ejpmr, 2018,5(9), 474-477

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

INVITRO WASH- OFF COMPARISSION STUDIES OF METRONIDAZOLE MUCOADHESIVE MICROSPHERES USING DIFFERENT POLYMERS

Sujatha Banavath[1]*, Samreen Unnisa, Pidugu Nandhini Mudhiraj[1], Marla Mahesh[1], Ragya Eslavath[2], R. Suthakaran[1] and Goli Venkateshwarlu[1]

[1]Vijaya College of Pharmacy, Munaganoor, Hayathnagar, Hyderabad, Telangana-501511.
[2]Poona College of Pharmacy, Bharathi Vidyapeeth Deemed University, Pune Maharastra-411038.

***Corresponding Author: Sujatha Banavath**
Vijaya College of Pharmacy, Munaganoor, Hayathnagar, Hyderabad, Telangana-501511.
Email ID: eslavathragya89@gmail.com, venkipharma75@gmail.com

Article Received on 20/07/2018 **Article Revised on 11/08/2018** **Article Accepted on 31/08/2018**

ABSRACT

The present work is to prolong the gastric residence time of Metronidazole by formulating in to muco adhesive control release microspheres. The muco adhesive microspheres were prepared by ionotropic gelation method of polyelectrolyte complexation technique using sodium alginate as control release polymer and cabopo -l934 as muco adhesive polymers in different proportions and calcium chloride as agent of multivalent cations. The prepared microspheres were characterized by micromeritic properties, mean particle size, in vitro wash-off test, in vitro drug release and compatibility studies. The data obtained in this study suggests that a micro particulate muco adhesive dosage form of Metronidazole can be successfully formulated to give prolonged residenc time.

KEYWORDS: Metronidazole, gastric residence time, sodium alginate, Cabopo-l934, inotropic gelation method.

INTRODUCTION

Metronidazole is used for the treatment of amoebiasis, and other parasitic diseases. is an antibiotic and antiprotozoal medication.[1] It is used either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis.[3] It is effective for dracunculiasis, giardiasis, trichomoniasis, and amebiasis.[3] It is an option for a first episode of mild-to-moderate Clostridium difficilecolitis if vancomycin or fidaxomicin is unavailable.[1,2,3,4,5,6] Metronidazole is available by mouth, as a cream, and intravenously.[7] Common side effects include nausea, a metallic taste, loss of appetite, and headaches.[8] Occasionally seizures or allergies to the medication may occur.[9] Some state that metronidazole should not be used in early pregnancy while others state doses for trichomoniasis are safe.[10] It should not be used when breastfeeding.[5]

MATERIALS AND METHODS

Materials

Metronidazole obtained from the Natco pharma ltd kothur telangana India *Sodium alginate*, cabopol-934, calcium chloride were purchased from SD fine chemical private Ltd, Mumbi, Maharastra.

Method

Ionotropic gelation method

Metronidazole mucoa dhesive microspheres were prepared by ionotropic gelation method using polyelectrolyte complexation technique. In this method the required amount of metronidazole, sodium alginate, carbopol 934 and calcium chloride were weighed and passed through sieve no ≠ 60. Sodium alginate and Carbopol were dissolved in water to form a homogenous polymer solution by continuous stirring to which metronidazole was added. The resultant drug dispersion was loaded into dry disposable syringe with needle size no 20 and added drop wise into 2% w/v solution of calcium chloride under constant stirring. The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce the spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at room temperature for 24 hours. Total 6 formulations were prepared by using different drug and polymer ratios.

SL.NO	FORMULATION CODE	DRUG: POLYMERS	RATIO
1.	F1	Metronidazole: Sodium alginate	1 : 2
2.	F2	Metronidazole:Sodiumalginate: Cabopol 934	1 : 1.8 : 0.2
3.	F3	Metronidazole : Sodium alginate	1 : 4
4.	F4	Metronidazole:Sodiumalginate: cabopol 934	1 : 3 : 1
5.	F5	Metronidazole:Sodiumalginate: cabopol 934	1 : 2 : 2
6.	F6	Metronidazole:Sodiumalginate: cabopol 934	1 : 1 : 3

Evaluation of Mucoadhesive Microspheres

Micromeritic properties: The mucoadhsive microspheres were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index Hausner's ratio and angle of repose.

A) Tapped density: The prepared mucoadhesive Were transferred to a measuring cylinder and tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of microspheres to volume of microspheres after tapping gives tapped density.
Tapped density= Mass of microspheres in grams / Volume of microspheres after tapping.

B) Bulk density: The prepared mucoadhesive Were transform to a measuring cylinder and the volume occupied by the microspheres was noted. This volume is bulk volume and it includes true volume of the power and the void space among the microspheres.
Bulk density = Weight of microspheres in grams/ Bulk volume of microspheres in cm^3

C) Carr's compressibility index: The compressibility index is a measure of flow of a powder to be compressed. It was determined from the bulk and tapped densities.
Carr's compressibility index = Tapped density- Bulk density x100/Tapped density

D) Hausner's ratio: Tapped density and bulk density were measured and the Hausner's ratio was calculated using the following formula:
Hausner's Ratio = Tapped density/Bulk density

The values less than 1.25 indicate good flow where as greater than 1.25 indicates poor flow.

Angle of repose: Angle of repose is defined as the maximum angle possible between the surface of the pile and the horizontal plane.
Formula
$\theta = Tan^{-1}h/r$

BATCH CODE	ANGLE OF REPOSE (θ)	BULK DENSITY (g/cm2)	TAPPED DENSITY (g/cm2)	HAUSNERS RATIO	Cars s index
F1	16	0.71	0.81	1.14	12.34
F2	12	0.79	0.85	1.07	7.05
F3	14	0.68	0.81	1.19	16.04
F4	11	0.80	0.87	1.09	8.04
F5	13	0.70	0.76	1.08	7.89
F6	15	0.61	0.68	1.09	10.29

Particle size: The particle size was measured by microscopic technique with the help of ocular and stage micrometre. A drop of suspension was mounted on a slide and observed under optical microscope about 100 particles were measured and their average size was determined.

Entrapment Efficiency: The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency of all formulations were shown in table no 9 and is calculated using following equation,
% Entrapment = Actual content/Theoretical content x 100.

BATCH CODE	PARTICLE SIZE µm	ENTRAPMENT EFFICIENCY
F1	170	70%
F2	140	78%
F3	190	75%
F4	285	82%
F5	200	91%
F6	225	87%

In vitro wash off test

The mucoadhesive properties of the microspheres were evaluated by the in vitro wash off test. A2 X 3 cm piece of goat intestine mucosa was tied on to a glass slide using thread. Microspheres were spread (~50) onto the wet, rinsed, tissue specimen and the prepared slide was hung onto to the one of the grooves of the USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was

given regular up and down movements in the beaker containing the simulated gastric fluid USP pH 1.2 and pH 6.8 buffer. At the end of 30 minutes, 1hr and at hourly intervals up to 8 hrs the number of microspheres still adhering onto the tissue was counted. The results of in vitro wash off test of batches B1 to B7 were shown in table no 10 and 11.

Entrapment Efficiency: The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency of all formulations were shown in table no 9 and is calculated using following equation,

% Entrapment = Actual content/Theoretical content x 100.

In Vitro drug release

To carry out In Vitro drug release, accurately weighed 50 mg of loadedmicrospheres were dispersed in dissolution fluid in a beaker and maintained at 37±2°C under continuous stirring at 100 rpm. At selected time intervals 5 ml samples were withdrawn through a hypodermic syringe fitted with a 0.4 µm Millipore filter and replaced with the same volume of pre- warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug.

percent mucoadhesive property of all formulations in pH 1.2 buffer

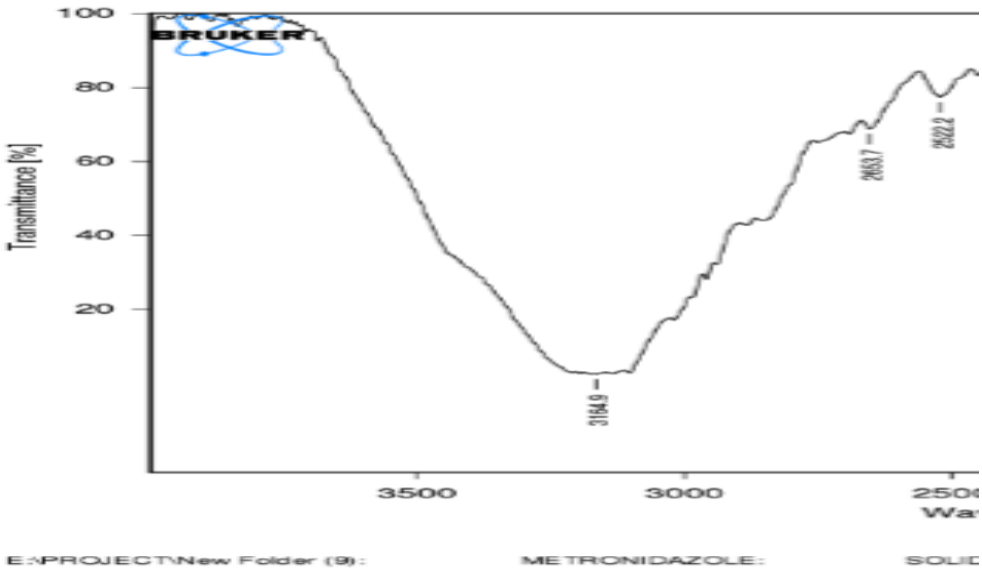
Time (hr)	F1	F2	F3	F4	F5	F6
0.5	35%	70%	45%	78%	82%	75%
1	20%	65%	27%	78%	78%	69%
2	02%	53%	05%	71%	78%	67%
3	---	40%	---	71%	72%	65%
4	---	30%	---	68%	72%	65%
5	---	25%	---	68%	72%	60%
6	---	17%	---	68%	70%	58%
7	---	05%	---	65%	70%	50%
8	---	---	---	60%	68%	40%

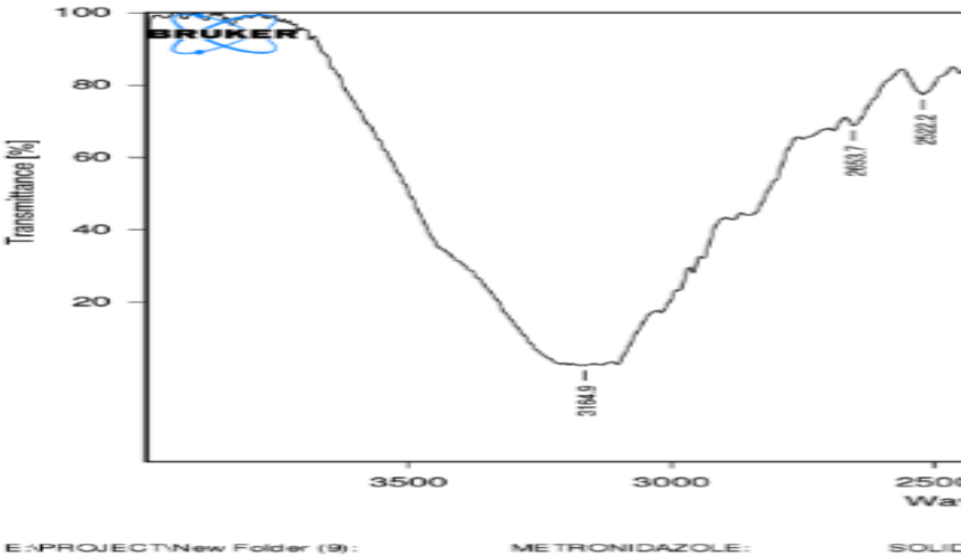
Percent mucoadhesive property of all formulations in pH 6.8 buffer.

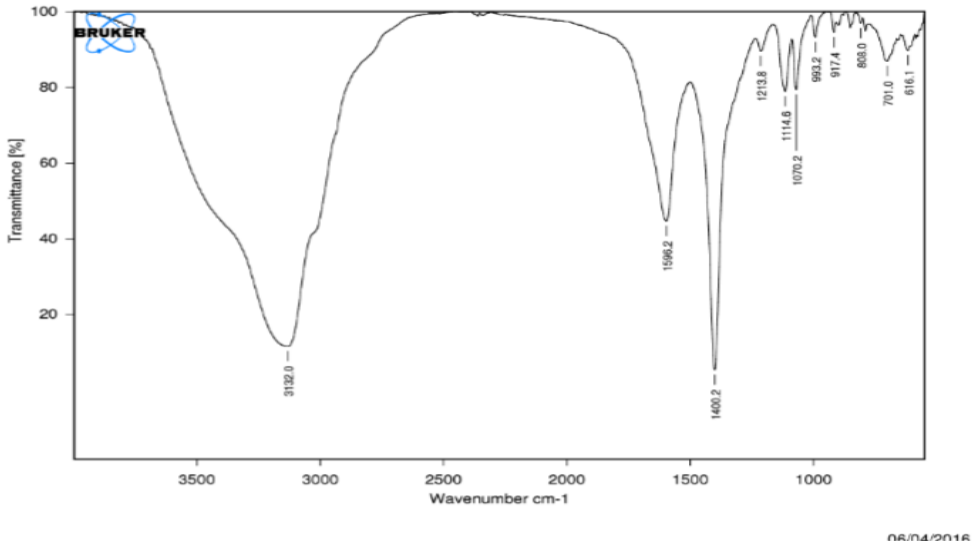
Time (hr)	F1	F2	F3	F4	F5	F6
0.5	30%	65%	45%	78%	88%	71%
1	15%	58%	37%	72%	81%	69%
2	---	55%	08%	70%	81%	62%
3	---	45%	---	68%	81%	62%
4	---	41%	---	68%	78%	62%
5	---	38%	---	68%	78%	55%
6	---	31%	---	60%	72%	55%
7	---	24%	---	58%	68%	51%
8	---	08%	---	55%	65%	40%

Drug polymer interaction (FTIR) study

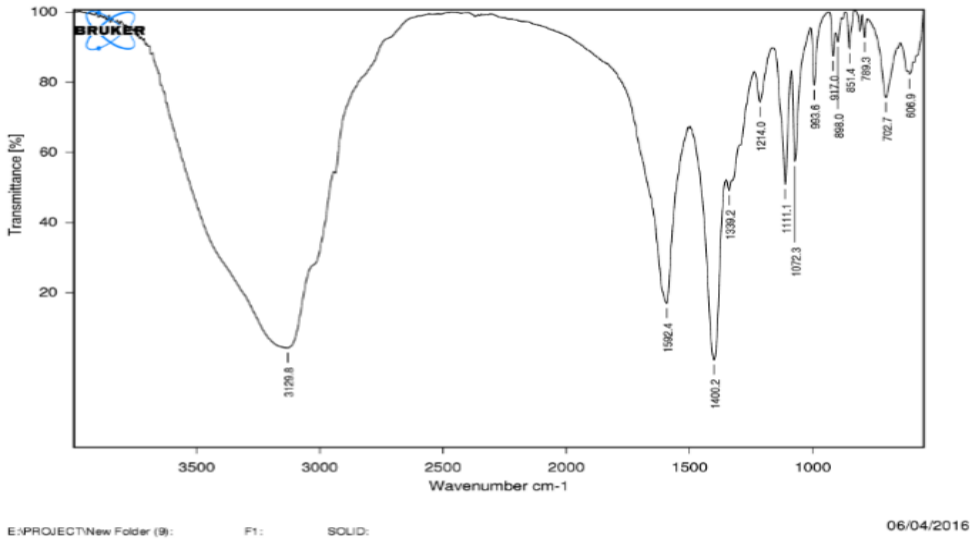
IR spectroscopy can be performed by Fourier transformed infrared spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm^{-1}. FTIR study was carried on pure drug, physical mixture, formulations and empty microspheres.







FTIR of metronidazole,



FTIR of metronidazole, sodium alginate and carbopol.

RESULTS AND DISCUSSION

The muco adhesive microspheres were prepared by ionotropic gelation method of polyelectrolyte complexation technique using sodium alginate as control release polymer and cabopo -l934 as muco adhesive polymers in different proportions and calcium chloride as agent of multivalent cations. The prepared microspheres were characterized by micromeritic properties, mean particle size, in vitro wash-off test, in vitro drug release and compatibility studies. The data obtained in this study suggests that a micro particulate muco adhesive dosage form of Metronidazole can be successfully formulated to give prolonged residenc time. From all the six formulation predict some values which are ratios were successfully formulated by ionotropicgelation method. All the formulations have shown good flow properties and good particle size. The in vitro washoff comparison test, in vitro drug release Were carried out in 1.2pH and 6.8 pH buffers and F5 formulation has shown good muco adhesion Property and in vitro release amongst all the 6 formulations. Formulation F5 has shown good drug and excipien tcompatibility.

CONCLUSION

The muco adhesive microspheres of Metronidazole using carbopo l934 and sodium alginatein different Ratios were successfully formulated by ionotropicgelation method. All the formulations have shown good flow properties and good particle size. The in vitro washoff comparison test, in vitro drug release Were carried out in1. 2 pH and 6.8pH buffers and F5 formulation has shown good mucoadhesion Property and in vitro release amongst All the 6 for mulations Formulation F5 has shown good drugs all the 6 formulations. Formulation and excipient compatibility.

REFERENCES

1. "Flagyl, Flagyl ER dosing, indications, interactions, adverse effects, and more". Medscape Reference.
2. Archived from the original on 7 April 2014. Retrieved 3 April 2014.
3. Brayfield, A, ed. (14 January 2014). "Metronidazole". Martindale: The Complete Drug Reference. Pharmaceutical Press. Retrieved 3 April 2014.
4. "Metronidazole". The American Society of Health-System Pharmacists. Archived from the original on September 6, 2015. Retrieved July 31, 2015.
5. Mc Donald, LC; Gerding, DN; Johnson, S; Bakken, JS; Carroll, KC; Coffin, SE; Dubberke, ER; Garey, KW; Gould, CV; Kelly, C; Loo, V; Shaklee Sammons, J; Sandora, TJ; Wilcox, MH (15 February 2018).
6. "Metronidazole Use During Pregnancy | Drugs.com". www.drugs.com. Archived from the original on 1 January 2017. Retrieved 1 January 2017.
7. Ahmad F.J., Sahni J. and Khar R.K., Designandin-vitro characterization of bucco adhesive drug delivery system of Insulin, 2008; 70(1): 61-65.
8. Ameela S.R., Misra A. and J ayakrishnan A., Cross-linked chitosan microspheres as carriers for prolonged delivery of macromolecular drugs, J. Biomater. Sci. Polym, 1994; 6: 621-632.
9. Aminabhavi T.M., Agnihotri S.A. and Mallikarjuna N.N., Recent advances on chitosan-based micro-and nanoparticles in drug delivery, J. Controlled Rel, 2004; 100: 5-28.
10. Anders R. and Merkle H.P., Evaluation of laminated mucoadhesive patches for buccal drug delivery, Int. J. Pharm, 1989; 49: 231-240.
11. Andrade F., Goycoolea F., Chiappetta D.A., Sosnik A. and Sarmento B., Chitosan-Grafted copolymersand Chitosan-Ligand conjugates as matrices for pulmonary drug delivery, Int. J. Carbohy. Chem, 2011; 86: 1-14.