie in a glass cylinder and make the membrane just touched the receptor medium surface. The diffusion medium was stirred at required 50 rpm using magnetic stirrer. At pre-determined time interval one ml of the sample was taken and replaced by an equal volume of the receptor medium. The sample was analysed spectrophoto-metrically at 211 nm.

**Stability study:**

Stability study of optimized formulation was carried out at 25± 2 ºC/ 60 ± 5% and 40 ± 2 ºC/75± 5% RH for a period of three months. During stability study in situ gel was analysed for pH, viscosity, drug content and *in vitro* drug release**.**

## RESULTS AND DISCUSSION

Results of all the evaluation parameters such as Characterization of *in situ* gels, Gelling capacity, pH of prepared gel, Drug content uniformity, Syringeability of in situ gel, In vitro drug release study were found to be within the official limites. compatibility studies not shown presence of any extra peaks for new functional groups indicating no chemical interaction between drug and mucilage, hence stable formulation could be prepared. In in-vitro drug release, among all formulations, formulation F3 showed 60% of drug released in sustained manner at the end of 8 hours, hence F3 was selected as optimized formulation for periodontal treatment.

## CONCLUSIONS

In this present study *in situ* gel of Calcitriol for the treatment of Orthodontics was successfully formulated using carbopol as gel base. This *in situ* gel formulation possesses muco-adhesive properties, results of which prolong residence time at the site of application, which in turn exhibited better therapeutic effects. In addition, *in situ* gel provides intimate contact between the drug and the absorbing tissue which may result in high drug concentration in local area. Thus, based upon obtained results it can be concluded that the formulation containing 1.0% carbopol was considered as an optimized formulation and provided sustained drug release over an extended period of time i.e. more than 50% drug was released in 8hrs this may leads to better patient compliance. Further, clinical trials have to be conducted to study the effect of these in situ gels on patients when administered locally for the better treatment with respect to periodontal diseases.

Table 2: Gelation temperature and time of various Calcitriol *in situ* gel formulations.

| Carbopol 934 Concentration (%) | Gelation temperature (ºc) | Gelation time (min) |
|---|---|---|
| 0.6 | 38.23ºc | 8.5 |
| 0.8 | 37.52ºc | 9.2 |
| 1.0 | 35.02ºc | 4.6 |

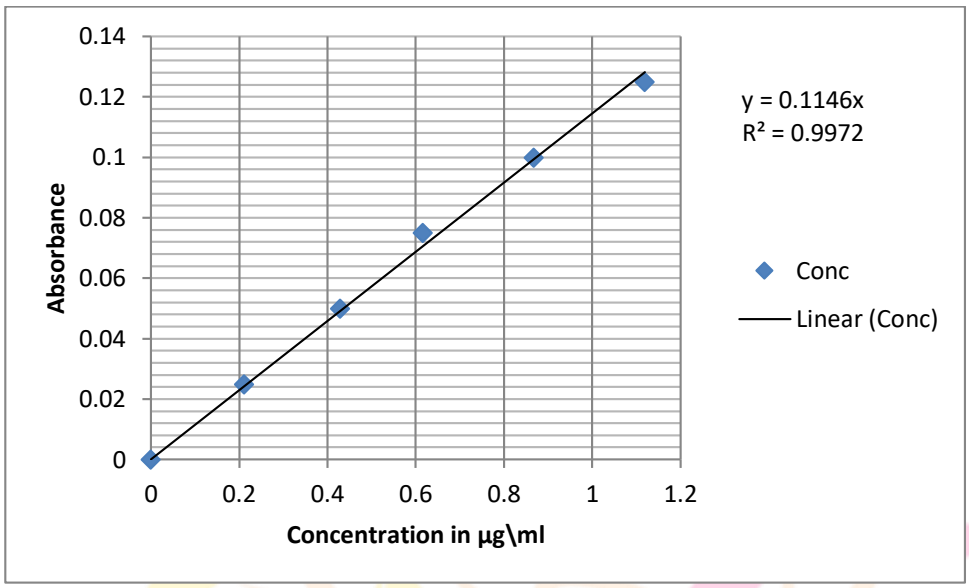
Table 3 :Characterization of *in situ* gels

| **Formulation code** | **Clarity** | **Gelling capacity (min)** | **pH** | **Drug content (%)** | **Syringebility** | ***In vitro* drug release (%)** |
|---|---|---|---|---|---|---|
| F1 | Clear | + | 5.7 | 85.74% | Pass | 85.02% |
| F2 | Clear | + | 5.8 | 89.28% | Pass | 75.19% |
| F3 | Clear | ++ | 5.6 | 93.42% | Pass | 63.24% |

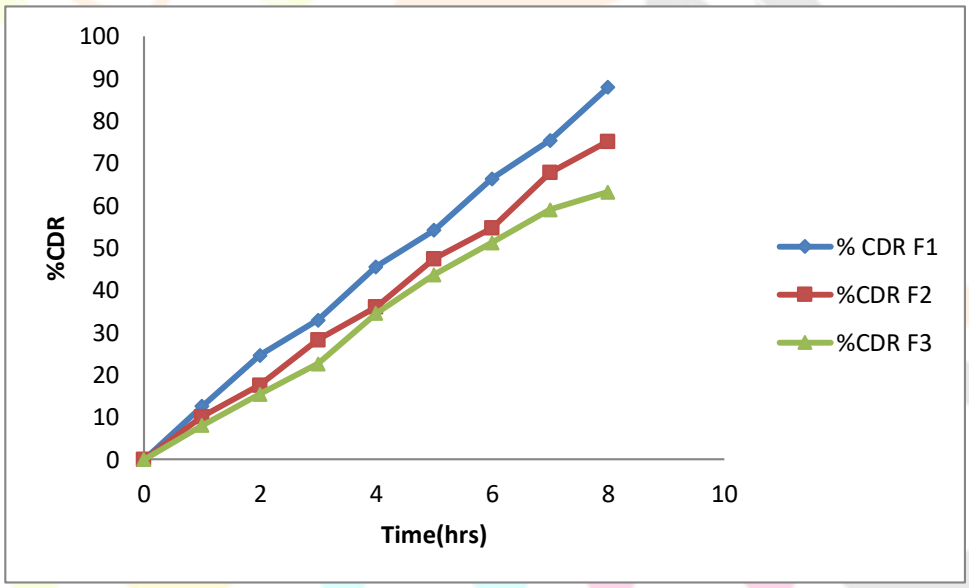
(+), gelation immediate, remains for few hours; and

(++), gelation immediate, remains for an extended period

Graph 1:Standard graph of pure drug.




Graph 2: comparative in vitro drug release from F1 to F3

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