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Research Article

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Synthesis and characterization of ornidazole, 5-ASA azo adduct for colon targetting

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ABSTRACT

The main objective of our research work is to prepare Ornidazole azo adduct with 5-ASA for colon targeting . We synthesized Ornidazole 5-ASA azo adduct and examine the effect of enzyme azo reductase on the release rate of ornidazole and 5-ASA in the gastrointestinal contents of rats. By using this approach two drugs can be targeted at the same time in the colon so as to treat the various disease of colon such as Crohn's disease and ulcerative colitis. The azo adduct did not release drug in acidic environment of stomach, but when the azo adduct drugs will enter into colon the enzyme azo reductase break the azo bond and releases the dual drugs. By using this approach two drugs can be released at same time in colon .The azo adduct was evaluated for its color, solubility, R_f value, melting point and IR spectral analysis. It was further subjected for evaluating its colon targeting property by in-vitro method using rat fecal matter.

Keywords: Ulcerative Coltis, Crohn's disease, Azo adduct, Azoreductase, 5-ASA

INTRODUCTION

Targeted drug delivery into the colon is used for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.[1,2] Oral route is the most convenient and preferred route. Rectal administration is the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and possess less compliance to patient.[3] Colon possess high water absorption capacity of the colon, due to which colonic contents are considerably viscous and their mixing is not efficient,which decreases availability of most drugs . Ornidazole is a drug that cures some protozoan infections. It has been investigated for use in Crohn's disease after bowel resection. [4].5-ASA can be effective in treating Crohn's disease and ulcerative colitis if the drug can be delivered topically onto the inflamed intestinal lining. If pure 5-ASA and Ornidazole is taken orally, however, most of the 5-ASA and Ornidazole would be absorbed in the stomach and the upper small intestine, and very little 5-ASA and Ornidazole would reach the ileum and colon. To be effective as an oral agent in treating Crohn's disease and ulcerative colitis, 5-ASA and Ornidazole has to be modified chemically to escape absorption by the stomach and the upper intestines.

Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides. [5]Azo conjugation has been used as tools to deliver the drugs especially to the colon. The azo bond remain intact in the

physiological environment of stomach and small intestine but once the dosage form enters the colon, the enzyme azo reductase act on the colon and break the azo bond which releases the drug into colon [6-7] .

As on date the 5-ASA and Ornidazole are delivered in individual dosage form.A research was focused to improve the bioavailability of both drugs by various approaches like sustained release and prolonged release in order to reduce the dose frequency. But the uniqueness of this research is delivering dual drug safely to colon region by synthesizing a azo adduct conjugate.

Scheme

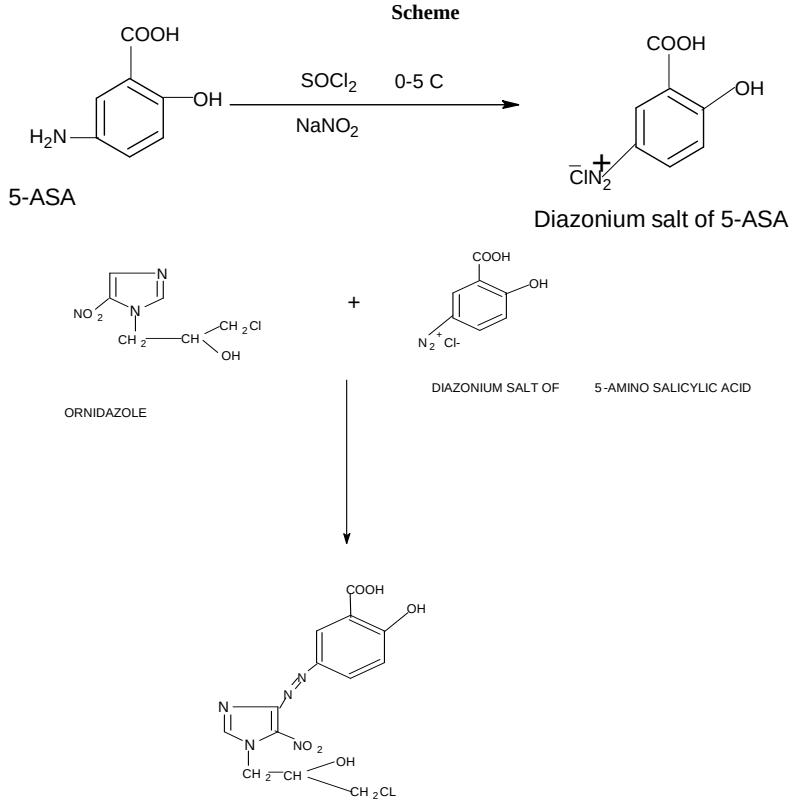

Figure 1: Synthesis of 5-ASA Ornidazole Azo adduct

EXPERIMENTAL SECTION

Preparation of 5-ASA Ornidazole Azo adduct

Diazotization of 5-ASA was carried out by dissolving 0.02 M 5-ASA in methanol then cool it by adding crushed ice and maintained the temperature of 0-5 °C, then add 10 ml conc. hydrochloric acid ,5ml sodium nitrite(10%) nitrite and 1 ml thionyl chloride ,orange diesters was form. The obtained product was coupled with 0.02 M ornidazole in 2M sodium hydroxide. The product was then stirred for 24 hrs and temperature of 0-5°C was maintained during the experiment.

Characterization

The TLC was taken by using toluene, ethylacetoacetate and formic acid (5:4:1) at different time interval and visualization of spots was done by using iodine chamber. The obtained product was confirmed by m.p.The azo complex formation was confirmed by IR, spectral studies.

Analytical methods

IR Spectra was taken on a Shimadzu Spectrophotometer. ^{1}H NMR spectra were taken on a Bruker AvanceII 400 NMR Spectrophotometer. Melting and decomposition points were conducted in a melting point apparatus. The IR spectrum of the synthesized compound was obtained from Laureate Institute; Himachal Pradesh.

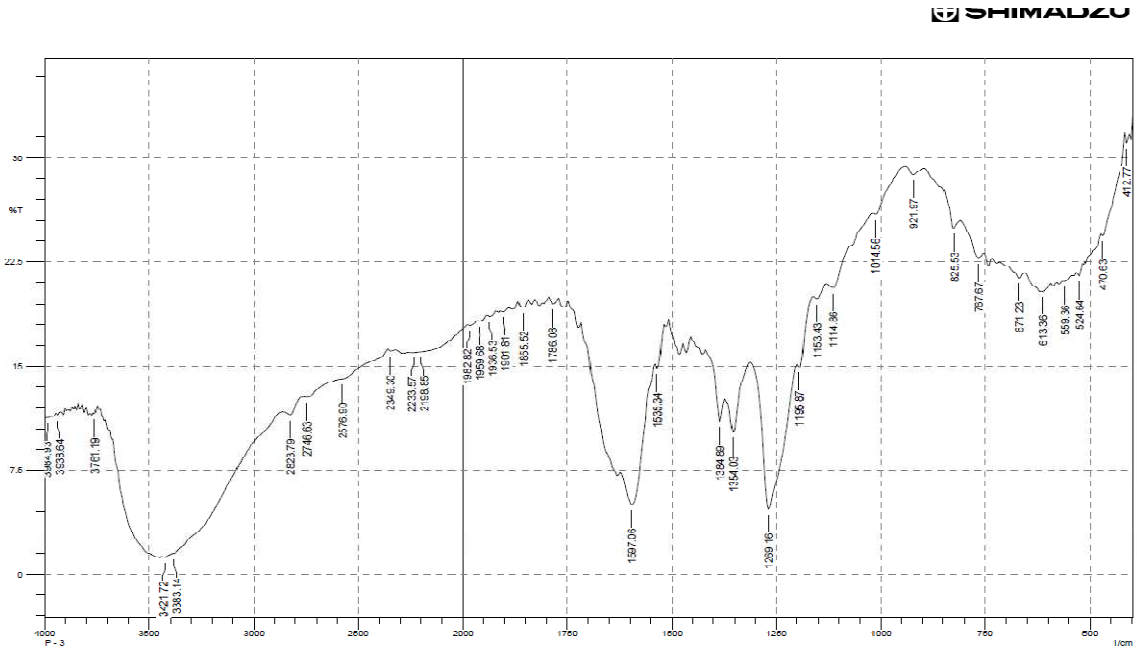

Figure2 :IR SPECTRA OF ORNIDAZOLE 5-ASA AZO ADDUCT

Acute Toxicity Study

The azo adduct was evaluated for acute toxicity study. The protocol was approved by the Institutional Animal Ethical Committee. OECD 423 guide-lines were followed in the procedures. Two groups of 6 albino rats, one for test and other for control, were used for the study. The study was performed by administering the Ornidazole 5-ASA azo adduct at 2g/kg body weight for the test group animals. The acute toxicity study was evaluated for a period of 14 days, changes in the skin colouration, observing body weight, corneal reflex, behavioral patterns, and convulsions and compared with the control group animals (Madhav and Shankar, 2011[8].

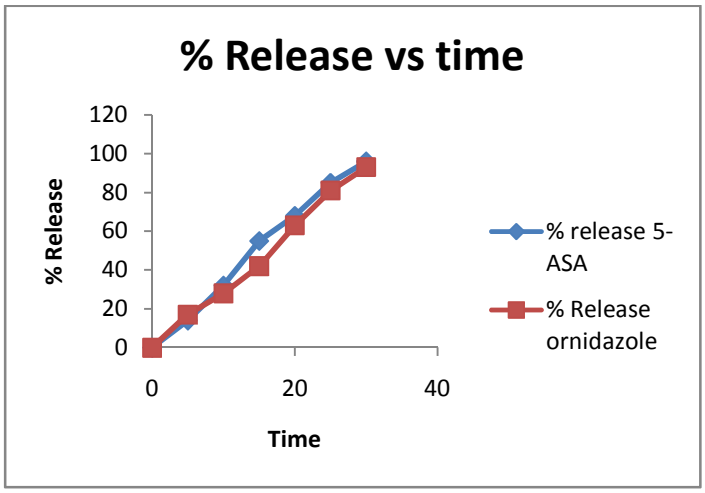

Figure 3:Release rate of 5-ASA and Ornidazole from azo adduct

In vitro release study

The derivative was further subjected for in vitro release using a rat fecal material using phosphate buffer of Ph 7.4. Shimadzu 1800 UV spectrophotometer was used for this purpose 1 gm of rat fecal material was taken in 6 test tube. 1 ml of drug solution (10 microgram/ml) was added in each test tube. Then 5ml of phosphate buffer was added in each test tube and incubate it for half hour at 37 ^{0} C for different interval of time. Filter the solution and absorbance was evaluated using U.V.Spectrophotometer at 302 nm and 318.5 nm for 5-ASA and Ornidazole respectively[9].

RESULTS AND DISCUSSION

From the IR spectra of 5-ASA Ornidazole Azo adduct, the Azo peak was observed at 1593.20cm^{-1} in addition to the peaks originated from 5-ASA and ornidazole. IR (KBr):3421.72(O-H Stret), 1597.06(-N=N- stret.), 1535.54(Aromatic C-H in plane bending),1354,1384.89 (Aromatic Ter Amine,-COOH), 1786.08(Keto) 2823, 2742[C-H Stret (sym, asym.)]. M.p-245°C, Rf-0.62, Colour-Orange.Solubility- Soluble in phosphate buffer ph-7.4 and insoluble in dil. hydrochloric acid. No sign of acute toxic effects were observed in rats.

CONCLUSION

Our research study result reveals that azo adduct having significant colon specificity hence this method is feasible for preparing colon targeted delivery and this complex is used for treating various diseases of colon such as Crohn's disease and Ulcerative colitis. The conclusion was drawn that this method is so beneficial, economic and patient compatible for targeting drug to colon region in effective manner

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