INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SOLUBILITY ENHANCED DOSAGE FORMS OF TINIDAZOLE FOR LOCAL TREATMENT OF BACTERIAL VAGINOSIS

S. Bhilegaonkar*, A. Nadkerny and S. Dessai

PES's Rajaram and Tarabai Bandekar College of Pharmacy,
Ponda, Goa-403 401, Panaji, India.

ABSTRACT

Drugs given by the intra-vaginal route have a higher bioavailability compared to the oral route. This is because the drug enters immediately into the systemic circulation without passing the metabolizing liver. The vaginal wall is very well suited for the absorption of drugs for systemic use, since it contains a vast network of blood vessels.

Tinidazole, a BCS class II drug, is an anti-protozoal drug commonly used to treat infections like bacterial vaginosis, which is a vaginal condition that can produce vaginal discharge and results from an overgrowth of normal bacteria in the vagina. The marketed formulations reported are mostly for oral use, which is quite high in concentration and hence may produce some of the commonly occurring side effects. The marketed intra-vaginal formulations of tinidazole reported are in combination with other drugs. Therefore to reduce the dose, side effects, improve the bioavailability and to achieve increased local absorption the study focuses on vaginal delivery of tinidazole.

Tablet dosage forms were developed to achieve slow release upto 12 hours of drug dose. Different polymers were tried based on solubility such as eudragit RS 100 , corbopol 940 and guar gum. Prepared tablet formulations were evaluated for physicochemical characteristics, drug content and drug release. It was seen that tablets with carbopol and guar gum were able to sustain the release up to 12 hours with more than 95% drug release at the end of it.

Keywords: Tinidazole, sustain release, eudragit, carbopol, guar gum, tablets, bacterial vaginosis.

INTRODUCTION

Bacterial vaginosis (BV) is a vaginal condition that can produce vaginal discharge and results from an overgrowth of normal bacteria in the vagina. The most typical symptoms of BV (watery, superfluous gray discharge and the typical fishy smell) can be confirmed by an increased vaginal pH (> 4.7) and a typical microscopy (granular flora) with so many bacteria on the epithelial cells (clue cells) and it is impossible to count them as they are numerous and overlay each other.[1]

Mucoadhesive polymers such as polycarbophil, cellulose ethers, chitosan and polyvinylpyrrolidine were used for the preparation of tablet formulations. The manufacturing process of vaginal bioadhesive controlled release matrix tablets consists of the preparation of a matrix mixture comprising the pharmaceutically acceptable excipients. The release mechanism is based on drug diffusion through the swollen polymers and progressive erosion /dissolution of the gel matrix. The controlled-release properties of the vaginal tablets may be modified by the presence in the dosage form of soluble and insoluble fillers and by their weight ratio. The insoluble excipients can be selected from the group of microcrystalline cellulose, calcium phosphate tribasic, dibasic calcium phosphate, calcium sulphate and dicalcium phosphate. Either anhydrous or hydrated dicalcium phosphate is preferred. The soluble excipients can be selected from the group of lactose, sorbitol, xylitol, mannitol, amylose, dextrose, fumaric acid, citric acid, tartaric acid, lactic acid, malic acid, ascorbic acid, succinic acid, polyethylene glycols of various molecular weight, soluble hydroxyalkylcelluloses, polyvinylpyrrolidones, gelatins, sodium carbonate and sodium bicarbonate. The marketed intravaginal formulations of Tinidazole reported are in combination with other drugs.[6]

MATERIALS AND METHODS

MATERIALS

Materials	Use	Manufacturer
Tinidazole	Antibacterial Drug	Zydus Cadila, Kundaim, Goa
Triethanolamine	pH adjuster	S.D. Lab Chemical Centre, Mumbai
Guar gum	Tablet binder	Genuine Chemical CO, Mumbai
Eudragit RS 100	Tablet binder	Evonik Industries, Mumbai
Dicalcium phosphate	Tablet binder	Ozone International, Mumbai
Magnesium stearate	Tablet lubricant	HiMedia Laboratories Pvt. Ltd., Nashik
Talc	Tablet glidant	S.D. Fine Chemicals Ltd., Mumbai
Citric acid	Buffer	S.D. Fine Chemicals Ltd., Mumbai
Sodium citrate	Buffer	Avra Synthesis Pvt Ltd, Hydrabad

METHOD

Preparation of plain drug tablets

Blend preparation and direct compression

The following various drug polymer blends were prepared and tablets were compressed using B/D toolings.

a) Eudragit RS 100 tablets

The formula of this tablet formulation is given in table 1.

b) Carbopol 940 tablets

The formula of this tablet formulation is given in table 2.

c) Guar gum tablets

The formula of this tablet formulation is given in table 3.

Evaluation of tablet blend

Prepared tablet blends with various polymers were evaluated for following parameters

a. Bulk density and Tapped density

The blends were introduced in a 100 ml measuring cylinder and initial volume was noted as the bulk density. After the initial volume was observed, the cylinder was allowed to tap its own weight from a height of 2.5 cm. This was done using a tapped density apparatus. The tapped density was measured after 100 taps until no further change in the volume was noted.

Bulk density and tapped density were determined by the following formulae,

$$\text{Bulk density (BD)} = \frac{\text{Weight of blend}}{\text{Initial Volume}}$$

$$\text{Tapped density (TD)} = \frac{\text{Weight of blend}}{\text{Tapped volume}}$$

b. Compressibility Index

The compressibility index of the blends was determined by Carr's Compressibility index.

$$\text{Carr's index (\%)} = \frac{\text{(TD-BD) x 100}}{\text{TD}}$$

Grading of powders was done according to table 4.

c. Hausner's Ratio

Hausner's ratio was determined by the following equation,

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Hausner's ratio less than 1.25 indicated good flowability while greater than 1.25 indicated poor flowability.

d. Angle of Repose

The angle of repose was determined by fixed funnel method. A funnel was fixed at a height of 2 cm above a flat horizontal surface. The powder was allowed to flow through the funnel and the height 'h' of the pile and radius 'r', of base was noted.

Angle of repose was determined by following equation,

$$\theta = \tan^{-1}(h/r)$$

where, θ is the angle of repose, 'h' is height of the pile, 'r' is radius of base. Relation between angle of repose and flow properties was determined according to table 5.

Evaluation of tablets

a) Weight Variation

20 tablets from each formulation were weighed and mean and standard deviation of the weight were determined. Percentage deviation was determined as according to table 6.

b) Tablet Thickness

Ten tablets were randomly selected from each batch and the thickness of each individual tablet was measured using a Digital Vernier Calliper.

c) Hardness

The hardness of the tablet was measured with the help of a Monsanto hardness tester. Three tablets from each batch of formulations were

tested. Then average hardness was calculated.

d) Friability

The friability test was done using Roche's Friabilator. Twenty tablets from each formulation were weighed (w) and tested at a speed of 25 rpm for 4 min. After removing of dust, tablets were re-weighed (w_1) and friability percentage was calculated using the following equation:

$$\text{Friability (\%)} = \frac{w_1 - w_2}{w_2} \times 100$$

The minimum weight loss of the tablet should not be more than 1 %.

e) Swelling Study

The swelling behavior of tablet is described as the water absorbing capacity. Tablets were weighed individually; initial weight was considered as W_1 and placed separately in Petri-dish containing 15 ml of citrate buffer (pH 4.4) solution. Tablets were completely immersed in the buffer solution. At regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr to till 24 hrs), the tablets were carefully removed from the Petri-dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed W_2.

The degree of swelling (water uptake) was calculated according to the following equation:

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

Where,

W_1 = Weight dry of tablet, W_2 = Weight of wet tablet

f) Drug Content

Weight of mixture corresponding to 0.1 g of tinidazole was taken. The mixture was suitably diluted with methanol to get a final concentration of 20 µg/ml which was subsequently analyzed using UV spectrometer at 310 nm.

g) In vitro dissolution studies

These were carried out using USP type 1 basket dissolution apparatus. Dissolution medium was 500 ml citrate buffer pH 4.4. The paddle speed was 50 rpm and temperature was maintained at 37 ± 0.5°C. 5 ml aliquots of dissolution fluid were withdrawn at specified interval for 12 hours from reservoir and each time replaced with equal volume of fresh dissolution medium. Withdrawn samples were diluted and analyzed using UV spectrophotometer at 318 nm.

h) Stability studies

The tablets were subjected to accelerated conditions of temperature and relative humidity i.e. 40°C ± 2°C / 75% ± 5% RH for a period of 3 months. At the interval of 1 month, 2 months and 3 months the suppositories were evaluated for physical appearance and drug content.

RESULT AND DISCUSSION

Preparation of plain drug tablets

Blend preparation and direct compression

The blends were prepared and evaluated for blend flow properties .Subsequently tablets were compressed using suitable tooling. The prepared tablets were evaluated for physicochemical characterisation , swelling index , drug content and drug release.

Evaluation of blend flow properties

The blends of different formulations were evaluated for bulk and tapped density, Carr's compressibility index, Hausners ratio and angle of repose as shown in table 7.

Hausner's ratio of all the blends was less than 1.25 indicated good flowability. Though all the blends exhibited Carr's index in the range of 5-15 i.e. these tablet blends had excellent flowability, but Guar gum tablet blend was noted to be the most flowable. In case of Eudragit RS-100 blends, the Carr's index was in the range of 18-21, i.e. the flowability was passable. The angle of repose of all the blends was less than 25, which indicated excellent flowability of these tablet blends.

Characterization of Tablets

a) Weight variation

All the tablet formulations, as shown in table 8, passed the weight variation test according to IP.

b) Thickness

The thickness of all tablet formulations was determined using vernier caliper and the obtained results are given in table 9.

c)Hardness

The hardness varied from 4-5 in case of Guar gum and Carbopol 940 tablets and was noted least in case of Eudragit RS 100 tablets.

d) Friability

The results of the friability testing are shown in table 10.

Friability ranges for Eudragit RS 100, Guar gum and Carbopol tablets were ranging from 1.2-1.3%, 0.5-0.67 % and 0.55-0.69 %

Except Eudragit RS 100 tablets, all other formulations complied with friability

specification i.e. minimum weight loss should not be more than 1 %.

e) Swelling index (%)

The swelling index was highest in case of Carbopol 940 tablet (CF 2) and least was reported in Guar gum tablet (GF 1), which can contribute to a slower release of drug Carbopol tablets as compared to Guar gum tablets as shown in table 11.

f) In vitro dissolution studies

In vitro diffusion studies of all tablets was carried out for period of twelve hours to see the total release. At the end of release studies it was found that the drug release from the Guar gum tablets of drug and polymer of 1:1 ratio (GF 1) exhibited the highest drug release i.e. 94.59 % at the end of 12 hours.

The order of drug release from the tablets is as follows as shown in figure 1.

GF 1 > GF 2 > CF 1 > EF 1 > CF 1 > EF 2

The reason for a higher drug release can be attributed to increased penetration of aqueous fluid through Guar gum matrix (wicking/capillary action) as compared to other two polymers and the rapid pore formation lead to increased tinidazole release from Guar gum tablets (94.59% release at the end of 12 hours).

g) Drug Content

The drug content of all the tablets were reported to meet the acceptable limits of label claim. The highest drug content was reported in GF 1 i.e. 97.73% as shown in table 12.

h) Stability studies

Tablets were examined at the end of 0 month, 1 month, 2 month and 3 months for percent drug content and physical changes, shown in table 6.33. There were no significant changes in physical appearance of all tablets. It was noted that Guar gum tablets exhibited highest stability in terms of drug content.

CONCLUSION

Tinidazole was found to be effective in many cases, and the marketed dosage forms reported are mostly for oral use hence the main focus of this research was to formulate tablet dosage forms of tinidazole for vaginal drug delivery. This objective was successfully achieved in present research which leads to formation of a stable slow release tinidazole tablet with guar gum with complete release of the drug at the end of 12hours.

The future scope of the study can be long term stability testing and scaling up of the formulations.

ACKNOWLEDGEMENTS

Researchers are thankful to Cadila Healthcare Ltd., Goa for providing gift sample of tinidazole.

Table 1: Formula of Eudragit RS 100 tablets

Ingredients	Quantity taken	
	EF 1	EF 2
Tinidazole B.P.	0.1 g	0.1 g
Eudragit RS 100	0.1 g	0.2 g
Dicalcium phosphate	0.1 g	0.1 g
Magnesium stearate	0.5 %	0.5 %
Talc	0.5%	0.5 %

Table 2: Formula of Carbopol 940 tablets

Ingredients	Quantity taken	
	EF 1	EF 2
Tinidazole B.P.	0.1 g	0.1 g
Eudragit RS 100	0.1 g	0.2 g
Dicalcium phosphate	0.1 g	0.1 g
Magnesium stearate	0.5 %	0.5 %
Talc	0.5%	0.6 %

Table 3 : Formula of Guar gum tablets

Ingredients	Quantity taken	
	GF 1	GF 2
Tinidazole B.P.	0.1 g	0.1 g
Guar gum	0.1 g	0.2 g
Dicalcium Phosphate	0.05 g	0.05 g
Magnesium stearate	0.5 %	0.5 %
Talc	0.5 %	0.5 %

Table 4: Grading of Powders for their flow properties

Carr's %	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
> 40	Very very poor

Table 5: Relation between angle of repose and flow properties

Angle of Repose (θ)	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Table 6: Percentage Deviation in Weight Variation

Average Weight of Tablet	% Deviation
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

Table 7: Blend flow properties

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose (°)
EF 1	0.40	0.45	1.125	11.11	23
EF 2	0.55	0.60	1.27	1.09	24
GF 1	0.45	0.48	1.06	6	22
GF 2	0.62	0.67	1.08	7.4	20
CF 1	0.50	0.44	1.13	12	25
CF 2	0.34	0.39	1.14	12.8	25

Table 8: Weight Variation of Plain drug tablets

Formulation code	Weight Variation
EF 1	298 ± 5%
EF 2	397 ± 5%
GF 1	248 ± 5%
GF 2	347 ± 5%
CF 1	247 ± 5%
CF 2	346 ± 5%

Table 9: Thickness of Plain drug tablets

Formulation Code	Average Thickness (mm)
EF 1	4.31
EF 2	4.66
GF 1	4.27
GF 2	4.33
CF 1	4.29
CF 2	4.36

Table 10: Friability of plain drug tablets

Formulation Code	Friability (%)
EF 1	1.2 %
EF 2	1.3 %
GF 1	0.5 %
GF 2	0.67 %
CF 1	0.5 %
CF 2	0.67 %

Table 11: Swelling index of plain drug tablets

Formulation code	Swelling index (%) Time (hours)						
	1	2	3	4	5	6	24
GF 1	20 %	52 %	70 %	78 %	87 %	95 %	111 %
GF 2	22 %	56 %	73 %	80 %	88 %	102 %	115 %
CF 1	25 %	55 %	76 %	82 %	91 %	113 %	120 %
CF 2	29%	58%	79%	81%	95%	117%	125%

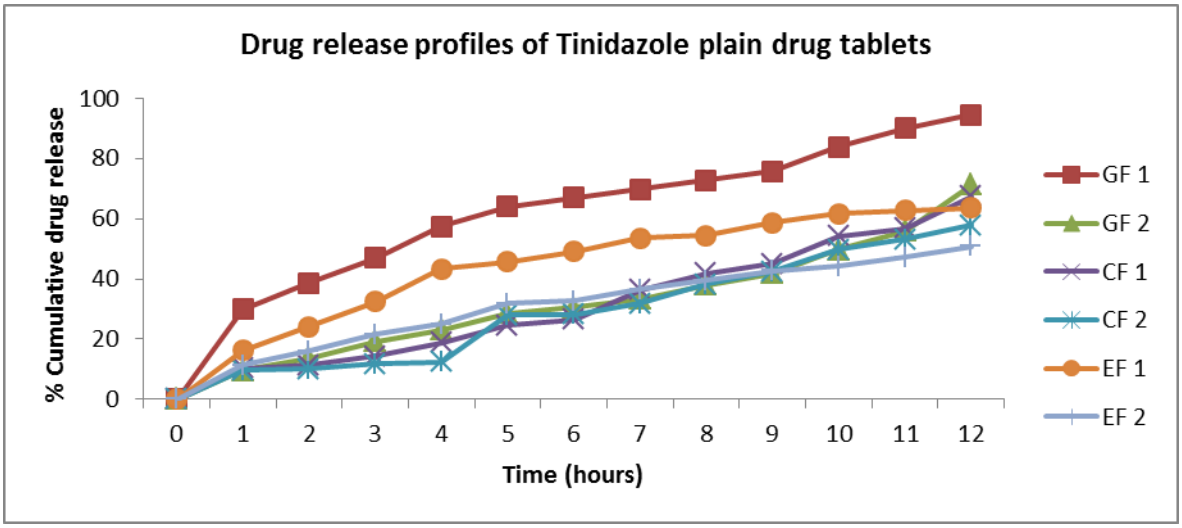

Fig. 1: Drug release profile of plain drug tablets

Table 12: Drug content of plain drug tablets

Months	Physical Appearance	% Drug Content					
		EF 1	EF 2	GF 1	GF 2	CF 1	CF 2
0	No significant changes were seen	95.68	95.36	96.85	96.79	95.77	95.51
1	No significant changes were seen	95.23	95.17	96.79	96.62	95.64	95.23
2	No significant changes were seen	95.18	94.76	96.67	96.34	95.36	95.11
3	No significant changes were seen	95	94.56	96.21	96.13	95.28	94.89

REFERENCES

1. Donders GG, Zodzika J and Rezeberga D. Treatment of bacterial vaginosis: what we have and what we miss. Expert Opinion on Pharmacotherapy. 2014;15(5):645-57.
2. Soper DE. Bacterial vaginosis and postoperative infections. American Journal of Obstertrics and Gynecology. 1993;169(2):467-469.
3. Bistoletti P, Fredricsson B, Hagstrom and Nord CE. Comparison of oral and vaginal metronidazole therapphy for nonspecific bacterial vaginosis. Gynaecologic and Obstertric Investigation. 1986;21(3):144-19.
4. Alton ME. Drug Design and Manufacture of Medicine, 3rd Edition, Churchill Livingstone, Hungary. 2007;614.
5. Jaiswal SB and Bramanker DM. Biopharmaceutics and Pharmacokinetics- A Treatise. 1st Ed. M.K. Jain for Vallabh Prakashan.1995;5-75,335-375.
6. Durgin JM and Hanan ZI. Pharmacy practice for technicians. 5th ED. Cengage Learning. 2015;260.
7. Garg S, Tambwekar KR, Vermani K, Garg A, Kaul CL and Zaneveld LJD. Compendium of Pharmaceytical excipients for vaginal formulations. Pharmaceutical Technology. 2001;14-24.
8. Preetha P, Rao AS and Banuteja Naik B. Formulation and evaluation of Stavudine as mucoadhesive tablets. International Journal of Pharmaceutical Sciences and Research. 2014;6(2):928-34.
9. Armstrong NR and Wilson JD. Tinidazole in the treatment of bacterial vaginosis. International Journal of Women's Health. 2009;1:59-65.
10. Indian Pharmacopoeia; Indian Pharmacopoeia Commission, Ghaziabad. 2007;2:2875.
11. Thoral C, Tchoreloff P, Mazel V, Busignies V and Nivoliez A. Inventors. Biose, Assignee. Mucoadhesive sustained-release vaginal tablet. US 20170014458 A1. 2017.
12. Singhvi G and Singh M. Review: In-vitro drug release characterization models. 2011;2(1).
13. Watson J, Rees JA and Smith I. Pharmaceutical practice. Churchill Livingstone Elsevier. 2014;353.