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DESIGN AND CHARACTERIZATION OF EMULGEL OF AN ANTIMICROBIAL DRUG METRONIDAZOLE

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ABSTRACT

Emulgel is one of the emerging topical drug delivery system for the delivery of hydrophobic drugs which overcome various disadvantages of ointments and creams such as greasiness and phase inversion. The aim of present work was to develop and evaluate Metronidazole emulgel with controlled release. The Metronidazole used in treatment of various bacterial and fungal infections such as cutaneous and subcutaneous diseases like acne and psoriasis. Different formulations (F1-F4) of Metronidazole emulgel was prepared by using sodium alginate with varying concentrations as gelling agent with oil phase such as mentha oil and Tween-20 and Span-20 as a emulsifying agent. The prepared emulgels were evaluated for physical appearance, pH, drug content, In-vitro diffusion studies. By the In-vitro diffusion studies it was observed that formulation F4 showed 93.20% of drug release after 6 hours and results concluded that the formulation F4 showed better releasing of drug.

KEYWORDS: Topical delivery, Antimicrobial agent, Emulgel.

INTRODUCTION

Topical drug administration is the simplest and easiest route of localized drug delivery anywhere in the body by routes as ophthalmic, rectal, vaginal, and skin.[1] Topical drug delivery systems are such system in which direct application of a formulation containing an active pharmaceutical ingredient to the skin to obtain the localizing effect of the drug.[2] Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration, drugs applied to the skin for their local action include antiseptics, antifungal agent, skin emollients, and protectants.[3] Emulgel is an emulsion, either of the oil in water or water in oil type, which is gelled by mixing with a gelling agent.[4] The main advantage of the emulgel that lipophilic drugs can be easily formulated as emulgels. Due to solubility problems, most of the lipophilic drugs cannot be formulated directly as a hydrogel. For this reason, emulgel provides better stability and release of the lipophilic drug in comparison with simple hydrogel base.[5] Metronidazole, which is a synthetic metronidazole derivative with antimicrobial and anti-inflammatory properties, has been reported to be effective in the treatment of rosacea through not only topical application but also systemic administration. As the first topical therapy approved for rosacea, Metronidazole has remained a cornerstone of rosacea management. Topical application of Metronidazole was shown to be as effective as systemic antibiotic therapy. Metronidazole is particularly effective against papules and pustules and is a well-tolerated alternative to oral antibacterial. The exact mechanism by which topical Metronidazole reduces inflammatory lesions and erythema in rosacea is unknown; it is suggested that its anti-inflammatory effect may be due to its antioxidant action.[6] Chemically metronidazole is 2-(2-Methyl-5-nitro-1H-imidazol-1-yl) ethanol-1, belonging to the category of the antiprotozoal drug.

The aim of this work was to develop an emulgel formulation of Metronidazole using sodium alginate as gelling agents. The influence of the gelling agent type and concentration was investigated. The rheological studies, spreading coefficient studies, pH, drug content, and in vitro drug release of the prepared emulgels were evaluated.

MATERIALS AND METHODS

Materials

Metronidazole was purchased from Alembic Pharmaceuticals, Ankleshwar, Sodium Alginate, light liquid Paraffin, Spans 20 and Tween 20 were obtained from Ozone International, Mumbai, India analytical reagent grade.

Methods

Determination of λ_{max} of Metronidazole

The stock solution (100µg/ml) was prepared by dissolving drug (10 mg) separately in 100ml of phosphate buffer 6.4. The UV spectrum of Metronidazole solution in phosphate buffer was scanned at 309 nm and observed the λmax by using UV spectroscopy.

Calibration Curve of Metronidazole

Calibration curve of Metronidazole in buffer pH 6.4 was obtained by preparing serial dilutions from a stock solution (0.5 mg/ml). Moreover, the samples were analyzed spectrophotometrically at their lambda maximum 309 nm. The absorbance of each sample was plotted versus concentrations.[7]

Fourier Transforms Infrared (FTIR) Spectroscopy

The infrared spectra of Metronidazole, sodium alginate and physical mixture of drug and sodium alginate (1:1) were recorded between 400 and 4000 cm−1 to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The resultant spectra were compared for any possible changes in the peaks of the spectra.[8]

Preparation of Metronidazole Emulgel

Different formulations were prepared using varying amount of gelling agent. The method of making gel and the preparation of emulsion was same in all the formulations. The gel phase in the formulations was prepared by dispersing Sodium alginate in purified water with constant stirring at a moderate speed using mechanical shaker. The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin. While the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol whereas Metronidazole was dissolved in purified water, and both solutions were mixed with the aqueous phase. Mentha oil was mixed in oil phase. Both the oily and aqueous phases were separately heated to 70–80℃, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel.[9]

Table 1: Composition of Metronidazole emulgel.

Ingredient	F1	F2	F3	F4
Metronidazole (gm)	1	1	1	1
Sodium alginate (gm)	0.25	0.50	0.75	1
Light liquid paraffin (ml)	7.5	7.5	7.5	7.5
Tween 20 (ml)	0.5	0.5	0.5	0.5
Span 20 (gm)	1	1	1	1
Propylene glycol (ml)	5	5	5	5
Methyl paraben (gm)	0.03	0.03	0.03	0.03
Propyl paraben (gm)	0.01	0.01	0.01	0.01
Mentha oil (ml)	4	6	8	10
Water (ml)	q.s.	q.s.	q.s.	q.s.

Characterization of Metronidazole Emulgel

Physical appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, grittiness, and phase separation.[10]

Measurement of pH

The pH of emulgel formulations was determined using digital pH meter at room temperature (25±1°C) after 24 h without dilution. Measurements were taken in triplicates.[11]

Rheology

The viscosity of the formulated batches was determined using a fungi lab viscometer with spindle 7, 6, and 5. The formulation whose viscosity was to be determined was placed in the beaker and was allowed to settle down for 30 min at room temperature before the measurement was taken. The spindle was lowered into the center of emulgel taking care that spindle did not touch the bottom of the beaker and rotated at a speed of 2, 2.5, 3, 4, 5, 6, 10, 12, 20, and 30 rpm.

The viscosity reading was noted down and the averages of three readings were taken.[12]

Determination of Spreadability

Spreading coefficient was determined by apparatus suggested by Mutimer. It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide.[13]

Determination of Drug Content

Drug content in the emulgel was determined by taking 1 g of the prepared emulgel which is equivalent to 100 mg of Metronidazole and transferred to 100 ml volumetric flask containing water then sonicated and filtered through a filter paper (0.45 µm, Millipore), then suitably diluted and analyzed using UV-visible spectrophotometer at λmax 309 nm using phosphate buffer (pH 6.4) as blank [14].

In-vitro Drug Release Studies

The in vitro drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer pH 6.4 was used as a dissolution media. The temperature of the cell was maintained at 37℃ by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead.[15]

RESULTS AND DISCUSSION

Determination of λ_{max} of Metronidazole

Scanning of Metronidazole stock solution (0.5 mg/ml) in phosphate buffer (pH 6.4) by UV spectrophotometer at 200–400 nm gave the spectrum shown in Fig. 1. The maximum absorbance (λmax) found to be 309 nm, which is similar to standard references.

Calibration Curve of Metronidazole

Fig. 2 shows the calibration curve of Metronidazole in phosphate buffer (pH 6.4); a straight line was obtained by plotting the absorbance versus concentration. This indicates that the calibration curve within this range of concentration obeys Beer-Lamberts law at λmax 309 nm.

Fourier Transforms Infrared (FTIR) Spectroscopy

The infrared spectra of Metronidazole, sodium alginate and physical mixture of drug and sodium alginate (1:1) were recorded between 400 and 4000 cm−1 to detect the drug-excipients interactions.

Physical Appearance

Total four formulas of emulgel were prepared; emulgel formulations prepared with sodium alginate were Brownish Gummy. All the formulas were viscous, creamy preparation with a smooth, homogeneous texture, and glossy appearance. Results have been discussed in Table 2

Measurement of pH

The pH of the emulgel formulations was in the range of 5.25 to 6.0 as shown in Table 2, which lies in the normal pH range of the skin and would not fabricate any skin irritation.

Rheology

Rheological behavior of the emulgel formulations exhibited non-Newtonian shear thinning pseudoplastic type of flow, i.e., decreases in viscosity at increasing shear rates. As the shear stress is increased, the disarranged molecules of the gelling material are caused to align their long axes in the direction of flow. Such orientation reduces the internal resistance of the material and decreases viscosity. The viscosity of the formulations increases as the concentration of polymer increases, Thixotropic, or time-dependent flow, occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurements. The viscosity of different emulgel formulations was determined by digital viscometer (Fungilab). The results are shown in Table no. 3.

Spreadability

The therapeutic efficacy of emulgel depends on its spread. The emulgel spreading helps in the uniform application to the skin, so the prepared formulas must have a good spreadability and satisfy the ideal quality in topical application. Furthermore, this is considered an important factor in patient compliance with treatment. The spreadability of the formulations F1, F2, F3, F4 were found to be 5.2, 5.9, 4.7, and 6.7 cm^2 respectively. Indicating spreadability of emulgel containing Metronidazole was good as compound to marketed gel. Result have been discussed in table no. 4.

Gel strength

50gm of prepared gel sample was placed in a 100ml measuring cylinder. Then, a 35g weight was positioned on a disc have wideness of 2.3 cm, a distance of 0.4 cm from the sidewall of the cylinder, and a thickness of 0.5 cm ,and this disc was positioned on the gel. Gel strength was measure as the time (in second) needed to move the disc downside (5 cm) through the gel. Gel strength was illustrated as the minimum weight that pressed down the device (5cm) through the gel. Result have been discussed in table no. 5.

Determination of Drug Content

The drug content in emulgel was found in the variable range, the lower drug content it may be due to the high concentration of liquid paraffin and emulsifying agent. The determined drug content values of all the formulations (F1-F4) ranged from 89.53 % to 98.64 % as shown in table no 6.

In-vitro Drug Release Studies

The release of metronidazole from the prepared emulgels was performed to study the effect of concentrations of polymers and the oil phase on the release of drug aiming to select the best formula. The in vitro release was carried out for all formulation using phosphate buffer pH 6.4 as medium. From the all from F4 showed high amount of drug release i.e, 93.20 % in 6 hrs. The in vitro release profile of Metronidazole from its various emulgel formulations is depicted in table 7. Graphical representation of % drug release data of formulation were shown in Fig no 6.

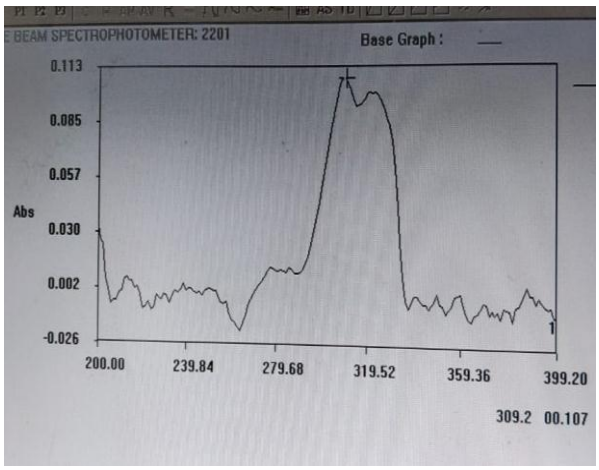

Fig. 1: Ultraviolet scan of Metronidazole in phosphate buffer pH 6.4.

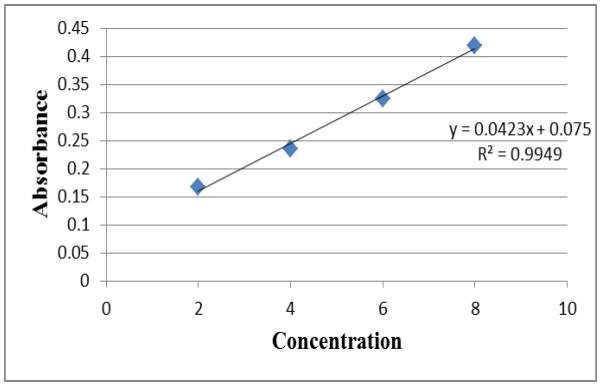

Fig. 2: Calibration curve of Metronidazole in phosphate buffer solution pH 6.4.

The infrared spectra of Metronidazole, Sodium Alginate and physical mixture of drug and polymer were recorded and shown in figure 3, 4 & 5 respectively.

FTIR spectroscopy

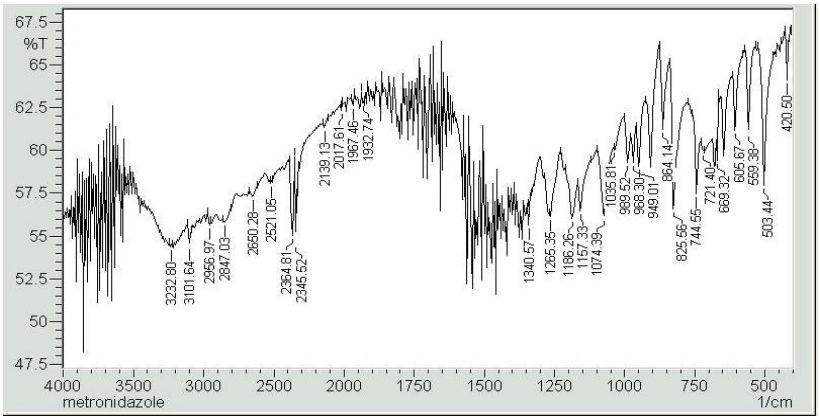

Fig. 3: Fourier transforms infrared spectrum of metronidazole.

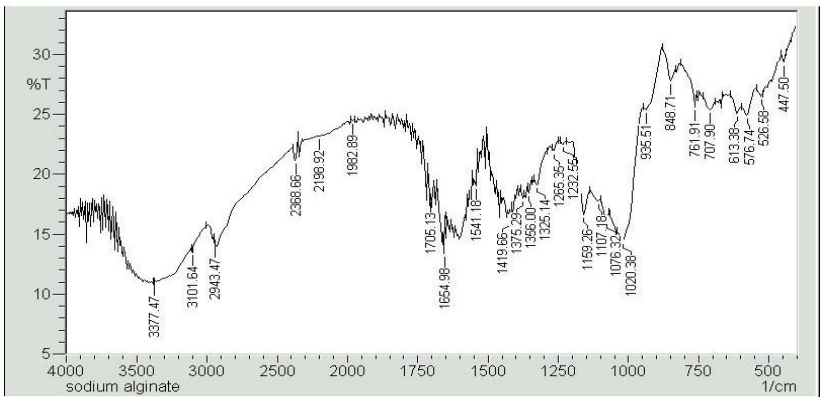

Fig. 4: Fourier transforms infrared spectrum of Sodium Alginate.

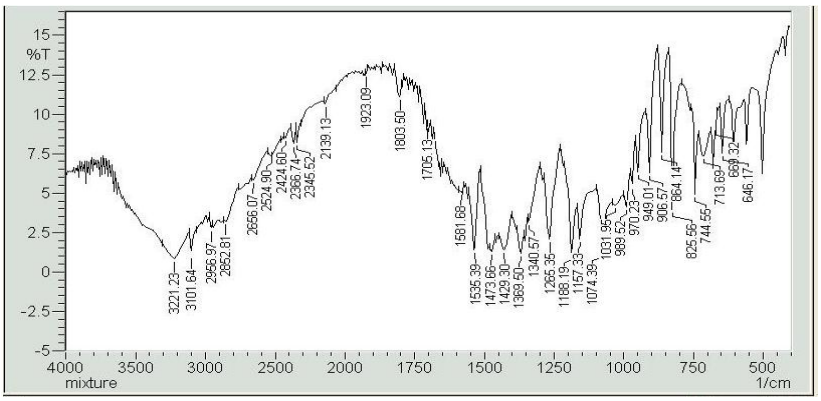

Fig. 5: Fourier transforms infrared spectrum of a physical mixture of Metronidazole and Sodium Alginate.

FTIR spectra showed that there were no interactions identified between drug and polymer. From the FTIR spectral analysis, all the principal peaks observed in pure drug were present in the FTIR spectra of the physical mixtures of best formulation since the absorption peaks of the drug still could be detected in the mixture as in Fig. 6.

Table 2: Physical characteristics of prepared Metronidazole emulgel.

Formula	Color	Homogeneity	Phase separation	pH
F1	Brownish Gummy	Excellent	None	5.25
F2	Brownish Gummy	Excellent	None	5.84
F3	Brownish Gummy	Excellent	None	6.0
F4	Brownish Gummy	Excellent	None	5.46

Table 3: Rheogram of Metronidazole emulgel formulations

Sr. No	Formulation	Viscosity (Centipoise)
1.	F1	1325.45
2.	F2	1612.44
3.	F3	1739.23
4.	F4	2288.56

Table 4: Spreadability of Metronidazole emulgel formulation

Sr. No	Formulation	Spreadability (gm.cm/sec)
1.	F1	5.2
2.	F2	5.9
3.	F3	4.7
4.	F4	6.7

Table 5: Data for gel strength of formulation.

Sr. No	Formulation	Gel Strength (Second)
1.	F1	110
2.	F2	150
3.	F3	385
4.	F4	465

Table 6: Drug Content of Metronidazole Formulation

Sr. No	Formulation	Drug Content
1	F1	93.12
2	F2	97.35
3	F3	89.53
4	F4	98.64

Table 7: In vitro drug release data of formulation.

Sr. No	Time (hrs)	F1	F2	F3	F4
1.	1	26.23	27.45	28.32	42.25
2.	2	31.65	39.14	50.24	56.83
3.	3	43.69	45.52	59.78	61.59
4.	4	55.12	56.45	75.57	71.00
5.	5	64.01	65.25	78.96	81.80
6.	6	74.28	82.02	88.36	93.20

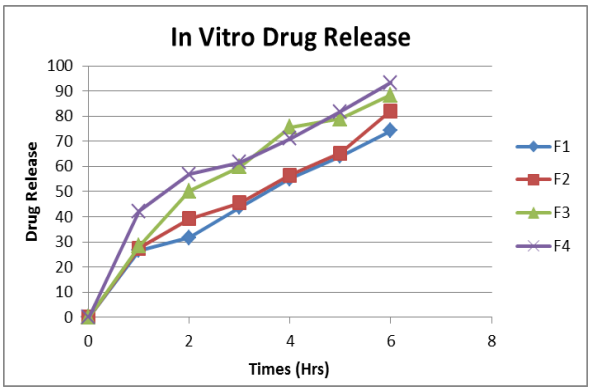

Fig. 6 In vitro drug release data of formulation.

CONCLUSION

It can be concluded from the above results that Metronidazole emulgel formulations prepared with sodium alginate (F4) showed acceptable physical properties, drug content, and drug release which deliver about 93.20% of drug within 6 h; thus, it can be suggested as a promising formula to prepare Metronidazole emulgel for the treatment of topical infections. However, further preclinical and clinical studies are required.

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