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Preparation and Evaluation of Dental Gels of Ornidazole for Periodontitis

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Abstract

Ornidazole is an anti-microbial drug used to treat dental and mouth diseases like Bad breath, tooth decease, oral cancer, mouth sores, tooth erosion, gingivitis and periodontitis are the teeth and mouth problem which are mainly due to the microbial infections. In the present study, an injectable controlled drug delivery system of Ornidazole gel implants were prepared by using natural biodegradable polymers like chitosan, Xanthan gum and Locust bean gum in different concentrations. All the formulated gels were subjected to various evaluation parameters such as compatibility study by TLC, surface pH, viscosity, drug content, in vitro release studies and antimicrobial susceptibility test and found good results. The *in vitro* release of the prepared gels showed an initial bursting followed by narrowed release. The first order, Higuchi and Kerseymeres Peppas plots were plotted. These results indicate that the release followed a zero order or first order kinetics. Hence we conclude the formulated dental gels of the antimicrobial agent Ornidazole is a promising dosage form for the treatment of various dental infections.

Keywords: Periodontitis, Injectability, Release Kinetics and Dental Gels.

Contents

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1. Introduction

Dental gels are a colloidal preparations containing solids in a liquid continuous medium with forming viscous semi rigid solution and are used to treat dental diseases like Gingivitis, Periodontitis etc. [1,2].The present study is aimed at formulating ornidazole gels using natural polymers to overcome the drawbacks of conventional preparations like low gingival crevicular fluid levels of antibiotics, Systemic side effects and Superinfection. Ornidazole is a 5-nitroimidazole derivative. It has the antimicrobial actions of metronidazoleused to treat protozoal and anaerobic bacterial infections[3].

2. Materials and Methods

Materials

Ornidazole used in the present study was obtained as Gift sample by Sun Pharmaceuticals, Mumbai. Gums like Chitosan, Xanthan gum and Locust bean gum were purchased from SD. Fine Chemicals, Mumbai. Other chemicals like Potassium dihydrogen orthophosphate, lactic acid, ethyl acetate, methanol, chloroform and ammonia were purchased from Loba Chemicals, Mumbai.

Methods

Standard calibration curve of Ornidazole in phosphate buffer (pH 6.6) and 0.1N sodium hydroxide

An accurately weighed 100 g of Ornidazole was dissolved in 100 ml of phosphate buffer pH 6.6 to get primary stock solution of 1000 μg/ml. From this stock solution 5 ml was pipetted out and diluted to 100 ml with phosphate buffer pH 6.6 to get secondary stock solution of 50 μg/ml. From these aliquots of 4, 8, 12, 16, 20 ml was pipetted out and diluted to 50 ml in order to get concentration range of 2-20 μg/ml. The absorbance was measured at 317 mm using UV spectrophotometer. Same procedure was repeated using 0.1 N NaOH and the standard curves were plotted using absorbance versus concentration in μg/ml [4].

Preparation of ornidazole containing gels:

Six formulations of Gels were prepared by dissolving gum at different concentrations in dihydrogen orthophosphate and Lactic acid (2%) with the help of a mechanical stirrer (For preparing gels with Xanthan and Locust bean gums were dissolved in hot water). Later Ornidazole was assimilated and agitated by using mechanical stirrer. Then Ornidazole was amalgamated and agitated with mechanical stirrer[4]. The concentration of ingredients taken was mentioned in Table 1.

Compatibility study of Ornidazole and formulation components:

compatibility of Ornidazole with the other excipients was determined using thin layer chromatography studies using Ethyl acetate : Chloroform : Methanol : Ammonia (25 : 25 : 15 : 5) as mobile phase and Silica gel G as Stationary phase. Standard solution is prepared by Dissolving 10 mg Ornidazole in 10 ml of methanol and a Sample solution is prepared by Dissolving 10 mg of formulation in 10 ml methanol for 10 min with constant shaking than allowed to stand for half an hour undisturbed. The clear supernatant liquid was taken for spotting. Standard TLC plates were prepared by spotting Ornidazole solution(10 ml methanol) at about 2 cm above the bottom. Six samples were dotted head-to-head to Standard at a distance of 1.5 cm apart. The plate was placed in saturated solvent system chamber. The solvent was permissible to upsurge and the expanse voyaged by solvent front was distinguished [5, 6]. The TLC plate was kept in UV chamber for detection and the Rf value of 6 samples were calculated using the following formula:

$$Rf = \frac{\text{Distance traveled by solute}}{\text{Distance traveled by solvent}}$$

Evaluation of Ornidazole Dental Gels:

Surface pH: The gel formulations must be nearer to neutral to overcome the irritation and the pH was measured using a glass electrode pH meter. pH was determined by placing electrode on the surface of the formulations for 1 minute.

Viscosity of the Gel:

The viscosity of formulated gels was estimated by using a Brookfield viscometer (spindle# 3 with 60 RPM and at 28 ± 2.0^0C). Triplicate values were recorded[7].

Uniformity of drug content:

The prepared gels containing 1 mg of drug was taken in 10 ml volumetric flask, dissolved in 0.1N NaOH, the volume made up to 10 ml with 0.1N NaOH. The absorbance readings were measured at λ_{max} of 317 nm. The concentrations of drug was determined from the standard calibration curve. [8]

Syringeability:

The formulated gels were evaluated for the ability to come out from a needle of 22 gauze using a syringe. This test gives information about the absence of any kind of lumps in the formulated gels.

***In vitro* diffusion study:**A cellophane membrane was boiled in distilled water for 1 h followed by drenching for 1 h in absolute alcohol then membrane was stored in PBS of pH 6.6 for 24 h. Specific quantity of gel containing 1 mg of drug was taken in a glass cylinder with both ends open that can act as *Donor compartment*was placed in a beaker containing 40 ml 0f PBS pH 6.6 which can act as a *Receptor compartment.*The cell was stirred with a magnetic stirrer and upheld at 37±1°C.A 5ml of sample was withdrawn at intervals of 1 day for 7 days the quantity of drug released was assessed using UV spectrophotometer at 317 nm [9].

Antimicrobial Susceptibility Test:

The antimicrobial action of prepared gels was determined by microbial assays using Ornidazole corresponding to 1mg. Under stringent aseptic environments the formulations and placebo were placed on blood agar plates containing *S. aureus* and incubated at 37±1°C for 24 h. The zone of inhibition was measured[10, 11].

3. Results and Discussion

Standard calibration curve of Ornidazole in PBS of pH 6.6& 0.1N NaOH: The absorbance readings of Ornidazole in PBS (pH 6.6) between 2-20 µg/ml at λ_{max} 317 nm were tabulated in Table 2.

Compatibility study:

The Rf values for prepared gels were found to be 0.76, 0.76, 0.76, 0.75, 0.76 and 0.76 respectively. The Rf values of standard and samples were found to be same and the result concludes that there was no drug polymer interaction. (Fig 1a & 1b)

Surface pH: The pH values of different gel formulations were in the range of 5.8 to 6.2 and shown in Table 3. All these values were nearer to neutral pH which indicates that the prepared gels doesn't cause oral irritation.

Viscosity: The viscosity values were tabulated in table 3. The result concludes that formulations F4, F5 and F6 are more viscous than F1, F2 and F3.

Uniformity in drug content:

This helps to certify minimum batch to batch variability and the values were represented in Table 3.From the table it was concluded the uniformity of active drug in all the formulations.

Syringe ability: Results revealed that the prepared gels were syringe able through 22 gauze needle.

***In vitro* release studies:**

The drug release data obtained for prepared gels were tabulated in table 5. The zero order release plots were shown in Fig.3a and the *in vitro* release of the prepared gels showed an initial bursting followed by narrowed release. The kinetic values were shown in table 5.The first order, Higuchiand Kerseymeres Peppas plots were plotted and shown in fig. 3b, 3c &3d respectively. These results indicate that the release followed a zero order or first order kinetics.

Results for antimicrobial susceptibility test:

The antimicrobial activity in the form of Zone of inhibition (mm) was shown in table 4. Fig.2a & 2b exemplifies the fallouts of antimicrobial studies. The mean zone of inhibition for formulations F1 to F6 on first day was found to be 21, 19, 20, 21, 21 and 20 mm respectively. On the second day the values were 14, 16, 12, 11, 15 and 15 mmon the third day the values were 11, 10, 9, 6, 9 and 6 mm theplacebo (P) did not show inhibition. The prepared gels showed a slight alteration in zone of inhibition on all the 3 days. Results discovered that the prepared gels were found to have antimicrobial actions against *S. aureus*.

Table 1: Gel Composition (% w/v)

Ingredients (mg)	Formulation					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Ornidazole	025	0.25	0.25	0.25	0.25	0.25
Chitosan	2.0	2.5	3.0	--	--	--
Xanthan gum	--	--	--	1.0	1.0	2.0
Locust bean gum	--	--	--	1.0	2.0	1.0
Lactic acid	2.0	2.0	2.0	--	--	--
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Data for Standard Calibration Plot of Ornidazole in Phosphate Buffer PBS & 0.1N NaOH

Conc. («g/ml)	Absorbance	
	PBS (pH 6.6)	**0.1N NaOH**
0	0.000	0.000
4	0.165	0.122
8	0.278	0.374
12	0.345	0.498
16	0.559	0.655
20	0.775	0.845

Table 3: Surface pH, Data for Viscosity Study and content Uniformity of Formulated Gels

Formulation	Surface pH	Viscosity dyne/cm^2 at 60rpm, spindle No.3	Content uniformity (mg)
F1	6.13±0.057	1357.33±4.72	0.975±0.0005
F2	5.86±0.057	1588.66±3.05	0.987±0.0005
F3	5.86±0.057	1687.33±8.67	0.997±0.0013
F4	6.20±0.100	1740.33±5.03	0.987±0.0014
F5	6.20±0.100	1858.33±4.04	0.987±0.0132
F6	6.23±0.057	1876.00±11.06	0.977±0.0147
All Values Mentioned Were mean ± SD of trials (n) =3			

Table 4: Data for Zone of Inhibition of Formulated Gels

Formulation	Zone of Inhibition (mm)		
	Day 1	Day 2	Day 3
F1	21	14	11
F2	19	16	10
F3	20	12	9
F4	21	11	6
F5	21	15	9
F6	20	15	6

Table 5: Kinetic Values obtained from Different Plots of *in vitro* Drug Release study of Different Formulations of Ornidazole

Formulation	Zero Order Plots		First Order Plot		Higuchi's Plot		Peppa's Plot	
	n	r	n	r	n	r	n	r
F1	0.6712	0.7584	-0.0149	0.9885	7.6529	0.9825	12.9836	0.9881
F2	0.6485	0.7435	-0.0129	0.9758	7.2857	0.9810	12.8300	0.9848
F3	0.6258	0.7385	-0.0121	0.9456	7.0457	0.9787	12.0152	0.9815
F4	1.0122	0.8348	-0.0940	0.8895	9.8133	0.9910	14.3470	0.9896
F5	0.8554	0.8445	-0.0401	-0.8454	8.9322	0.9938	10.7573	0.9910
F6	0.8695	0.8119	-0.0321	0.9769	9.1163	0.9860	11.9503	0.9780
*n=slope, r=Regression coefficient								

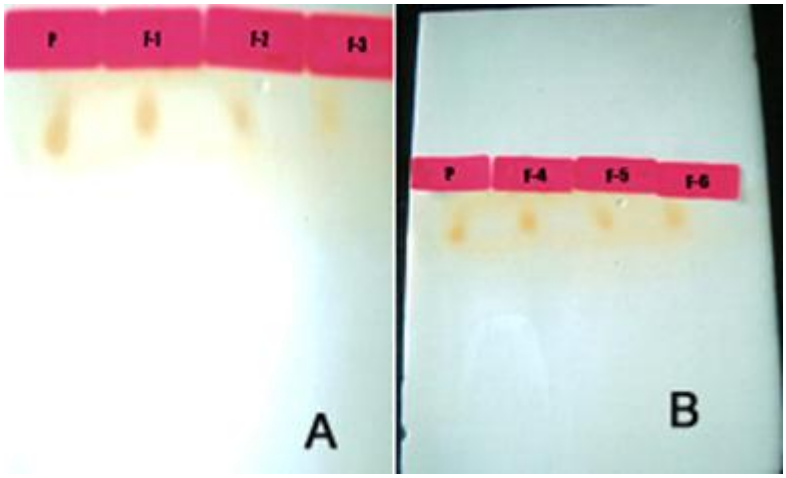

Figure 1: A: TLC of F1, F2, F3 and Pure Drug; B: TLC of F4, F5, F6 and Pure Drug

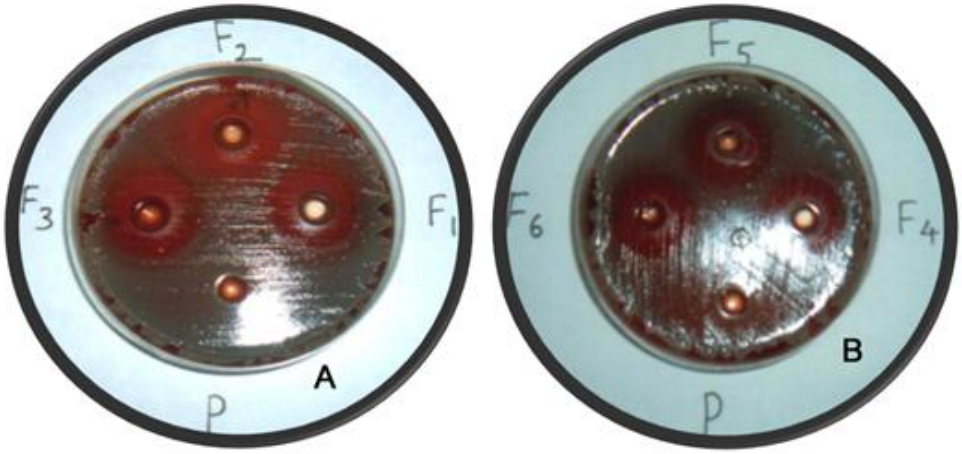

Figure 2: A: ZOI for F1, F2, F3 & Placebo; B: ZOI for F4, F5, F6 & Placebo

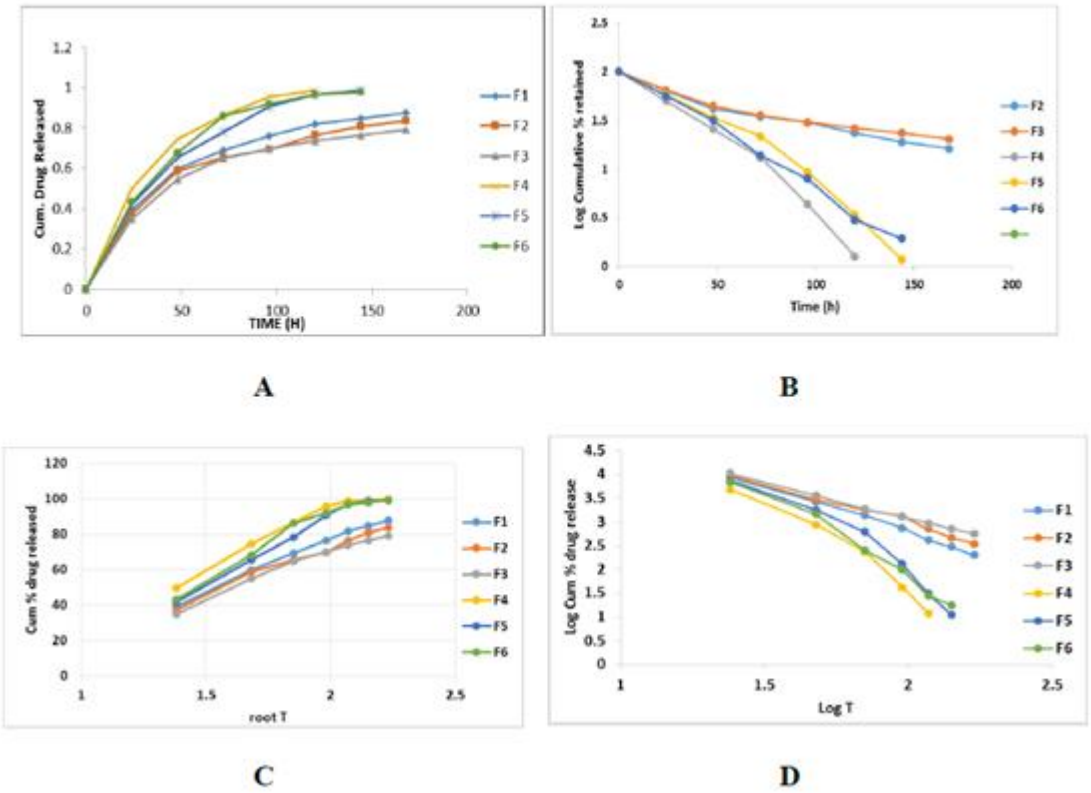

Figure 3: A: Zero order release kinetics, B: First order release kinetics, C: Higuchi release kinetics, D: Korsmeyer Peppas release kinetics

4. Conclusion

Number of delivery systems have been investigated for administration of antibacterial / antimicrobial agents into the periodontal pocket for local action in treatment of plaque. These include prolonged release devices, films, fibers, strips and gels which are kept at the site of action. In the present study, an injectable controlled drug delivery system of Ornidazole gel implants were prepared by using natural biodegradable polymers like chitosan, Xanthan gum and Locust bean gum in different concentrations. All the formulated gels were subjected to various evaluation parameters such as compatibility study, surface pH, viscosity, drug content, bioadhesion study, in vitro release studies and antimicrobial susceptibility test and found good results. Hence we conclude the formulated dental gels of the antimicrobial agent Ornidazole is a promising dosage form for the treatment of various dental infections.

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