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FORMULATION AND EVALUATION OF TINIDAZOLE MUCOADHESIVE BUCCAL GELS

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ABSTRACT

In the present work mucoadhesive gels of Tinidazole that adhere with gums for an extended time period were prepared and evaluated. Tinidazole (TZ) is an antibacterial drug used for treatment of Periodontitis. Different gel formulations were prepared using the bio adhesive polymers like carbopol 974, sodium alginate and sodium carboxy methyl cellulose. The other additives used are triethanolamine as an emulsifier and surfactant, glycerol as a means of improving smoothness, providing lubrication and as humectants, mannitol as the isotonic agent and methylparaben as a preservative. The physicochemical compatibility of the drug and the polymer was assessed by FTIR spectroscopy. The prepared gels were evaluated for various parameters like viscosity, pH, drug content, swelling index, spread ability and *Ex-Vivo* drug permeation. Release of Tinidazole from the gels formulated by employing carbopol 974 extended the drug release up to 6hrs. So the formulations F_7, F_8, and F_9 were found to be optimized formulae.

KEYWORDS: *Tinadazole, Mucoadhesive Buccal gels, Periodontitis and Ex- Vivo drug permeation*

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INTRODUCTION

The dental diseases like Periodontitis are treated by using a systemic antibiotics or a local drug delivery system with an antibiotic. Large doses of the systemic antibiotics must be taken in order to achieve adequate concentrations of the drug in the gingival cervicular fluid of the periodontal pocket. Hence such dosage forms may not produce a required concentration of the drug at the site of action and high doses of antibiotics may cause many side effects. A suitably designed controlled release drug delivery systems for localized action can be major advance towards solving the problems associated with the offered drug delivery systems.[1] During recent years, pharmaceutical aspects of mucoadhesion have been the subject of great interest because it provides the possible avoidance of destruction of the dosage form by the git contents or to bypass the hepatic first pass metabolism. These systems are used to immobilize and restrict a drug delivery tool in the preferred region. These systems helps to maintain the residence time of the drug by providing contact of the drug with the epithelial tissue of the oral cavity which helps to maintain effective concentration of the drug at the site of action that might progress the disease treatment.[2,3] The microbiological treatment of periodontitis is through either the use of systemic antibiotics or a localized delivery system incorporating an antibiotic. In the systemic use, large doses must be taken in order to achieve sufficient concentrations in the gingival cervicular fluid of the periodontal pocket. Such administration may not produce an sufficient concentration at the action site as well as the problems associated with the side effects of high doses of an antibiotic. Alternatively to compensate such problems the local administration of the drug in a controlled release delivery system is selection of research. Appropriate materials for bioadhesion are mainly hydro gel-forming polymers may be used for such hypothesis.[4] Several buccal devices were formulated with Tinidazole which is close analogue to Metronidazole for treatment of periodontitis like Tinidazole dental implant and Tinidazole stilus. In the present work mucoadhesive gels of Tinidazole that adhere with gums for a prolonged period of time were prepared. The mucoadhesive gels were prepared by using hydrophilic polymers like carbopol, sodium alginate and sodium carboxymethylcellulose.[2,5]

Mucoadhesive buccal drug delivery systems

Bioadhesion means the phenomena of maintaining two biological materials together for a long period of time by means of interfacial forces. Bioadhesive systems applied to mucous membrane are known as mucoadhesive systems. Mucoadhesives are natural or synthetic polymers that adhere to the mucus membrane for a prolonged period of time at the localized sites of the body there by civilizing bioavailability of the drugs with low bioavailability.[6]

Advantages

- Extends the residence time of the drug at the site of drug absorption.
- Localization of the drug action at a given target site.
- Ease of administration with more patient compliance.
- As the drug is not subjected to the destructive acidic environment of the stomach and enzymatic alkaline environment of the small intestines`, the drug bypasses the hepatic first pass metabolism.
- Side effects can be reduced by this route which is associated with the other routes of drug administration.
- The buccal mucosa is highly per -fused with blood vessels and offers a greater permeability than the skin and hence systemic absorption is rapid through this route.
- This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects[2].

Limitations

- Drug administration via the buccal mucosa has certain limitations.
- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.

Rationale of mucoadhesive gels of tinidazole

The microbiological treatment of periodontitis is through either the use of systemic antibiotics or a localized delivery system incorporating an antibiotic. In the systemic use, large doses must be taken in order to achieve sufficient concentrations in the gingival cervicular fluid of the periodontal pocket. Such administration may not produce an sufficient concentration at the action site as well as the problems associated with the side effects of high doses of an antibiotic. Alternatively to compensate such problems the local administration of the drug in a controlled release delivery system is selection of research. Appropriate materials for bioadhesion are mainly hydro gel-forming polymers may be used for such hypothesis.[7] Several buccal devices were formulated with Tinidazole which is close analogue to Metronidazole for treatment of periodontitis like Tinidazole dental implant and Tinidazole stilus. In the present work mucoadhesive gels of Tinidazole that adhere with gums for a prolonged period of time were prepared. The mucoadhesive gels were prepared by using hydrophilic polymers like carbopol, sodium alginate and sodium carboxymethylcellulose.[8] Medications that are currenly used in the treatment of periodontitis was shown in the table no.1.

Table 1
Medications that are currently used in the treatment of Periodontitis

Medications	Contains	Uses
Prescription antimicrobial mouthrinse	A prescription mouthrinse containing an antimicrobial called Chlorhexidine	To treat gingivitis, helps to reduce swelling and redness of the gums
Antiseptic chip	A tiny piece of gelatin packed with the medicine Chlorhexidine	To reduce the size of periodontal pockets, control bacteria
Antibiotic gel	A gel that contains the antibiotic Doxycycline	To control bacteria and reduce the size of periodontal pockets
Antibiotic microspheres	Tiny, round particles that contain the antibiotic Minocycline	To reduce the size of periodontal pockets, control bacteria
Enzyme suppressant	A small dose of the medication Doxycycline.	To hold the body's enzyme response If not controlled, break down gum tissue by certain enzymes.
Oral antibiotics	Antibiotic tablets or capsules	For the short term treatment of an acute persistent periodontal infection

MATERIALS AND METHODS

Tinidazole was purchased from Global Pharmaceuticals Limit., Hyderabad. Sodium alginate, Sodium carboxy methyl cellulose and Mannitol were obtained from SD fine chemicals, Mumbai. Carbopol974 was purchased from NR Chem., Mumbai. Methylparaben, Glycerin and Triethanolamine were purchased from Molychem Limit., Badipur. All other ingredients used were of analytical grade.

Procedure for calibration curve of Tinidazole

The U.V scanning of drug sample was carried out using a solution of drug dissolved in phosphate buffer solution of pH 7.4 at λ_{max} 282nm. 100mg of Tinidazole was weighed and dissolved in 100mg of phosphate buffer of pH 7.4 which makes the concentration of 1mg/ml. From the above solution 1ml was withdrawn into a 100ml volumetric flask and make up the volume up to the mark with the phosphate buffer 7.4 which makes the concentration of 0.1mg/ml. From the above solution pipette out 1 of 12 ml and made up to 100ml with the phosphate buffer 7.4 to get the solutions of concentrations 2, 4, 6, 8, 10 and 12µg/ml. The absorbance of these solutions was measured at 282nm using U.V-Visible spectrophotometer the result is shown in table 2 and the calibration graph was drawn by taking concentration on X-axis and absorbance on Y-axis (Fig 1).

Table 2
Absorbance Vs Concentration at 282nm

Concentration(µg/ml)	Absorbance
0	0
2	0.0745
4	0.1394
6	0.2033
8	0.2627
10	0.3346
12	0.3991

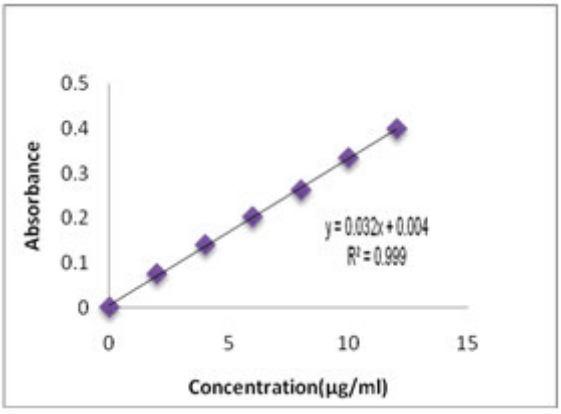

Figure 1
Calibration Curve Of Tinidazole

Physicochemical Compatibility studies

The physicochemical compatibility of the drug and the polymer was assessed by FTIR spectroscopy. FTIR spectra of the drug and the optimized formulation were recorded in the range of 4000-400 cm^{-1}. FTIR spectrophotometer was used to perform the compatibility studies. The characteristic absorption peaks of Tinidazole were obtained at 1297.02cm^{-1}, 2910.36 cm^{-1}, 1363.63 cm^{-1},2316.49 cm^{-1} and 1450.18 cm^{-1} (Fig 2). In the present study, it has been observed that there are no chemical interactions between the drugs and the excipients used. The interpritations are shown in the table 3.

Table 3
Interference of Characteristic peaks in a mixture of Drug and all Excipients

S.no	Peak obtained in drug [frequency (cm^{-1})]	Description	Peak obtained in mixture [frequency(cm^{-1})]	Interference
1	1297.02	C-N Stretch	1297.13	nill
2	2910.36	C-H Stretch	2909.83	nill
3	1363.63	0	1365.01	nill
4	2316.49	-C=C-	2330.54	nill
5	1450.18	$>CH_2$	1449.54	nill

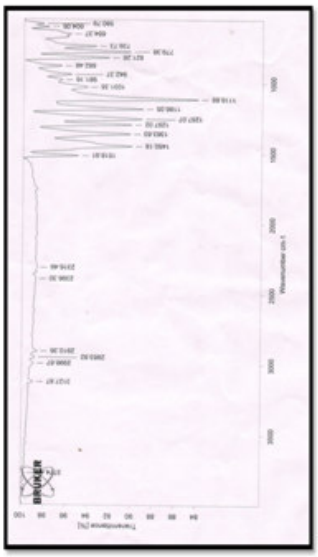

Figure 2
FTIR spectra of pure drug Tinidazole

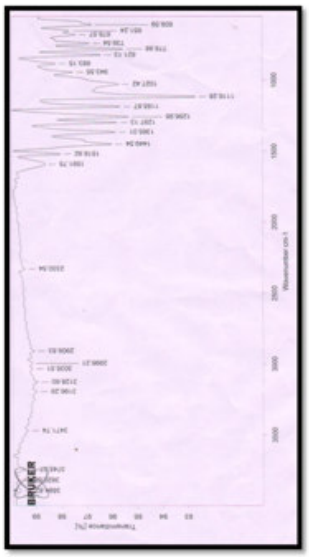

Figure 3
FTIR spectra of mixture Drug and all Excipients

Formulation development
Gels were formulated using polymers such as sodium alginate, sodium carboxy methyl cellulose and carbopol 974 and excipients such as mannitol, triethanolamine, methylparaben and glycerin. The mucoadhesive gels were developed by changing the various polymer concentrations without changing the drug concentration. The concentration of the polymers was chosen based on the polymer used in the formulation of the gels.[9]

Preparation of the polymer gel bases
The required quantities of different polymers were weighed. The weighed polymers were slowly added to the beaker containing 2gms of mannitol and 30ml of distilled water with continuous stirring at 500 rpm using a mechanical stirrer. The mixture was stirred continuously for 30 minutes and was allowed to soak for 24 hours.[10]

Preparation of Tinidazole Gels
Accurately weighed amount of the drug, Tinidazole (0.5gms), was slowly added to the previously prepared polymer gel base with continuous stirring. 1ml of triethanolamine was added for neutralization of the gels. Glycerin as moistening agent and methylparaben as preservative were added to the gels by continuous stirring without any air entrapment. The formed gels were kept aside for 24 hrs for complete desolvation of polymers and until the homogeneous Tinidazoles gels were formed.[11]

Table 4
Formulation of Mucoadhesive Tinidazole Gels

INGREDIENTS	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Tinidazole (gms)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium alginate(gms)	2	3	4	-	-	-	-	-	-
Sodium carboxymethylcellulose(gms)	-	-	-	1	1.5	2	-	-	-
Carbopol 947(gms)	-	-	-	-	-	-	0.5	1	1.5
Mannitol (gms)	2	2	2	2	2	2	2	2	2
Methylparaben (gms)	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22
Triethanolamine (ml)	1	1	1	1	1	1	1	1	1
Glycerin (ml)	1	1	1	1	1	1	1	1	1
Dist.Water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Characterization of gels

Physical examination

The prepared gel formulations are examined visually for their color, homogeneity, consistency and phase separation.

Viscosity

The viscosity of different gel formulations is determined by Brookfield viscometer with spindle no.64 rotated at 20 rpm at 25°C which was connected to a thermostatically controlled circulating water bath.[13] The results are shown in table 5.

pH of the Gels

An acidic or alkaline formulation may cause irritation on mucosal surface and hence this parameter assumes importance in the formulation of mucoadhesive dosage forms. Digital pH meter was used to determine the pH of the mucoadhesive buccal gels. [14] The results are shown in table 5.

Spreadability

Spreadability test was important to know the behavior of the gels that comes out of from a tube. It was determined by measuring the diameter of 1gm of gel that was placed between two horizontal plates (10×10 cm^2).[15] The results are shown in table 5.

Percentage yield

The empty container in which the gels stored were weighed and noted the values as W_1. Then the containers with the gels were weighed and noted the values as W_2. The practical yield was calculated by using the formula

$$\text{Practical yield} = W_2 - W_2$$

The percentage yield of all formulations was calculated by using the following formula and the results are shown in table 5.

$$\text{Percentage yield} = \frac{\text{practical yield}}{\text{theoretical yield}} \times 100$$

Swelling index

1gm of the gel was placed into a stainless steel basket with 200 mesh of aperture and noted the weight as W_0. The basket was then placed in a beaker which contains phosphate buffer of pH-7.4 allowing the gel to swell at room temperature for 5 hrs. Then the baskets were taken out from the beaker and weighed by swiping out excess amount of the buffer from the surface of the basket with a filter paper and values are recorded as W_t.[16] The percentage swelling was calculated by using the formula and the results are shown in table 5.

$$\%\text{swelling} = \frac{W_t - W_0}{W_0} \times 100$$

Drug content

1gm of gel was weighed in a 100ml volumetric flask and dissolved in 25ml of methanol. The flask was closed and shaken for 15minutes, then the mixture was filtered and the filtrate was made up to the 100ml with methanol. From the above solution 1ml was withdrawn and made the volume up to 10ml. Again pipette out 1ml from the above solution and made up the volume up to 10ml. the absorbance of the solution was measured at 282 nm using U.V-visible spectrophotometer. The total content of the drug, Tinidazole was determined by comparing the absorbance of the resultant solution to that of the standard curve of the Tinidazole.[17] The drug content was determined by using following formula and the results are shown in table 6.

$$\text{Drug content} = \frac{\text{absorbance}}{\text{slope}} \times \text{dilution factor} \times \frac{1}{1000}$$

***Ex- Vivo* permeability of the drug**

Ex-Vivo permeation study for mucoadhesive buccal gels was carried out by using modified Franz diffusion cell apparatus. The details were given as below

- **Drug Name** : Tinidazole
- **Dosage Form** : Mucoadhesive Buccal Gels
- **Apparatus** : Modified Franz Diffusion Cell
- **Medium** : Phosphate Buffer pH-7.4
- **Medium Volume** : 200ml
- **Speed** : 100rpm
- **Temperature** : 37±0.5°C
- **Wavelengt** : 282nm

Procedure

The study was carried out by using 200ml phosphate buffer pH-7.4 in a beaker as a receptor compartment which was subjected to magnetic stirring at a speed of 100rpm. A glass tube with two open ends was taken as a donor compartment. 1gm of gel was placed on porcine buccal mucosa and then fixed to one end of the test tube. Then with the help of the holder the test tube was dipped into the beaker such that the buccal mucosa touches the surface of the buffer. An aliquot of 5ml of the medium was withdrawn from the receptor compartment at the time intervals of 1, 2, 3, 4, 5 and 6 hrs and replaced with fresh medium at each time to maintain the sink conditions. Then finally the samples were analyzed by using U.V-visible spectrophotometer at a wavelength of 282nm.[17]The results are given in table 7 and the graph is shown in figure 4.

STATISTICAL ANALYSIS

All experiments were performed in triplicate for validity of Statistical analysis. Results were expressed as mean mean ±SD(standard deviation).ANOVA(analysis of variance) and Student t-test were performed on the data sets generated using SPSS version 13 .The difference were considered to be significant at p<0 .05.

RESULTS AND DISCUSSION

In the present work mucoadhesive gels of Tinidazole that adhere with gums for a prolonged period of time were prepared and evaluated. The standard curve of Tinidazole was prepared in phosphate buffer 7.4, at λ_{max} of 282nm.the curve showed linear relationship between concentration and absorbance. The value of regression coefficient (R^2) was found to be 0.998 and the regression equation generated was y=0.033(Fig 1). The curve obeyed Beer's law at the given concentration range of 2-12µg/ml and the absorbance results were shown in the Table 2. FTIR studies performed for the pure drug Tinidazole and the physical mixture of the pure drug with polymers like carbopol 974, sodium alginate and sodium carboxy methyl cellulose to detect the drug polymer interactions which would be reflected by a change in the position or disappearance of any characteristic peaks of the compounds(Fig 2 and 3).From the infrared spectral analysis, it was clear that the characteristic absorption peaks of Tinidazole were found in the physical mixture of drug and excipients, so it indicates that there was no interaction between drug and excipient shown in table 3. The formulated gels had viscosity ranging from 47000 to 97000cps .This showed that the viscosity of the gels increased with the carbopol content, which may be due to increase in three dimensional gross structures of formulated gels.The values of pH were within the range of neutral pH range i.e., 6.9-7.3 which indicates that the formulations can be used without any irritation in the oral cavity. Spreadability test was carried out for all formulations and it was found that the spreadability of the gels decreases with the increase in the polymer concentration which indicates that the gel formulations with the carbopol had less spreading capacity .The percentage yield of all the formulations was determined. The swelling index of all the formulations were determined which depends on the nature and the polymer present in the formulation. The polymers with high hydration properties will swell and persuade the mobility in the polymer chains in order to improve the interpenetration between the polymer and mucin. From the swelling studies it was found that the gel formulations with carbopol showed high swelling properties. From this it was concluded that the carbopol has high bioadhesive force that attached to the oral mucosa up to 6 hrs. The results were shown in table5.

Table 5

Comparative evaluation of gels using different parameters

Formulation Code	Viscosity (Cps)	Percentage Swelling (%)	Ph	Percentage Yield(%)	Spreadability gm.cm^2
F-1	47000	32.91±0.02	7.1±0.026	96.39	16.81±0.06
F-2	56000	40.72± 0.012	6.9±0.027	97.14	16±0.017
F-3	69000	45.24±0.031	7.2±0.021	905.67	14.06±0.011
F-4	35000	34.89±0.022	7.3±0.015	98.33	14.44±0.015
F-5	51000	41.33±0.042	7.2±0.028	97.75	12.6±0.018
F-6	68000	46.51±0.032	7.1±0.020	96.23	11.28±0.012
F-7	71000	36.89±0.036	7.3±0.023	98.20	11.19±0.013
F-8	73000	47.33±0.011	7.2±0.020	97.41	10.56±0.02
F-9	97000	49.05±0.01	7.3±0.017	95.26	9.93±0.014

****average of 3 determinations (n=3),p < 0 .05 are significant***

Drug content was estimated by using U.V-visible spectrophotometer at a λ_{max} of 282nm. The drug content was found to be within the acceptable range of 95-98% which indicates that the process employed to prepare the gels was capable of developing the gels with uniform drug content

Table 6
Data for drug content of all formulations

Formulation Code	Drug Content Uniformity (%) (n=3)Mean ±SD
F-1	97±0.0351
F-2	96±0.119
F-3	98±0.098
F-4	97±0.256
F-5	97±0.226
F-6	95±0.598
F-7	96±0.085
F-8	96±0.085
F-9	98±0.191

average of 3 determinations (n=3) and he limit is 80-110%

Ex-Vivo drug permeability studies

The drug release studies of all the formulations of Tinidazole gels were carried out in phosphate buffer-7.4 using a modified Franz Diffusion Cell. It was concluded that the drug release was decreased by increasing the polymer concentration as the polymer concentration increase, viscosity decreases. On basis of physical parameters and release pattern F_7, F_8 and F_9 were selected as best formulations. The results revealed that the release rate of the Tinidazole was controlled for a period of 6hrs with formulation containing carbopo974.

Table 7
Ex-vivo drug permeability data for all formulations

Time (hrs)	Cumulative % drug release(% CDR) F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	28.53±0.142	26.28±0.145	25.22±0.144	26.99±0.141	27.62±0.121	28.21±0.140	17.82±0.142	17.63±0.141	17.53±0.141
2	56.72±0.133	51.85±0.135	56.12±0.132	51.48±0.134	53.33±0.033	54.50±0.135	42.75±0.134	38.07±0.124	37.48±0.006
3	77.25±0.038	76.27±0.033	78.18±0.036	74.00±0.032	75.10±0.045	76.00±0.352	64.62±0.032	56.25±0.052	55.18±0.017
4	87.37±0.315	85.15±0.032	92.32±0.330	85.02±0.374	86.24±0.062	88.08±0.388	84.50±0.034	81.62±0.008	76.28±0.032
5	96.64±0.361	97.42±0.38	98.56±0.368	94.56±0.359	95.48±0.144	96.12±0.362	93.22±0.359	92.46±0.019	89.13±0.045
6	-	-	-	-	-	-	98.56±0.042	97.55±0.212	96.46±0.22

average of 6 determinations (n=6),p < 0 .05 are significant

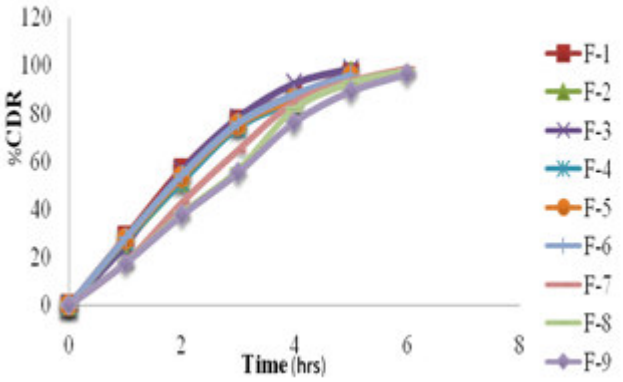

Figure 4
Ex-vivo drug permeability study for all formulations

CONCLUSION

Mucoadhesive drug delivery system uses the property of bioadhesion of some water soluble polymers which are used for targeting a drug to a particular region of the body for long period of time. Tinidazole mucoadhesive buccal gels were found to be beneficial in terms of reduction in frequency of administration. It was concluded that Tindazole gels can be successfully prepared by using mucoadhesive polymers like crabopol 974, sodium alginate and sodium CMC which can be used in the treatment of periodontitis and also by decreasing dosing frequency the bioavailability increases that result in better patient compliance with minimum side effects. The prepared gels were air bubble free, homogeneous, smooth and transparent.

CONFLICT OF INTEREST

Conflict of interest declared none.

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