An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND CHARACTERIZATION OF MICRO SPONGE LOADED TOPICAL GEL PREPARATION OF METRONIDAZOLE

Sarad Pawar Naik Bukke*[1], Yenumula Nettekallu[1], Purushothama Reddy. K[2]

[1]Department of Pharmaceutics, Pratishta Institute of Pharmaceutical Sciences, Suryapet, Telangana, India

[1]Department of Pharmaceutics, Pratishta Institute of Pharmaceutical Sciences, Suryapet, Telangana, India

[2]Department of Pharmacy Practice, Rao's College of Pharmacy, Nellore, A P, India

***Corresponding author E-Mail:** saradpawarnaik@gmail.com

ARTICLE INFO

Key Words

Metronidazole topical gel, Micro sponge formulation, Over-the-counter (OTC) Permeation enhancer

ABSTRACT

Micro-sponge containing Metronidazole as active constituent with four different formulations by changing the proportions of drug (Metronidazole), polymer (ethyl cellulose), emulsifier (Poly vinyl alcohol) were obtained successfully using emulsion solvent diffusion method. Metronidazole topical gel is used in the treatment of fungating tumours, rosacea. The drug was chosen because unavailable micro sponge dosage forms in the market in order to decrease the skin irritation by preventing excess accumulation of drug on epidermis. The size of the micro sponges can be varied, usually from 5-300 μm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. The micro sponge system can also avoid unnecessary accumulation of ingredients within the epidermis and the dermis. Potentially, they can reduce considerably the irritation of effective drugs without reducing their efficacy. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. The drug and excipients were characterized using Fourier Transform Infrared (FTIR) techniques. This microsponge formulation was prepared as gel in carbopol and studied for drug content, in-vitro release studies. At 8^{th} hr the drug release of all formulations in ascending order is $F_0>F_3>F_2>F_1$. Highest release is from F_0 as it is free drug loaded. Among microsponge loaded formulations F_3 is having highest drug release at 8^{th} hour, i.e. 55.64%. This may be due to lower viscosity and higher content of permeation enhancer.

INTRODUCTION:

From past few decades there is a mythological modification in designing various drug delivery systems to attain control release of drug topically by incorporating into a carrier system. One such modification is use of microsponge drug delivery, as these are porous microspheres; biologically inert particles that are made of synthetic polymers protect the trapped drug compound from physical and environmental degradation. Microsponge particles are extremely small, inert, durable spheres that do not pass

through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. The size of the microsponges can be varied, usually from 5-300 μm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. The microsponge system can also avoid unnecessary accumulation of ingredients within the epidermis and the dermis. Potentially, they can reduce considerably the irritation of effective drugs without reducing their efficacy. MDS technology is now being presently used in cosmetics, over-the-counter (OTC) skin care, sunscreens and prescription products. These products are normally presented to the consumer in conventional forms like creams, gels, lotions, ointments, powders and share a broad package of benefits[1-4]. Metronidazole topical gel is used in the treatment of fungating tumours, rosacea. The drug was chosen because unavailable microsponge dosage forms in the market in order to decrease the skin irritation by preventing excess accumulation of drug on epidermis.

MATERIALS AND METHODS: Metronidazole was supplied as gift sample by A to Z pharmaceuticals, Chennai. Carbopol- 940 was supplied by Shree Chemical Ltd. Ahmedabad. Ethyl cellulose(EC), poly vinyl alcohol (PVA) are purchased from HiMedia labs, Mumbai, Dichloro methane and Tri-ethanol amine are purchased from bross chemicals, Tirupathi.

Compatibility studies: Pure drug (Metronidazole) and polymer (ethyl cellulose) and their physical mixture were examined by Fourier Transform Infrared (FT-IR) spectra. The spectra were recorded in a Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 cm-1 at the spectral resolution of 20 cm-1.

Preparation of Metronidazole microsponges[5-7]: Four batches of micro sponges coded by M1, M2, M3, M4 employing dissimilar proportions of ethyl cellulose (EC) and poly vinyl alcohol (PVA) were prepared by emulsion solvent diffusion method. briefly, the dispersed phase consist of Metronidazole(100mg) and required quantity of ethyl cellulose(table No. 1) dissolved in 20ml of dichloromethane was slowly added to a certain amount of poly vinyl alcohol(table No.1) in 150 ml of aqueous continuous phase. The reaction mixture was stirred at 2000 rpm for two hours on a mechanical stirrer. The microsponges were collected by filtration and dried at room temperature for 24 hours. The dried microsponges were stored in vacuum desiccators to ensure the removal of residual content.

Characterization of micro sponges: Determination of loading efficiency[8]: A sample of dried microsponges equivalent to 10 mg was taken in to mortar and pestle and add little amount of phosphate buffer of pH 5.5 and allowed to stand for 24 hours. Then transfer content in to 100 ml volumetric flask and make up volume to 100 ml with phosphate buffer of pH 5.5. The solution was filtered through whatmann's filter paper. From the resulting solution take 1 ml in to 100 ml volumetric flask and then make up volume to 100 ml with phosphate buffer of pH 5.5. Drug content was determined by UV spectrophotometer at 253 nm. The entrapment was calculated by using following formula.

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

Loading efficiency = (Actual drug in microsponges / Theoretical drug concentration) 100

Size analysis of microsponges[9]: The mean diameter of 100 dried microsponges was determined by optical microscopy (Metzer, India). The optical microscope was fitted with a stage micrometer by which the size of microsponges could be determined.

Preparation of micro sponge loaded carbapol gels: Gel forming polymer was soaked in water for 2 hours and then dispersed by agitation at approximately 600 rpm with the aid of magnetic stirrer to get a smooth dispersion. The dispersion was allowed to stand for 15 min to expel entrained air. To this aqueous solution of triethanolamine (2 % v/v) was added with slow agitation .At this stage microsponges and permeation enhancers were incorporated into the prepared base as ethanolic solution.

Drug content studies:

1.0 g of each gel formulations were taken in 100 ml volumetric flask containing 20 ml of phosphate buffer (pH 5.5) and stirred for 30 minutes and allowed to stand for 24 hours in case of microsponge loaded gel formulations. The volume was made up to 100mL and 1mL of the above solution was further diluted to 50 mL with phosphate buffer (pH 5.5). The resultant solution was filtered through membrane filter (0.45 μm). The absorbance of the solution was measured spectrophotometrically at 319 nm using placebo gel as reference.

***In vitro* diffusion studies:**

Modified frenz diffusion cells were used in the in-vitro diffusion studies. The egg membrane was mounted between the compartments of the diffusion cell. In this study, 200 ml of phosphate buffer (pH 5.5) solution was used as receptor medium. The receptor medium was maintained at 37±0.5°C and stirred magnetically at 500 rpm. 1 ml of sample were withdrawn from the receptor compartment at predetermined time interval for 8 hours period, and replaced by same volume of fresh pre-warmed phosphate buffer (pH 5.5) solution to maintain constant volume. The amounts of Metronidazole in the samples were assayed spectrophotometrically at 319 nm against appropriate blank.

RESULTS AND DISCUSSION:

Compatibility studies:

FTIR spectrum of Metronidazole micro sponges along with ethyl cellulose and physical mixture were obtained. The characteristic peaks of Metronidazole shows 1069.04 (C-O stretch), 2882.55 (C-H stretch), 1361.92 (N=O stretch). Whereas the FTIR spectrum of Metronidazole microsponge formulation shows characteristic peaks at 1052.72 (C-0 stretch), 2972.70 (C-H stretch), 1371.94 (N=O stretch).This indicates that characteristic peaks were present even in formulated Metronidazole microsponges, indicates that the drug was found to be compatible with the polymers used.

Characterization of micro sponges;

Loading efficiency: The loading efficiency of Metronidazole microsponge formulations are given in Table 4. The loading efficiency calculated for all microsponges ranged from 89.27 to 94.15 %. Loading efficiency is varied by changing the proportions of drug, polymer, and emulsifier. Higher loading efficiency is achieved with the formulation consists of drug, PVA, EC the ratio of 1:3:3 coded by M2 which is selected for the gel preparation.

Particle size: Particle size of micro sponges is varied along with the change in the ratio of polymer (ethyl cellulose) and emulsifier (PVA). By keeping polymer concentration constant, particle size is increased by decreasing the emulsifier (M1), (M4). Optimum size is obtained by taking polymer and emulsifier at equal proportions (M2).

Table 1: Formulae for microsponges of Metronidazole

SL. NO.	Formulation Code	Metronidazole (mg)	Polyvinyl alcohol (mg)	Ethyl - cellulose (mg)	Dichloro methane (ml)	Distilled water (ml)
1.	M_1	100	300	200	20	150
2.	M_2	100	300	300	20	150
3.	M_3	100	200	300	20	150
4.	M_4	100	200	200	20	150

Table 2: Formulae for microsponge loaded gels of Metronidazole

S.no	Ingredients	F_0	F_1	F_2	F_3
1.	Metronidazole (mg)	100	-	-	-
2.	Micro sponges (mg)	-	Equivalent to100 mg of drug	Equivalent to 100 mg of drug	Equivalent to 100 mg of drug
3.	Triethanolamine (ml)	2.0	2.0	2.0	2.0
4.	Ethanol (ml)	20	20	20	20
5.	Propylene glycol (ml)	-	-	10	-
6.	DMSO (ML)	-	-	-	10
7.	Carbapol (mg)	200	200	200	200
8.	Distilled water (ml)	Qs to make up 100 ml	Qs to make up 100 ml	Qs to make up 100 ml	Qs to make up 100 ml

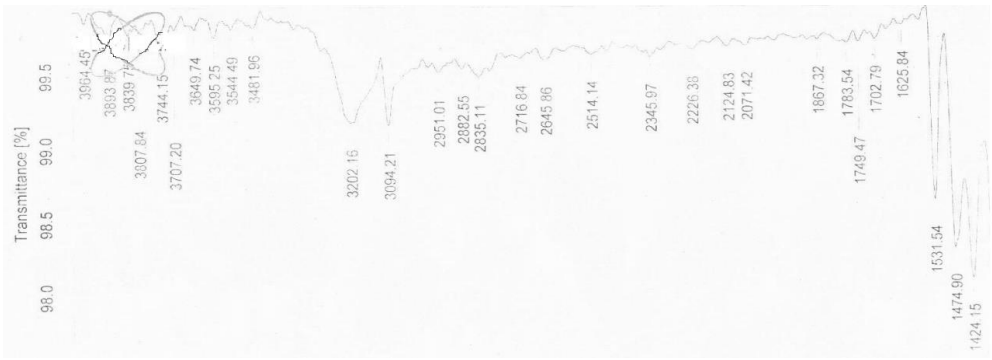


Fig 1: FTIR spectrum of Metronidazole

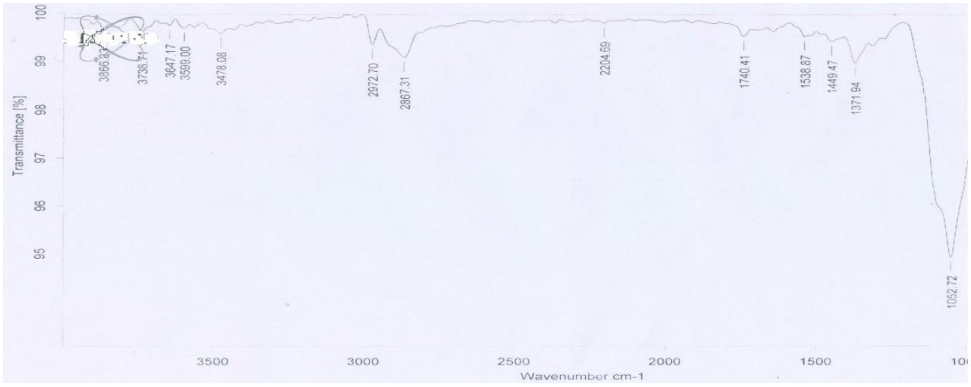
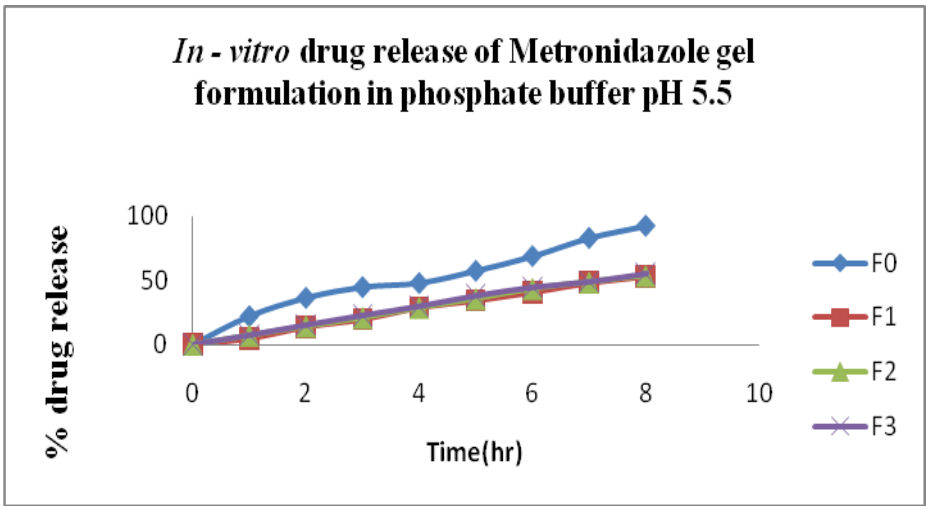


Fig 2: FTIR spectrum of Metronidazole microsponges

Table 3: Characterization of microsponges

SL. NO.	Formulation code	Loading efficiency (%)	Mean particle size (µm)
1.	M_1	90.56	42.1
2.	M_2	94.15	37.4
3.	M_3	89.27	31.6
4.	M_4	92.59	45.2



Graph 1 - *In vitro* drug release of Metronidazole gel formulations in phosphate buffer pH 5.5

Lesser size is obtained by taking lesser proportion of emulsifier than polymer (M3).

***In vitro* diffusion studies:** At 8th hour the drug release of all formulations in ascending order is F0>F3>F2>F1. Highest release is from F0 as it is free drug loaded i.e., 92.32%. Among microsponge loaded formulations F3 is having highest drug release at 8th hour, i.e. 55.64%. This may be due to lower viscosity and higher content of permeation enhancer. Remaining formulations F1, F2 showed drug release at 8 hours 52.85% and 53.69% respectively. Drug release profile has been depicted in graph 1.

CONCLUSION:

Quasi – emulsion solvent diffusion method seems to be anticipating for the preparation of Metronidazole microsponges as it is a rapid, easy, consistent method and has an advantage of nullifying solvent toxicity. It was observed that as drug: polymer ratio increased, particle size decreased. This is likely due to the fact that at higher relative drug content, the amount of polymer available per microsponge to encapsulate the drug becomes less, thus reducing the thickness of the polymer wall and hence, smaller microsponges. Microsponge formulation M2 showed a good physical parameter study and was used for formulating into gel, incorporated in the carbopol. At 8th hour the drug release of all formulations in ascending order is F_0>F_3>F_2>F_1.

REFERENCES:

1. Shyam Sunder Mandava and Vedavathi Thavva et al., Novel approach: Microsponge drug delivery system, International journal of Pharmaceutical

Sciences and Research, 2012; Vol. 3 (4): 967 - 980.

2. Neelam Jain, Pramod Kumar Sharma, Arunabha Banik et al., Recent advances on microsponge delivery system, International Journal of Pharmaceutical Sciences Review and Research, May – June 2011; Volume 8 (2): 99 – 104

3. Saroj Kumar Pradhan et al ., Micro sponges as the versatile tool for drug delivery system, International journal of research in pharmacy and chemistry, 2011; Volume 1(2): 44 – 51

4. Parikh B.N, Gothi G.D, Patel T.D, Chavda H.V, and Patel C.N. et al., Micro sponge as novel topical drug delivery system, Journal of global pharmacy technology, 2010; Volume 2 (1): 17 – 29.

5. Saboji, J. K.,1 Manvi, F. V., Gadad, A. P. and Patel, B. D.et al., Formulation and evaluation of ketoconazole microsponge gel by quassi emulsion solvent diffusion, Journal of cell and tissue research, 2011; Volume 11(1): 2691 – 2696.

6. D'souza, J.I., Jagdish, K., Saboji, S.G. and Killedar, H.N. et al., "Design and Evaluation Of Benzoyl Peroxide Microsponges To Enhance Therapeutic Efficacy In Acne Treatment", Accepted For Presentation In 20th Fapa Congress, Bangkok , Thailand , Nov'30 – Dec, Volume 3, 2004.

7. Comoglu, T., Gonul, N. and Baykara, T.et al., II Farmaco, Volume 58: 2003, 101-106.

8. Kilicarslan, M., Baykara, T. et al., The effect of the drug/polymer ratio on the properties of Verapamil HCl loaded microspheres, International Journal of Pharmaceutical sciences, Volume 25 (2), 2003: 99–109.

9. Martin A., Swarbrick J., Cammarrata A. et al., Formulation and evaluation of ketoconazole microsponge gel, In Physical Pharmacy- Physical Chemical Principles in Pharmaceutical Sciences, 3rd edition, 1991; page: 527.