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AN OVERVIEW ON 5-NITROIMIDAZOLE DERIVATIVE "SATRANIDAZOLE"

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ABSTRACT

Precious role of nitrogen containing heterocyclic drugs has been available from ancient time for the treatment of microbial infections. 5-nitroimidazoles have widened exploration yet. Right now these agents used to cure sever treatment like anaerobic pathogenic bacteria and protozoa. 5-nitroimidazoles are a well-established group of antiprotozoal and antibacterial agents that inhibit the growth of both anaerobic bacteria and certain anaerobic protozoa, such as Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia. Satranidazole is a type of antiprotozoal drug which belongs to the 5-nitroimidazole group. It is highly effective, well accepted and clinically useful against protozoa. It is two times more active than other nitroimidazole against amoebiasis and giardiasis. It is also more active against anaerobes than other nitrogen containing imidazoles. The present review provides a brief account of various works already done on satranidazole drug.

KEYWORDS: HPLC, HPTLC, Satranidazole, Metronidazole, UV.

INTRODUCTION

Nitro-heterocyclic compounds have a wide variety of applications, ranging from food preservatives to antibiotics. Nitroimidazoles have therapeutic uses as anaerobic antibacterials and antiprotozoal agents.[1] 5-nitroimidazoles are a well-established group of antiprotozoal and antibacterial agents.[2] The antimicrobial activity of these chemotherapeutic agents inhibits the growth of both anaerobic bacteria and certain anaerobic protozoa such as Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia.[3] They have other interesting biological activities of therapeutic potential such as, radiosensitizers in treatment of cancer, control of fertility, and antitubercular therapy. 2-Nitroimidazoles play a major role

as bioreductive markers for tumour hypoxia. Satranidazole is a novel 5-nitromidazole derivative. It is a light lemmon yellow crystals and and slightly hygroscopic in nature. It is not official in any of the pharmacopoeia. It is more active towards anaerobes than many 5-nitroimidazoles because its relatively high redox potential may make it more resistant to inactivation by oxygen. It shows activity against E. hystolytica and Giardia. Chemically, it a first derivative which combines nitroimdazole and imidazolidinone rings in their structure. It posses C-N linkage at second position of imidazole ring.

DRUG PROFILE

Name : Satranidazole

Synonyms : Satranidazol [Spanish], Satranidazolum [Latin].

IUPAC name :1-(1-Methyl-5-nitro-1H-imidazol-2-yl)-3-(methylsulfonyl)-2-imidazolidinone

Molecular formula : $C_8H_{11}N_5O_5S$

Category : Antiamoebic and Antiprotozoal

Identification : By HPLC and HPTLC

Molecular weight : 289.26844 [g/mol]

Solubility : Insoluble in water, soluble in dioxane and dimethyl formamide (DMF).

Description : A yellowish, crystalline powder and slightly hygroscopic in nature

Storage : Store in a room temperature away from light.

Standards : Satranidazole contains not < 99.67 percent.

Assay : By liquid chromatography

Half life : Plasma elimination half-life of 1.01 hr

Dose : 300 mg -600mg

Uses : Satranidazole commonly used in amoebic liver abscess, Trichomoniasis, Giardiasis.

Adverse effects : Headaches, palpitations, high blood pressure, hot flushes, weakness, dizziness, nervousness, dry mouth, change in taste.

Over dosage : High doses for prolonged periods are carcinogenic.[4]

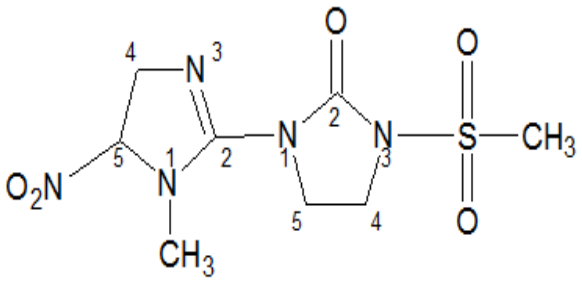

Fig.1

Mechanism of action

As per other nitromidazoles, satranidazole also act on the nucleic material of the cell. It has been observed that during reduction, its ability to break DNA. Substantial breakdown to DNA was measured by viscometry. The satranidazole produces extensive DNA breakage characterized by strand breakage and helix destabilization.[5] Its comparison with other 2 and 5-nitroimidazoles indicate it may be more potent towards anaerobes other 5-nitroimidazoles because its high redox potential are more resistant to inactivation by oxygen. It is recently introduced as an anti-protozoal agent in tablet dosage form. It is a highly potent, well-tolerated, and clinically useful agent against common protozoa. It is rapidly absorbed and exhibits higher plasma and liver concentration than metronidazole.

Design of hydrogel beads of satranidazole for targeted drug delivery to the colon

Development of satranidazole chitosan hydrogel beads exploiting pH-sensitive property and specific biodegradability for colon-targeted delivery of satranidazole. Satranidazole chitosan hydrogel beads were prepared by the cross-linking method followed by enteric coating with Eudragit S100. All formulations were evaluated for particle size, encapsulation efficiency, swellability, and in vitro drug release. The size of the beads was found to range from 1.04±0.82 mm to 1.95±0.05 mm. The amount of the drug released after 24 hours from the formulation was found to be 97.67%±1.25% in the presence of extracellular enzymes as compared with 64.71%±1.91% and 96.52%±1.81% release of drug after 3 and 6 days of enzyme induction, respectively, in the presence of 4% cecal content. Degradation of the chitosan hydrogel beads in the presence of extracellular enzymes as compared with rat cecal. Results of release studies indicate that Eudragit S100– coated chitosan beads offer a high degree of protection from premature drug release in simulated upper GIT conditions. Eudragit S100–coated chitosan beads deliver most of the drug load in the colon, an

environment rich in bacterial enzymes that degrade the chitosan and allow drug release to occur at the desired site.[6]

Measurement of potency of satranidazole and metronidazole in patients of liver abscess

To study the efficacy, side effects, and tolerance of metronidazole and satranidazole in patients of amebic liver abscess. Twenty-five patients received metronidazole (800 mg Thrice in a day) and 24 received satranidazole (300 mg Thrice in a day with placebo at mealtime). Patients recorded side effects and tolerability through a performa. The time taken for resolution of fever and pain and the fall in abscess size was not significant. However, tolerance of satranidazole as reported by the patients was significantly better than metronidazole. The incidence of adverse effects was significantly lower in the group given satranidazole. The incidence of nausea and metallic taste was significantly lower in the patients given satranidazole.[7] Thus, despite having a similar efficacy, satranidazole showed a far lower incidence of side effects and had a significantly better tolerance than metronidazole.

Antibacterial exploration

A large number of nitroimidazoles have been examined for in vitro activity against three anaerobes -Bacteroides fragilis (Bf), a strain of Bf resistant to metronidazole and Clostridium perfringens and many found to be active. Among these may be mentioned 1-methyl-5-nitroimidazoles carrying N - bound hetetocycles at position 2, such as satranidazole.[8]

Satranidazole was tested for its activity against reference strains and clinical isolates of anaerobic bacteria in vitro and in two murine models of anaerobic infection in comparison with metronidazole, tinidazole, ornidazole and clindamycin. The MIC_{90} of satranidazole against 50 clinical isolates of anaerobes was 0.25 mg/l which was four-fold lower than the MIC_{90} of metronidazole, tinidazole and ornidazole (MIC_{90} = 1.0 mg/l). In a fatal murine infection with Fusobacterium necrophorum. In a subcutaneous Bacteroides fragilis abscess in mice, satranidazole alone produced a three log reduction in colony forming unit of the infecting organism at 10 mg/kg, the lowest dose tested. At 100 mg/kg, only satranidazole and clindamycin effected a complete sterilization of abscesses.[9]

A comparison study by HPLC of Satranidazole and Metronidazole in rat plasma

Pharmacokinetic properties of metronidazole and satranidazole in the golden hamster (Mesocricetus auratus) at a dose of 80 mg/kg blood and liver samples were collected at

frequent time intervals and assayed for metronidazole and satranidazole by HPLC. Satranidazole exhibited significantly higher plasma concentrations than metronidazole at 1 and 2 hr post-dose, but the comparative $C_{(max)}$ values were not significantly different. The satranidazole plasma elimination half-life of 1.01 hr was significantly shorter than the corresponding metronidazole half-life of 3.62 hr. The comparative liver pharmacokinetic parameters $C_{(max)}$, $T_{(max)}$ and $T_{(1/2)}$ did not differ significantly. Satranidazole however exhibited significantly higher liver concentrations at 1 hr post-dose and $C_{(max)}$ and $AUC_{(o-\infty)}$, values were approximately 35% higher. The in-vivo amoebicidal activity of both compounds was evaluated in the acute hamster hepatic model of amoebiasis. Both metronidazole and satranidazole were administered as single graded doses, and their dose-response profiles were characterized. Satranidazole demonstrated significantly greater amoebicidal activity than metronidazole with an ED_{50} value of 19.5 mg/kg, compared to an ED_{50} value of 45 mg/kg for metronidazole.[10] These data suggest that higher plasma and liver concentrations of satranidazole and greater intrinsic potency probably contribute to superior amoebicidal activity in the hamster model of hepatic infection.

Estimation of satranidazoleby UV in pharmaceutical dosage form

Satranidazole dosage form estimated by two spectrophotometric methods (I and II) under visible region for the estimation of satranidazole in bulk drug and pharmaceutical formulations. Methods I and II are based on the reaction of reduced satranidazole with p-dimethyl amino benzaldehyde (PDAB) and p-dimethyl amino cinnamaldehyde (PDACA) in acidic conditions to form orange red and purple coloured chromogens with absorption maxima at 511 nm and 568 nm respectively. The reduction of satranidazole was carried out with zinc granules and 4N hydrochloric acid at room temperature in ethanol. Beer's law was obeyed in the concentration range of 10-50 µg/ml for both the methods.[11] The results of analysis have been validated statistically and by recovery studies. The methods were found to be simple, rapid, accurate, reproducible and economic.

Determination of effect of super disintegrants on the release of Satranidazole from fast dissolving tablets.

A Study has done to determine the effect of varying concentrations of super disintegrants used in the satranidazole formulation (tablets). This study was to formulate directly compressible fast dissolving tablets of Satranidazole with sufficient mechanical integrity, and content uniformity and to show the effect of different concentrations and different

combinations of superdisintegrants such as crospovidone and croscarmellose sodium on dissolution rate. Tablets were evaluated for weight variation, hardness, friability, drug content, and in vitro drug release. Other parameters such as wetting time, water absorption ratio and invitro dispersion time were also evaluated.[12] Based on the results obtained, formulation containing equal proportions of crospovidone and croscarmellose sodium is selected as the optimized formulation.

Development and validation of a stability-indicating HPTLC-densitometric method for satranidazole

HPTLC method for analysis of satranidazole both as a bulk drug and in formulations. The method employed TLC aluminium plates precoated with silica gel 60F-254 as the stationary phase. The solvent system consisted of toluene/acetonitrile (60:40, v/v). Densitometric analysis of satranidazole was carried out in the absorbance mode at 314 nm. This system was found to give compact spots for satranidazole (R_f value of 0.53±0.02, for six replicates). Satranidazole was subjected to acid and alkaline hydrolysis, oxidation, and photo degradation. The drug undergoes degradation under acidic and basic conditions, oxidation, and photo degradation. Also, the degraded products were well resolved from the pure drug with significantly different R_f values. Linearity was found to be in the range of 100-500 ng/spot with a significantly high value of correlation coefficient. The limit of detection and limit of qualification were 50 and 85 ng/spot, respectively.[13] The proposed HPTLC method was utilized to investigate the kinetics of the alkali degradation process.

Development of Satranidazole mucoadhesive gel for the treatment of Periodontitis

Different mucoadhesive gels of satranidazole were prepared, using various gelling agents like sodium carboxy methyl cellulose poloxamer 407, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, and the mucoadhesive polymer carbopol 934P. The selected formulations (based on the mucoadhesive force) were studied for different mechanical properties, such as mucoadhesive strength, hardness, compressibility, adhesiveness, and cohesiveness through Texture Profile Analyzer. In vitro satranidazole release from the prepared formulations was also determined and compared with marketed preparation of metronidazole (Metrogyl gel). The formulation Satranidazole mucoadhesive gel (containing sodium carboxy methyl cellulose 3% w/v) showed maximum mucoadhesive strength and adhesiveness, with low hardness and compressibility and moderate cohesiveness.[14] The same formulation exhibited long term release. Thus, Satranidazole

mucoadhesive gel with 3% sodium carboxy methyl cellulose was evaluated for its clinical effectiveness along with marketed metronidazole gel. This study confirmed the acceptability and effectiveness of satranidazole gel for treatment of periodontitis.

Method development for the simultaneous estimation of Satranidazole and Gatifloxacin in tablet dosage form by HPLC

A development of RP-HPLC method for the estimation of satranidazole and gatifloxacin simultaneously in combined dosage forms. A column (Lichrospher 100 C-18) and mobile phase comprises of Water: Acetonitrile: Triethylamine (75:25:0.35, v/v/v) were used for separation. Measurements were made at the effluent flow rate of 1.0 ml/min with injection volume 20 µl and ultraviolet (UV) detection at 320 nm, as both components shows reasonable good response at this wavelength. The retention times of satranidazole and gatifloxacin were 6.0 min and 3.44 min, respectively. Linearity of satranidazole and gatifloxacin was in the range of 1-70 µg/ml and 1-70 µg/ml, respectively. Average percentage recoveries obtained for satranidazole and gatifloxacin were 99.80 % and 100.20 %, respectively. The limit of detection and limit of quantification were found to be 0.3 and 1.0 µg/ml for satranidazole, respectively and for gatifloxacin were 0.5 and 1.0 µg/ml, respectively.[15] This method was simple, sensitive, precise, reproducible and accurate and hence can be used in routine for the simultaneous determination of satranidazole and gatifloxacin in bulk as well as in pharmaceutical preparations.

Method development for simultaneous estimation of Ofloxacin and Satranidazole in tablet dosage form by reverse phase HPLC

A development of simple, selective, rapid and precise reverse phase HPLC method for the simultaneous estimation of Ofloxacin and Satranidazole in tablets. The analyte was resolved by using a mobile phase 0.05M phosphate buffer and acetonitrile in the ratio of 65:35 v/v at a flow rate of 1.0 ml/min on an isocratic HPLC system at a wavelength of 320 nm. The linearity was obtained in the concentration range of 5-40 µg/ml for Ofloxacin and Satranidazole, respectively. Boopathy D et al., 2010 developed and validated a method for simultaneous determination of Ofloxacin and Satranidazole in pharmaceutical dosage form by RP-HPLC. A Phenomenex Luna C18 (4.6*250 mm, 5µ) column was used for the separation. The mobile phase was Phosphate buffer: Acetonitrile (70: 30 % v/v) and pH 6.0 at a flow rate of 1.2ml/min with detection at 300nm.[16] The retention time of Ofloxacin and Satranidazole was 3.720 and 6.130 min, respectively.

Estimation of Satranidazole in bulk and in dosage form by UV Spectrophotometry

A simple, precise and accurate spectrophotometric method has been developed for the determination of Satranidazole in bulk drug and in pharmaceutical dosage form. This method was based on reduction of nitro group followed by diazotization and coupling reaction with phloroglucinol forming yellow coloured chromogen exhibiting absorbance maximum at 430nm. The molar absorptivity value of Satranidazole was found to be 1.76 x 103 mole-1 cm-1. Beer's law was obeyed in the concentration range of 10 – 50µg/ml.[17] Thus the developed method is simple, accurate, precise, reproducible, less time consuming and effective. Hence it could be used for routine analysis of Satranidazole in pharmaceutical formulation.

Estimation of Satranidazole and Ofloxacin in tablet dosage form by HPLC

Study has done to estimate satranidazole and ofloxacin simultaneously in tablet dosage form by high performance liquid chromatography. Chromatographic separation of these drugs were performed on Kromasil C18 column (250 x 4.6 mm, 5 µ) as stationary phase with a mobile phase comprising of 20 mM potassium dihydrogen phosphate: acetonitrile in the ratio of 60:40 (v/v) containing 0.1% glacial acetic acid at aflow rate of 1 mL/min and UV detection at 318 nm. The linearity of satranidazole and ofloxacin were in the range of 1.5 to 3.6µg/mL and 1.0 to 2.4µg/mL respectively. The recovery was calculated by standard addition method. The average recovery was found to be 100.63% and 100.02% for satranidazole and ofloxacin respectively.[18]

Determination of Satranidazole and Ofloxacin in combined dosage form UV Spectrophotometry

Accurate and precise spectrophotometric methods for simultaneous determination of satranidazole and ofloxacin in pharmaceutical fixed dosage form. The method A involves simultaneous equation using 297.3 and 317.0 nm as the wavelengths of detection while method B is two wavelength method where 281.5nm, 309.0nm were selected as λ_1 and λ_2 for determination of satranidazole and 300.0 nm, 333.1nm were selected as λ_1 and λ_2 for determination of ofloxacin.[19] The Beer's law limits for each drug individually and in mixture was within the concentration range of 5-25 µg/ml. Linearity of satranidazole and ofloxacin were in the range of 80-120% of the label claim. The proposed methods have been applied successfully to the analysis of the cited drugs either in pure form or in pharmaceutical formulations with good accuracy and precision.

CONCLUSION

On basis of above literature survey, it could be concluded that satanidazole are very important class of nitroimidazoles with wide range of biological activities. Also it could be understood that satranidazole is active against bacteria and protozoa which are responsible for diseases with high morbidity. Satranidazole can also pharmacologically screen agents other than gram negative and positive bacterias. There is huge scope of existing nitroimidazole (satranidazole) drug molecule to develop different dosage form and compare with other existing nitroimidazole derivatives. Direct compression method of preparing orodisperable tablet of Satranidazole was an effective method for enhancing the dissolution rate. Mucoadhesive gel of satranidazole shows excellent mucoadheve strength against treatment of periodontitis. So Satranidazole gel could be a boon remedy in future. Newer methods have been developed that can be utilized for estimation of satranidazole in individual or in combination preparations as well as they can be exploited for estimating the purity of the compounds.

REFERENCES

1. Mital A. Synthetic Nitroimidazoles: Biological activities and mutagenicity relationships. Scientia pharmaceutica, 2009; 77: 497–520.
2. Celik A, Aras Ates N, Drug Chem Toxicol. The frequency of sister chromatid exchanges in cultured human peripheral blood lymphocyte treated with metronidazole in vitro**,** 2006; 29: 85–94.
3. Upcroft JA, Campbell RW, Benakli K, Upcroft P. Efficacy of new 5-nitroimidazoles against metronidazole-susceptible and -resistant Giardia, Trichomonas, and Entamoeba spp. Antimicrob Agents Chemother, 1999; 43: 73–76.
4. Free encyclopedia, E- Journal, from www.wekipidia.com
5. Zahoor A, Knight RC, Whitty P, Edwards DI. Satranidazole: mechanism of action on DNA and structure-activity correlations. Journal of Antimicrobial Chemotherapy, 1986; 18(1): 17-25.
6. Jain SK, Jain A, Gupta Y, Ahirwar M. Design and development of hydrogel beads for targeted drug delivery to the colon. AAPS Pharm Sci Tech. Journal, 2007; 8(3): 56.
7. Muzaffar J, Madan K, Sharma MP, Kar P. Randomized, single-blind, placebo-controlled multicenter trial to compare the efficacy and safety of metronidazole and satranidazole in patients with amebic liver abscess. Journal of Digestive Diseases and Sciences, 2006; 51(12): 2270-3.

8. Nagarajan K, Gowrishankar R, Arya VP, George T, Nair MD, Shenoy SJ, Sudarsanam V. Nitroimidazole: Part IV. 1-Suphonyl (carbamoyl/thiocarbamoyl 1-methyl-5-nitroimidazole-2-yl)-2-imidazolidinone. Indian Journal of Experimental Biology, 1992; 30(3): 193-200.
9. Gowrishankar R, Phadke RP, Oza SD, Talwalker S. Satranidazole: experimental evaluation of activity against anaerobic bacteria in vitro and in animal models of anaerobic infection. Journal of Antimicrobial Chemotherapy, 1985; 15(4): 463-70.
10. Onkar J, Vijaya G. HPLC determination of satranidazole in rat plasma. Journal of Chemistry, 2011; 23(1): 4317-4320.
11. Mruthyunjayaswamy BHM, Patil SM, RAJU A. Spectrophotometric methods for the estimation of satranidazole in pharmaceutical formulation. Indian Journal of Pharmaceutical Sciences, 2001; 433-453.
12. Manju M, Kilimozhi D, Kuppuswamy S. Effect of super disintegrants on the release of Satranidazole from fast dissolving tablets. Research Journal of Pharmaceutical Biological and Chemical Sciences, 2015; 6(2): 1881-86.
13. Patel MB. Development and validation of a stability-indicating HPTLC-densitometric method for Satranidazole. Journal of Liquid Chromatography & Related Technologies. 2007; 30(18): 2755-2767.
14. Bansal K, Rawat MK, Jain A, Rajput A, Chaturvedi TP, Singh S. Development of Satranidazole mucoadhesive gel for the treatment of Periodontitis. AAPS Pharm Sci Tech. Journal, 2009; 10(3): 716-23.
15. Patel AB, Shah NJ. Development for the simultaneous estimation of Satranidazole and Gatifloxacin in tablet dosage form by HPLC. International Journal of Chem Tech Research, 2009; 1(3): 587-590.
16. Wankhede SB, Prakash A, Chitlange SS. Development for simultaneous estimation of Ofloxacin and Satranidazole in tablet dosage form by reverse phase HPLC. International Journal of PharmTech Research, 2009; 1(4): 1136-1138.
17. Xavier R, Sundarapandian M, Rexy I. and Rameshmoorthy KM. spectrophotometric estimation of satranidazole in bulk and in dosage form. International Journal of Research in Pharmacy and Chemistry, 2011; 1(4): 970-75.
18. Sachin R, Bhoir I. Simultaneous estimation of Satranidazole and Ofloxacin in tablet dosage form by HPLC. Journal of Chemistry, 2010; 7(1): 198-202.

19. Sherje AP, Tawade AP, Vyas M. Simultaneous Spectrophothometric Determination of Satranidazole and Ofloxacin in Combined Dosage Form. International Journal of PharmTech Research, 2010; 1(5): 511-14.