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FORMULATION AND EVALUATION OF METRONIDAZOLE MOUTH ULCER GEL

Priyanka D. Debaje, Ashwini A. Bachhav*, Nayan A Gujrathi , Anil G. Jadhav

Department of Pharmaceutics, Sandip Institute of Pharmaceutical Sciences, Mahiravani, Nashik-422213, India

*Corresponding author E-mail: ashwini.bachhav@sandippharmacy.com

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ABSTRACT

Aim: The present work aimed at preparing mouth ulcer gel of Metronidazole benzoate with the purpose of developing a dosage form for a very quick onset of action. **Objectives:** The main objective of this study was to develop a local, oral metronidazole benzoate (MET) delivery system that can be applied and removed by the patient for the treatment of periodontal diseases. **Material and Methods:** All ingredients were weighed accurately according to the required quantity. Carbapol 934 and propylene glycol were mixed in water. Metronidazole benzoate was dissolved in suitable quantity of ethanol in another beaker. This dissolve drug was added to above solution .Then the Peppermint oil, preservative and Triethanolamine were added. Prepared gel characterized for appearance, pH, spredability, drug content and *in vitro* drug release. **Result and Discussion:** The drug release was dependent on the concentration of carbapol and concentration of propylene glycol. The Mouth ulcer gel of Metronidazole benzoate showed acceptable mechanical characteristics and satisfactory % drug release. The prepared gel was transparent with smooth surface without any interactions between drug and polymer. B3 formulation showed best results because all the parameter showed satisfactory results.

INTRODUCTION

Metronidazole Benzoate practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, dichloromethane, slightly soluble in alcohol. Metronidazole is a synthetic nitro-imidazole derivative. It is an anaerobic antibacterial agent and an antiprotozoal (trichomoniasis, amoebiasis, and giardiasis).

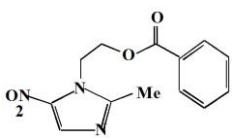

Figure: Metronidazole Benzoate

However, the mechanisms by which Metronidazole Gel acts in reducing inflammatory lesions of rosacea are unknown, but may include an antibacterial and/or anti-inflammatory mechanism. Drug has bioavailability of more than 90% after oral administration with half life8-9hrs.Drug is excreted in the urine (60-80%)[1]. Metronidazole benzoate comes under the category of antibacterial agents. Antibacterials are used to treat bacterial infections. The drug toxicity to humans and other animals from Antibacterials is generally considered low. Prolonged use of certain antibacterial can decrease the number of gut flora, which may have a

negative impact on health. Consumption of probiotics and reasonable eating can help to replace destroyed gut flora. Stool transplants may be considered for patients who are having difficulty recovering from prolonged antibiotic treatment, as for recurrent Clostridium difficileinfections. The discovery, development and use of antibacterial during the 20th century have reduced mortality from bacterial infections. The antibiotic era began with the pneumatic application of nitroglycerine drugs, followed by a "golden" period of discovery from about 1945 to 1970, when a number of structurally diverse and highly effective agents were discovered and developed. Since1980 the introduction of new antimicrobial agents for clinical use has declined, in part because of the enormous expense of developing and testing new drugs. In parallel there has been an alarming increase in antimicrobial resistance of bacteria, fungi, parasites and some viruses to multiple existing agents. Antibacterials are the agents or compounds used to either kill or inhibit the growth of only bacteria which infect the body. Antibacterial agent can be of two types: Bacteriocidal and Bacteriostatic. Bacteriocidal are the metabolic compounds which kill or completely destroy the harmful bacteria; Bacteriostatic inhibit the growth of bacteria. Many kinds of drugs are produced like Cephalosporin (isolated from fungus), Penicillin's, Tetracycline's, sulfa drugs and fluoroquinolones.The antibacterial agent is now found in products such as deodorants, mouthwashes, soaps, cutting boards, and baby toys. It will not be wrong to say that **'all antibiotics are antibacterial, but all antibacterial is not antibiotics**.'[2] Mouth Ulcer is Latin origin ULCUS means break in the skin. A mouth or oral ulcer is an open sore in the mouth, or rarely a break in the mucous membrane or the epithelium on the lips or surrounding the mouth. A mouth ulcer (also termed an oral ulcer, or a mucosal ulcer) is an ulcer that occurs on the mucous membrane of the oral cavity. They are painful round or oval sores that form in the mouth, mainly on the inside of the cheeks or lips. Mouth ulcers, also known as aphthous ulcers, can be painful while eating, drinking or brushing teeth[3]. Mouth ulcers are very common, and they occur in association with many diseases and by different mechanisms, but usually there is no serious underlying cause. The surface of an ulcer is covered by mass of fibrin with intermingled, dead and dying polymorphs which would dry on the skin to form a crust or scab. A superficial ulcer with no evidence of significant fibrinous exudation on the surface of polymorph exudation suggests the possibility of bullous disorder[4]. A heavy inflammatory infiltrate extends deep into the underlying connective tissue n blood vessels may show slight inflammatory vasculitis. Granulation tissue is formed with dilated blood vessels and heavy infiltrate of plasma cells, lymphocytes and polymorphs. Common causes of mouth ulcers include nutritional deficiencies such as iron, vitamins especially B12 and C, poor oral hygiene, infections, stress, indigestion, mechanical injury, food allergies, hormonal imbalance, skin disease etc[5]. Mouth ulcers include lesions, sores, laceration, abrasions, or any open break in the mucosa of the mouth, lips or tongue. Mouth ulcers may also be called stomatitis and are a symptom of a variety of mild to serious diseases, disorders and conditions. Mouth ulcers can result from vitamin deficiencies, infection, inflammation, trauma, malignancy and other diseases and abnormal processes. Mouth ulcers can occur in any age group or population. Mouth ulcers can be the result of a mild condition, such as a canker sore or excessive or overly aggressive tooth brushing. Mouth ulcers can also be the result of a moderate condition, disorder or disease, such as gingivitis or a cold sore. Mouth ulcers can also occur due to some diseases, disorders and conditions that can be serious, even life-threatening.

These include oral cancer and leukoplakia[6].

Material and Methods:

Metronidazole Benzoateand sucrose were received as a gift sample from TriveniInterchem PVT. LTD, Vapi, Carbopol 934, Propylene Glycole and Triethanolaminewere received as a gift sample from Alpha Chemika, Mumbai, SolvoChem, Ahmadabad and National Analytical Corporation, Mumbai respectively.All other reagentsused were of analytical reagent grade.

Method of preparation[7,8] All ingredients were weighed accurately according to the required quantity. Accurately weighed quantity of carbapol 934 was mixed with sufficient quantity of water in a beaker using magnetic stirrer. Specified quantity of propylene glycol was added in the solution with continuous stirring. Metronidazole benzoate was dissolved in suitable quantity of ethanol in another beaker. This dissolve drug was added to above solution with continuous stirring until the clear gel is formed. Then the Peppermint oil was added as a flavoring agent. Sufficient quantity of preservative is added. Triethanolamine is added in the solution to adjust the pH.

Evaluation of formulation:

Appearance[9, 10]: The prepared gel bases were inspected visually for clarity, colour and presence of any particles.

Viscosity Study[11]: Viscosity of gels was studied on Brookfield viscometer by using spindle number 3 at 60 revolutions per minute at constant temperature.

Surface pH of the gel[12]: 100 mg gel was kept in a 50 mL volumetric flask and then made up to volume with water to 50 ml. The pH of all gel formulations were measured by pH meter.

Spredability[13,14]: Spredability is expressed in terms of time in seconds taken by two slides to slip off from emulsified gel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. The Spredability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight tied on the upper plate. It is calculated by using the formula. S = M. L / T, Where, M = wt. tied to upper slide, L = length of glass slides, T = time taken to separate the slides

***In-vitro* release studies[15,16,17]:** Modified Franz Diffusion Cell was used for permeation study. Cellophane membrane was tied to one end of donor compartment. Gel was accurately weighed containing 1mg of drug and was taken in donor compartment. The receptor compartment contains40 ml of phosphate buffer (pH 6.6) and temperature 37±10ºC was maintained throughout the study. 5 ml aliquots were withdrawn periodically for 12 hrs and amount of drug was estimation from the equation of calibration curve.

RESULTS AND DISCUSSION:

Appearance: Appearance of all formulation was observed and noticed that each formulation transparent in appearance. The results are shown in Table 2.

Viscosity Study: Viscosity is an expression of the resistance of the fluid to flow. The higher the viscosity, the greater the résistance. Here, all formulation shows viscosity between 1069 Cps to 1831 Cps which is shown in Table 3.

Surface pH of the gel: pH of all formulations is found to be around 6-7 which is compatible with saliva pH and which is shown in Table 4. The observed pH is match with salvapH. Therefore, it reduces possibilities of irritation.

Spredability: The spreadability of all formulation batches was studied and it shows better spreadability and it is shown in Table 5. In that the spreadability of formulations ranged from 10.66 to 17.81 (g.cm/sec).

Table1: Formulation of mouth ulcer gel of metronidazole benzoate.

Formulation code		B1	B2	B3	B4	B5	B6
Drug (mg)		30	30	30	30	30	30
Carbapol 934 (%)		0.17	0.25	0.32	-	-	-
HPMC E-15 (%)		-	-	-	0.17	0.25	0.32
Propylene glycol (%)		10.62	12.12	15.38	10.62	12.12	15.38
Glycerine (ml)		2	2	2	2	2	2
Peppermint oil (ml)		0.05	0.05	0.05	0.05	0.05	0.05
Triethanolamine (ml)		q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methyl paraben (ml)		0.18	0.18	0.18	0.18	0.18	0.18
Solvent (ml)	Ethanol	2	2	2	2	2	2
	Water	18	18	18	18	18	18

Table 2: appearance of all formulations

Batch no.	Appearance
B1	Transparent
B2	Transparent
B3	Transparent
B4	Transparent
B5	Transparent
B6	Transparent

Table 3: Viscosity of all formulations

Batch no.	Viscosity Cps
B1	1228
B2	1831
B3	2258
B4	1069
B5	1384
B6	1692

Table 4: pH of all formulations

Batch no.	pH
B1	6.4
B2	6.7
B3	6.9
B4	6.2
B5	6.6
B6	6.7

Table 5: Spreadability of all formulations

Batch no.	Spredability(gm.cm/sec)
B1	13.23
B2	18.44
B3	21.92
B4	10.66
B5	14.34
B6	17.81

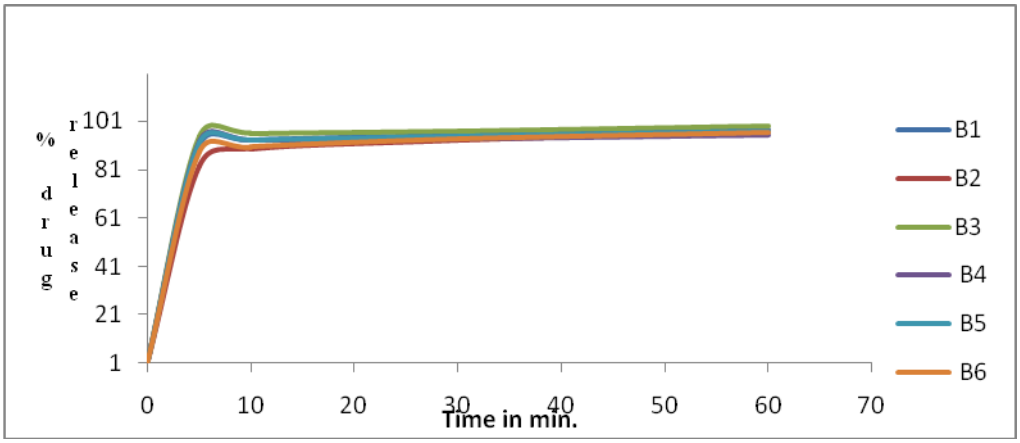

Figure: *In vitro* drug release of B1 TO B6

***In-vitro* release studies:**

In vitro release study shows maximum release 98.87% for B3 formulation this could the attributed to concentration of Carbapol 934 and lower concentration of propylene glycol in the formulation. From Table 1 and figure 6 it is clear that drug releases was dependent on the concentration of carbapol and concentration of propylene glycol.

CONCLUSION:

From present investigation it can be concluded that metronidazole benzoate mouth ulcer gel formulation can be successfully formulated by using combination of carbopol 934 and propylene glycol. It is concluded that the drug release was dependent on the concentration of carbapol and concentration of propylene glycol. The Mouth ulcer gel of Metronidazole benzoate showed acceptable mechanical characteristics and satisfactory % drug release. The prepared gel was transparent with smooth surface without any interactions between drug and polymer. B3 formulation showed best results because all the parameter showed satisfactory results.All batches were found to be satisfactory results for physical appearance, Spredability, pH, viscosity, in vitro release study. Mouth ulcer gel of metronidazole benzoate containing polymer carbapol 934 showed best result. The satisfactory diffusion profile was obtained.

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