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VIEWS

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Antiulcer activities of the hydroalcoholic extract of *Artocarpus heterophyllus* Lam fruits in rat

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ABSTRACT

The hydroalcoholic extract of the fruits of *Artocarpus heterophyllus* lam was investigated to determine its antiulcer activity in albino Wistar rats. Ulcers were induced by reserpine and pylorus ligation. By conducting acute toxicity study the extract was safe upto 2000mg/kg dose. Thus extract was administered at the dose of 200 mg/kg and 400 mg/kg. The ulcer index of the ethanol extract was found to be significantly reduced compared with control animals. The effect was also assessed in by determining the free acidity, gastric volume, pH, total acidity. Furthermore histopathological studies have shown that pretreatment with hydroalcoholic extract of the fruits of *A. heterophyllus* reduces reserpine and pylorus induced hemorrhagic necrosis in rats.

KEYWORDS : *Artocarpus heterophyllus*, Ulcer index, Free Acidity, Total Acidity, pH

Introduction

Ulcers are an open sore of the skin or mucus membrane characterised by sloughing of inflammed dead tissues [1]. There are many types of ulcers such as mouth ulcer, oesophagus ulcer, peptic ulcer and genital ulcer, of these peptic ulcer is seen among many people. Peptic ulcer are erosion of lining of stomach or the duodenum [2]. Peptic ulcer disease (PUD) ,which include gastric and duodenal ulcers, is the most prevelant gastrointestinal disorder and requires a well target therapeutical strategy. The pathophysiology of PUD involves an imbalance between offensive (acid, pepsin,and Helicobacter pylori) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide, and growth factors) [3,4]. A number of factor such as stress, chemical agents, bile salts, hyperosmolar NaCl, NSAIDs leads the gastro duodenal ulcers.[5] These agents have been implicated in the pathogenesis of gastric ulcer, including enhanced gastric acid and pepsin secretion, inhibition of prostaglandin synthesis and cell proliferation growth, diminished gastric blood flow and gastric motility [6]. As many as 70%-90% of such ulcers are associated with *Helicobacter pylori*, a helical shaped bacterium that lives in the acidic medium of the stomach. Ulcer can also be caused or worsened by drugs such as aspirin, ibuprofen and other NSAIDS.[7] The most effective classes of drugs available to treat PUD include Proton pump inhibitors, histamine 2 receptor blockers, and prostaglandin analogues [8]. The efficacy of these agents is marred by their numerous adverse effect which include gastrointestinal dysfunction ,mental state changes, and an increased risk of respiratory/enteric infections. Furthermore the various cytochrome enzyme interactions of these agents can also affect the therapeutic levels of other agents [9].

Artocarpus heterophyllus Lam commonly known as jack fruit belongining to family Moracea is evergreen tree which comes up well under humid and warm climate is cultivately widely in India, Malayasia, Bangladesh, Myanmar, Sri Lanka [10]. It leaves has been used for treatment of fever, boils. Fruits for laxative and aphrodisiac, seed are diuretic and constipation [11]. Various research has been carried out which assists *Artocarpus heterophyllus* Lam to have Antibacterial [12], Cardioprotective [13], Anti-inflammatory activity [14], Antifungal [15], Inhibition of melanonin biosynthesis [16] and Wound healing activity [17]. *Artocarpus heterophyllus* contains various chemical constituent as several flavones, colouring matters, dihydromorin, cynocurin, artocarpin, isoartocarpin, cycloartocarpin, artocarpesin, arcapetin,cycloartinone and artocarpanone [18]. The composition of carotenoids of *A. heterophyllus* is carotene, β carotene, α-carotene, β-zeacarotene, α-zeacarotene and β-carotene crocetin were identified [19]. Along with many other plants mention in ancient literature, *A. heterophyllus* is one such plant claimed to be used as anti ulcer. Thus present study was undertaken to assess the antiulcer potency of fruits of the plants.

Address for correspondence.

Material and Method

Plant Material

The *Artocarpus heterophyllus* Lam fruits were collected from Banglore, Karanataka (India). The plant was authenticated by a Pharmacognosist Dr. Jagadeesh Singh, Department of Pharmacognosy, East Point College of pharmacy, Bidarahalli, Bangalore-49.

Animal

Male wistar albino rats (150-250g) and swiss albino mice (25-30g) were used. Animal were procured from the animal house of East Point College of pharmacy. All animal were acclimatized and maintain under standard laboratory condition before the start of experiments. The Institutional Animal Ethics Committee of East Point College of pharmacy (Reg. no 194) approved the experimental protocol.

Extraction

The fruits were collected and air dried under the shades and was chopped and pulverized in electric grinder. The coarse powder was given to GREEN CHEM, in order to carry out the successive Soxhlet extraction by using hydro-alcoholic solvent (70%v/v) and stored in desiccators.

Phytochemical analysis

The hydroalcoholic extract of fruit of *A. heterophyllus* was subjected to following test for

Carbohydrate were identified by Molisch's test, Protein by ninhydrin test, Steroids by Libermann- Burchard test, Glycosides by Legal's test, Alkaloids by Dragendroff test, Flavonoids by Shinoda test, Saponin by Hemolytic and tannin by Braemer's test.

Determination of acute toxicity

The acute toxicity for hydroalcoholic extract of fruit of *Artocarpus heterophyllus* was determined in swiss albino mice maintained under standard condition. The animals were fasted overnight prior to experiment. Fixed dose (OECD guidelines no 425) method of CPCSEA was adopted for toxicity studies. There was no sign of toxicity for first 48 hours and no animals died on14 days of study at a dose of 2000 mg/kg.

Pharmacological Evaluation

Pylorus ligation method [20, 21]

Albino Wister rats of either sex weighing between (150-200 gms) are divided into five groups of animal. Each group contains six animal. Group A: Normal, Group B: Control, Group C: Standard, Group D: HAAH 200 mg/kg, Group E : HAAH 400 mg/kg. Animals were fasted in individual cage for 24 hours. Test drug or standard drug or control vehicle is administered 30 minutes prior to pyrolus ligation. Under light ether anaesthesia, the abdomen is opened and the pylorus was ligated. The abdomen is then sutured. At the end of 4 hrs after ligation the animals are sacrified with excess of anaesthetic ether and the stomach is dissected out gastric juice is collected were drained into tubes and were centrifuged at 1000 rpm for 10 minutes and the volume is noted . The pH of gastric juice is recorded by pH meter. Then the contents are subjected to analysis for free and total acidity. The stomach are then washed with running water to see for ulcers in the glandular portion of the stomach . The numbers of ulcers per stomach are noted and severity of the ulcers scored microscopically with the help of 10x lens. Histopathological studied were conducted by fixing stomach tissues in 10 % formalin for 24 h. the formalin fixed specimens are embedded in paraffin and section are stained with haematoxylin and eosin dye. The histochemical sections are evaluated by light microscopy

0 = Normal stomach, 0.5 = Red coloration , 1 = Spot ulcers, 1.5 = Haemorrhagic streaks, 2= ulcers> 3mm, 3= ulcers >5 mm.

Ulcer Index was calculated as;

$UI=UN+US+UPx10^{-1}$

Where, UI = Ulcer Index

UN = Average number of ulcer per animal

US = Average of severity score

UP = Percentage of animals with ulcer

RESERPINE INDUCED ULCER [22]

Adult albino rats weighing 150-180gms were fasted for 24hour. Animals were divided into different groups following water ad libitum. Group I of rats received distilled water as negative control, Group II of rats received Reserpine (5mg/kg) along with distilled water served as positive control, Group III of rats received Ranitidine (50mg/kg) and Reserpine (5mg/kg) as reference drug, and Group IV and V received Reserpine (5mg/kg) and HAAH (200mg/kg, 400mg/kg) will be test drug. Respirine (5mg/kg) administered intramuscularly to rats. 30 minutes after the administration of the standard/ test drug or control vehicle (distilled water) intraperitoneally. All the animals were sacrificed after 18 hour, their stomachs were removed, opened along with the greater curvature and sum of lengths (mm) of all lesions for each rat was used as ulcer index.

Results

Phytochemical analysis:

On phytochemical analysis of HAAH, the extract has shown the presence of carbohydrates, glycosides, phytosterols, phenolic compounds, tannins saponins and flavonoids. Tannins, saponin and flavonoids are known to affect the intergrity of mucousmembrane.[32] Tannin with their protein precipitating and vasoconstrictive effects prevent the development of ulcers. Flavonoids are free radical scavengers that are known to play an important role in ulcerative and erosive lesions of gastrointestinal tract. The

antiulcer activities of the ethanolic extract of this fruit could be attributed to its flavonoids and tannins.

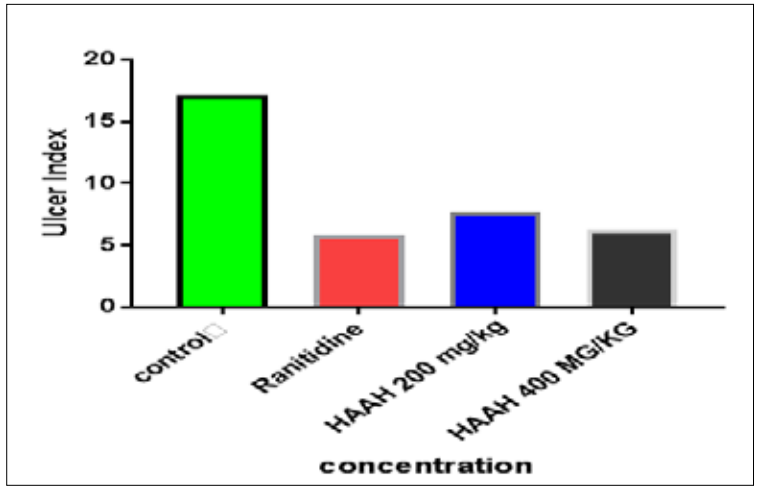
Pyloric ligation model

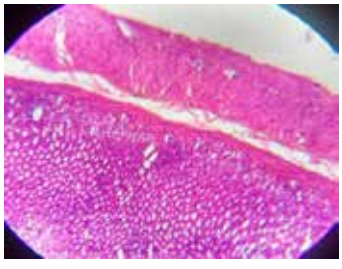
Gastric pylorus ligation in rats produced a characteristic gastric lesion. The pre-treatment with HAAH has reduced the gastric lesions compared with control. More activity was shown by 400mg/kg body weight compared with other extract (200 mg/kg). Free acidity, total acidity were also significantly decreased when compared with the control animals. The result indicates that the hydroalcoholic extract of the fruits of *A. heterophyllus* has potent protective effects against induced ulcers in animal models. A significant decreases in the ulcer index was observed following treatment with the hydroalcoholic extract of the fruits of *A heterophyllus* .

Effect of HAAH fruit in pH, Gastric Volume, Free Acidity, Total Acidity and Ulcer Index

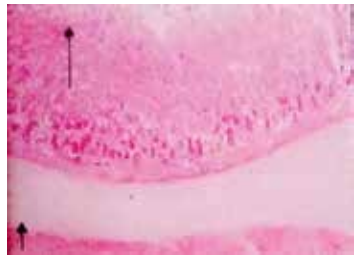
Sl. No	Treatment	Ph	Gastric Volume	Free Acidity	Total Acidity	Ulcer index
1	Normal	3.8± 0.05	3.0± 0.06	19.05± 0.03	45.32± 0.39	-
2	Control	2.5± 0.05	4.7± 0.05	35.03± 0.02	89.25± 0.32	17.10± 0.3011
3	Raniditine	3.4± 0.27**	3.17± 0.21*	22.67± 0.01*	50.32± 1.03**	5.83± 0.124**
4	HAAH	2.8± 0.32*	3.9± 0.32**	27.32± 0.23**	67.35± 1.12**	7.66± 0.523***
5	HAAH	3.2± 0.21**	3.4± 0.05**	25.42± 0.35**	58.22± 1.05**	6.25± 0.36**

Values expressed as mean ±SEM, n=6, ANOVA followed by Dunnett's multiple comparison test. Significant ***P<0.001, **P<0.01, *P<0.05 when compared with control.



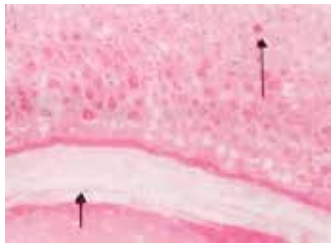


Normal group



Control group

Ranitidine treated group

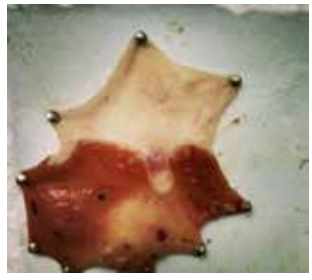


HAAH 200 mg/kg

HAAH 400 mg

Fig . Histopathology of stomach of rats in pylorus induced ulcer

- Ve Control



+Ve Control

ranitidine

HAAH 200 mg/kg

HAAH 400 mg/kg

Effect of different concentration of *Artocarpus heterophyllus* Lam in Pylorus Ligation Induced Ulcers in tissues rats stomach.

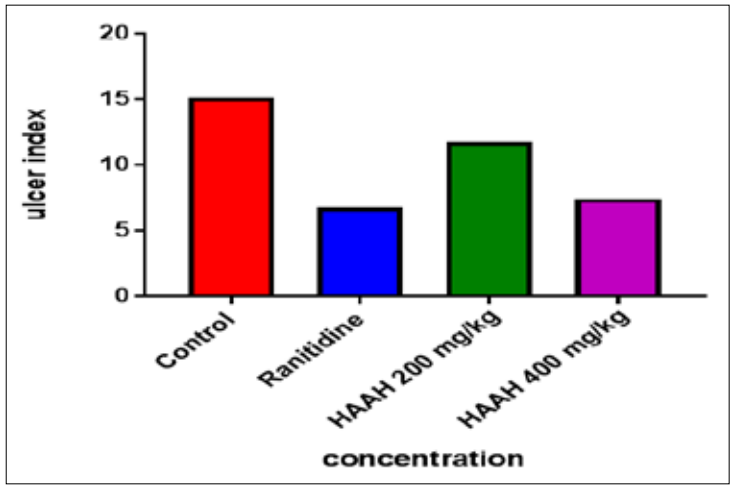
Reserpine induced ulcer

Reserpine in rats produced a characteristic gastric lesion. The pre-treatment with HAAH has reduced the gastric lesions compared with control. More activity was shown by 400mg/kg body weight compared with other extract (200 mg/kg). A significant decreases in the ulcer index was observed following treatment with the hydroalcoholic extract of the fruits of *A heterophyllus* . The result indicates that the hydroalcoholic extract of the fruits of *A. heyterophyllus* has potent protective effects against induced ulcers in animal models.

Group	Treatment	Ulcer Index
Control (-ve)	Vehicle	-
Control (+ve)	Reserpine (5 mg/kg)	15.16±2.18
Ranitidine	Reserpine (5 mg/kg)+ Ranitidine (50mg/kg)	6.75±-0.91***
HAAH	Reserpine (5 mg/kg)+ Extract (200 mg/kg)	11.75±0.55*
HAAH	Reserpine (5 mg/kg)+ Extract (400 mg/kg)	7.41±1.26***

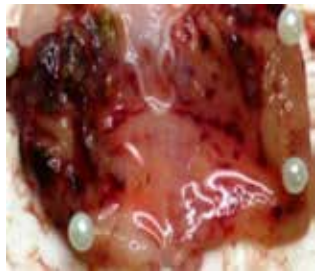
Effects of different dosage of HAAH on ulcer index in Reserpine Induced

Values expressed as mean ±SEM, n=6, ANOVA followed by Dunnett's multiple comparison test. Significant ***P<0.001, **P<0.01, *P<0.05 when compared with control.

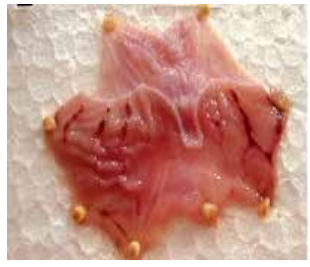


Graph showing effect of Different Concentration of HAAH on Ulcer Index in Reserpine induced ulcer.

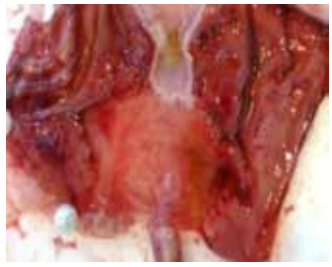
Normal



Reserpine



Reserpine+ Ranitidine



HAAH 200 mg/kg

HAAH 400 mg/kg

Effect of different concentration of HAAH on Ulcer Index in Reserpine Induced Ulcers in rats stomach.

DISCUSSION

Antiulcer activities were performed on albino wister rats of either sex using Pylorus ligation, and Reserpine induced ulcer models. The HAAH (200mg and 400mg/kg) showed significant antiulcer activity in all models. In Pylorus Ligation Induced Ulcer model, the ulcer is produced by excess secretion of acids and lowest pH. An increase in acid pepsin accumulation due to pyloric obstruction and subsequent mucosal digestion is the known mechanism of the induction of ulcer. The pylorus ligation study is the most important model to screen the antiulcer activity for evaluation of efficiency of extract. The antiulcer activities of HAAH in different concentration in pylorus ligation have shown a remarkable reduction in excess secretion of acids, pH, total acidity, free acidity, gastric volume and ulcer index. The reduction of reserpine induced ulcer by the extract in this study may be linked to its cytoprotective effect through antioxidant activity. The present study reveals that the hydro-alcoholic extract of *Artocarpus heterophyllus* Lam plant having the antiulcer activity in experimentally induced ulcer models in rats.

Conclusion

From present study of different concentration of extracts of *Artocarpus heterophyllus* Lam for antiulcer activities was concluded with a positive response in ulcer induced models such as Pylorus ligation, and Reserpine induced in compared with control. The reduction in ulcer index dose dependently in Reserpine and in Pylorus ligation induced ulcer by both 200 mg/kg and 400 mg/kg body weight both the extract of *Artocarpus heterophyllus* Lam fruit. In case of pylorus ligation ulcer there is decreased in volume of gastric juice, free acidity, total acidity, and increased in pH of gastric content by both the extracts. Histopathological investigation of the gastric mucosa of the rats pretreatment with hydroalcoholic extracts of fruits of *A heterophyllus* Lam reduces hemorrhagic necrosis in rats stomach in both models compared to control. The phyto chemical studies reveal the presence of flavonoids, tannin and polyphenolic compound in fruit extract. These compounds are responsible for protein precipation and vasoconstriction effect, destroy free radical and acts as anti oxidant. As fruit posses above activities thus may be responsible for anti ulcer activity.

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Evaluation of Prescription Pattren for Liver Cirrhosis; A Study in Government Teaching Hospital

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ABSTRACT

Liver cirrhosis is chronic, incurable condition that affects millions of people across the World. In this the prescribing practices in Liver cirrhosis patients were evaluated and monitored. Prospective observational study was conducted for 4 months on 25 cases. Study shows most of the patients belongs to the age group 31-40 followed by 41-50and 51-60 age groups. in which 22 patients are male and the remaining 3 were females. Almost all the patients are suffered from comorbidities such as portal hypertension, hepatic encephalopathy, and jaundice, diabetes. The assessment of drug interactions in this study shows drug interactions 16 prescriptions out of 25.In that 2 were major,12 were moderate,2 were minor. The major affected risk factor was Non-veg diet then alcohol, then Smoking. Majority of the patients are male, most of the people are middle aged, 64% drug interactions found, non;veg diet, alcohol are major risk factors, portal hypertension, hepatic encephalopathy are major comorbidities.

Keywords: liver cirrhosis, prescription, jaundice.

Introduction:

Liver cirrhosis is chronic, incurable condition that affects millions of people across the World. If not adequately managed, it can result in a range of complications that have clinical, social and economic implications. Commonly it affects middle age people. In this the prescribing practices in Liver cirrhosis patients were evaluated and monitored from time to time during the study period. From the literature survey various method of Rational treatment of liver cirrhosis,analysis of individual-level prescription data, Pharmaco-epidemiological study of prescription patterns,prescription database study,Prevalence and anti diabetic medication prescribing ,Evaluation of prescribing practices[6]. Drug interactions in prescriptions,prescription for elderly people[9] were reported[1]. But in present study the data is collected from various liver cirrhosis patients in Sri venkataramana ruya government(SVRRG) Hospital Tirupati. The study was conducted in the General medicine ward (inpatient) of SVRRG, Hospital Tirupati

AIM AND OBJECTIVE

The aim of the present study is evaluation of prescription pattern for liver cirrhosis and objective is to analyse age distribution, gender distribution, drug interactions involved in this study,co-morbid and risk factors involved in this study.

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METHODOLOGY

Place of the study:

Department of general medicine, Sri Venkata Ramnarain Ruia Government (SVRRG)general hospital, Tirupati.

Method of study:

Prospective observational study was conducted for 4 months (February 2013 to May2013) on 25 cases in the in-patient ward of General Medicine. The patients were followed from the date of admission till the date of discharge.

Design

The total no of patients enrolled in the study was 25. A data collection form was designed to collect patients' data including therapeutics management during hospitalization. All the liver cirrhosis patients from 30 to 80 years both male and female who are admitted in the department of general medicine were included in the study. Out patients, pregnant women and patients below 30 years were excluded from the study.

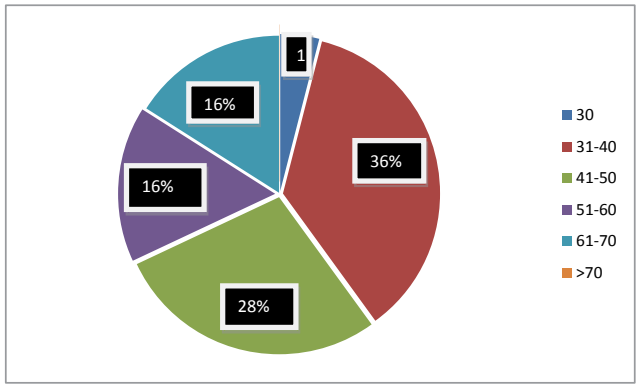
Procedure

The pooled data were analyzed to find the prescribing pattern of the drugs used in Liver cirrhosis patients. Analyzed drug-drug interaction, ADR &, with the help of www.drugs.com & other standard textbook (for drug interaction). The identified drug interactions were noted for further evaluation.The drug interactions, which were evaluated,

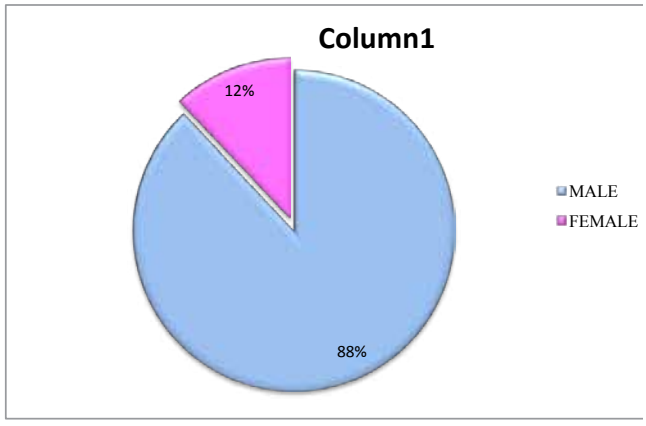
were made as report that includes the drug combination, effect, severity and clinical management.

RESULTS

Age Distribution:



Gender Distribution:



Risk factors involved in this study:

The risk factors for liver cirrhosis were assessed by their prescriptions ,Commonly affected risk factors were assessed in this study. The major affected risk factor was Non-veg diet ,the second priority goes to Alcohol, Next priority goes to Smoking.

Category	% distribution of total patients	% of male	% of female
Alcohol only	40	36	4
Smoking only	4	4	0
BothAlcoholic & smoking	32	32	0
Non-veg diet	44	60	12
Combination of Non-vegdiet &Alcoholic&Smoking	36	36	0

Liver Cirrhosis with co-morbidities:

Table 4

Liver Cirrhosis associated diseases:

S. No.	Associate diseases	Total No of patients	% distri-bution
1	Jaundice	1	4
2	portal hypertension	4	16
3	hepatic encephalopathy, portal hypertension	3	12
4	jaundice, hepatic encepha-lopathy	1	4
5	asthma, hepatic encephalopa-thy	1	4
6	anaemia, portal hypertension	1	4
7	bronchitis,hypertension	1	4
8	Diabetes	1	4
9	juandice,diabetes,portal hypertention	1	4
10	gastritis, pancreatitis	1	4

Drug interactions: The Drug interactions were assessed.16 prescriptions shows drug interactions out of 25.In that 2 were major, 12 prescriptions were moderate and 2 were minor Drug interactions[2].This information was given in figure 4.

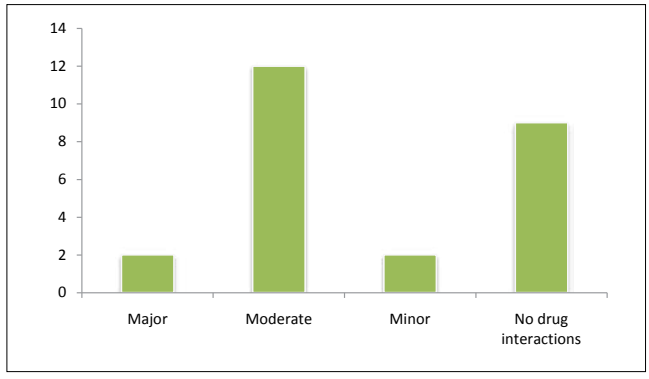


Fig 4.Drug interactions in liver cirrhosis

5. DISCUSSION:

The assessment of Age distribution in the study shows the majority of the patients belongs to the age group 31-40 followed by 41-50and 51-60 age groups. This study is saying that this disease is more in middle age people, there may be more chances to addict to alcohol and smoking .

In total of 25 patients were selected for the study who satisfies the inclusion and exclusion criteria in which 22 patients are male and the remaining 3 were females. From the results it can be assume that male are more than the female suffered by liver cirrhosis . One of the major reasons for this was most of male patients were addicted to alcohol and

smoking and female are less prone to alcohol and smoking in this locality. From the study we found that both of these two factors are more in males when compare to females.

After analyzing the commodities it is found that almost all the patients are suffered from other commodities such as portal hypertension, hepatic encephalopathy, and jaundice, diabetes etc[10]. The reason for this liver tissue unable to collect the blood from hepatic portal vein, unable to pump the blood to heart through superior venacava due to formation of scar tissue inside the liver. So the blood and fluid accumulated in the portal vein and remaining lower parts of the body. It leads to portal hypertension[4].

How cirrhosis associated with hepatic encephalopathy :

Alcohol's harmful effects on liver cells not only interfere not only with the normal functioning of the liver but also impact distant organs, including the brain. Prolonged liver dysfunction resulting from excessive alcohol consumption can lead to the development of a serious and potentially fatal brain disorder known as hepatic encephalopathy (HE). Analyses of brain tissue of HE patients found characteristic changes in the structure of supporting cells known as astrocytes[7].

Alcohol abuse and subsequent scarring of the liver cirrhosis can cause significant cell damage leading to jaundice.

The assessment of drug interactions in this study shows drug interactions 16 prescriptions out of 25.In that 2 were major,12 were moderate,2 were minor[2].Incase liver cirrhosis the liver unable to metabolises the drugs due to formation of scar tissue inside the liver and also the drug interactions may be due to the poor involvement of clinical pharmacist in medication chart reviewing[6].

The non-veg is a risk factor for fatty liver and it is the main reason for cirrhosis. This means that your liver is being stuffed with extra fat ,obese people are usually much prone to fatty liver. People who drink alcohol and consume a heavy, greasy, non-veg diet are the ones who usually suffer from fatty liver[8].

In fatty liver, normal healthy liver tissue is replaced by fat cells, thereby decreasing the efficacy of cleansing action of liver. Liver is the seat of all metabolism. Liver is responsible for metabolism of hormones, hunger, digestion, removal of toxins and many more important functions. The fatty liver is also palpable in some cases. Sometimes the liver enzymes are also raised in case of fatty liver. Liver is reddish pink in colour but the fatty liver become much yellower. The functions are all slowed down because of the clogging of the small channels by excess fat in and around liver cells. Poor liver function also affects levels of sugar and other hormones[9,10].

CONCLUSION:

Drug can be a useful tool in the prevention of and treatment of symptoms and diseases, but if not used properly, they may harmful and cause new symptoms or produce sub optimal effect. In this study prescribing practices in liver cirrhosis patients were evaluated. The sex distribution was analysed in this 88% were male and12% were female. Age distribution was also assessed the majority of people in between 31-40 only followed by41-50and51-60.

The drug interactions among the prescriptions analyzed was found to be 64%. Among the drug interactions found, 2 were minor, 12 moderate and 2 major[2]. Some adverse drug reaction was also found but not any serious event.The majorly occurred comorbidities were portal hypertension, hepatic encephalopathy[7].The Risk factors were assessed in this study majorly affected risk factor was Non-vegetarian such as 60%.The second one was Alcohol(36%).

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A Study on Pharmacotherapeutic Evaluation In Seropositives, Department of SVRR Government General Hospital, Tirupati, Andhra Pradesh, India

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ABSTRACT

Pharmacotherapeutic Evaluation is the evaluation of treatment whether it is appropriate or safe or effective.Here in case of HIV patients it is mandatory to evaluate drugs because different combinations of drugs have given and patient immune system also affected a lot so more chances to get Adverse drug reactions. Prospective observational study was conducted for 3 months on 16 cases in the in-patient ward.out of 16 45.4% are male patients between the age of 36-45 and 40% are female patients between the ages of 31-40 .HAART constituted 76% of the prescribed regimen.Before initiation of ART, Co-trimoxazole therapy of (31.25%) was observed for minimizing the opportunist infections ,more number of patients are associated with anemia (25%,The second most observed co morbid conditions include TB meningitis and malaria, peripheral neuropathy. The mostly prescribed ART is zidovudine combination therapy and then stavudine therapy, this therapy is appropriate . Adverse effects of ARV medicines are evident in patients taking first-line ARV regimens. Hence, in ART, alternative dosage regimen were followed to minimize the ART adverse reactions.

Keywords: seropositive, pharmacotherapy, ART..

Introduction:

Pharmacotherapeutic Evaluation is the evaluation of treatment or drug therapy whether it is appropriate or safe or effective. Here in case of HIV patients it is mandatory to evaluate treatment drugs because different combinations of drugs have given and patient immune system also affected a lot so more chances to get Adverse drug reactions[6].

Goals of ARV therapy

- To achieve maximal and durable virologic suppression (ideally a viral load < 50 copies/ml)
- To reconstitute and preserve immunologic function
- To reduce morbidity and mortality associated with both HIV infection and use of antiretroviral (ARVs)
- To improve quality of life
- Initiation of ART based upon CD_4 count
- Managing of opportunistic infections before starting ART
- Prophylaxis should be given for Opportunistic Infections[1]

Aim:

The aim of this work is to evaluate the rationale of pharmacotherapy in seropositive patients.

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Objective:

To analyze the appropriate usage of drugs, and its dose, and adverse drug reactions on seropositive patients. The co morbidities in seropositive patients were taken into account for classify the patient's category[9]. The drug induced anemia and peripheral neuropathy were also considered in patient treated for long term.

Methods:

Place of the study: Department of general medicine, Sri Venkata Ramnarain Ruia Government (SVRRG)general hospital, Tirupati.

Method of study: Prospective observational study was conducted for 3 months (August 2013 to October 2013) on 16 cases in the in-patient ward of General Medicine. The patients were followed from the date of admission till the date of discharge.

During the study, patients case records were reviewed and the following data were recorded in a patient proforma sheet namely demography, admitting diagnosis, case history, physician medication order sheet, nurses medication administration record and any other special findings.

Data Analysis:

Prescribed drug combinations were studied. Combinations were subsequently grouped into their

corresponding therapeutic category.These combination therapy include nucleoside analogue reverse trancriptase inhibitors (NRTIs) or highly active antiretroviral therapy (HAART) which includes 2NRTIs and either nonnucleoside reverse transcriptae inhibitors or protesase inhibitors[811,12]. Co-morbid conditions and therapy prescribed in that patients were also studied.Adverse drug reactions due to the therapy was studied and documented.

Results

Patient characteristics:

A total of 16 cases were studied among them data was collected from 13 patients on ARV therapy.

Table - 1

Demographic percentage of HIV-infected patients(sex), Tirupathi 2012.

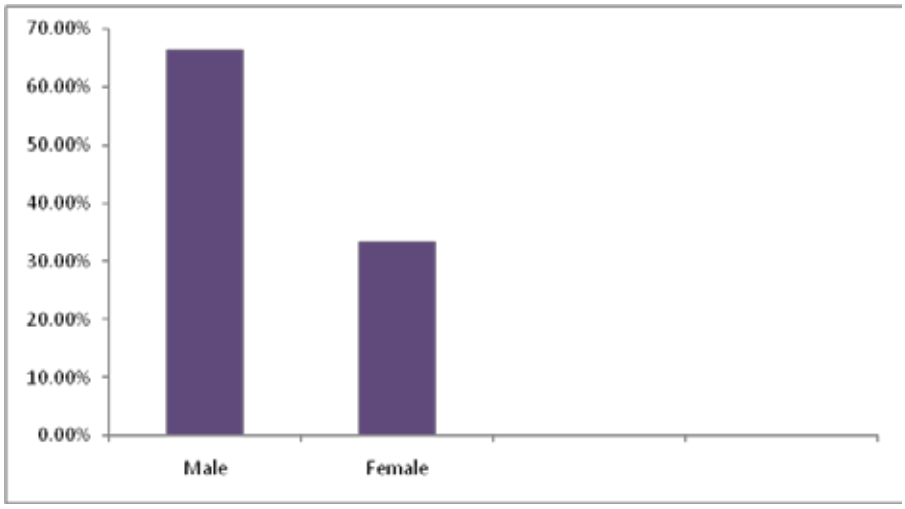


Table - 2

Demographic details of HIV-infected patients(age), Tirupathi 2012

Age	No of patients(%)
Range(years)	
Male	
26-35	4(36.4%)
36-45	5(45.4%)
46-55	1(9.1%)
56-65	1(9.1%)
Total	68.75% of men
Female	
21-30	1(20%)
31-40	2(40%)
41-50	1(20%)
51-60	1(20%)
Total	31.25% of women

Table - 3

Antiretroviral therapy use

Previous use of ARV therapy	No of patients
Yes	13(81.25%)
No	3(18.75%)

Table 4

HIV Patients with comorbid conditions

Comorbid conditions	No 0f patients
Drug induced Anemia	1(6.25%)
Congestive cardiac failure with drug induced with anemia	1(6.25%)
TB meningitis	2(12.5%)
Drug induced peripheral nephropathy	1(6.25%)
Malaria	2(12.5%)
Anemia and pyelonephritis	1(6.25%)
Pulmonary TB	1(6.25%)
Extra pyramidal syndrome	1(6.25%)
Anemia	4(25%)
Pyrexia of unknown origin	1(6.25%)
Seizures	1(6.25%)

Table 5

Number of HIV+/AIDS

HIV+ / AIDS	No of patients (%)
HIV+	5 (31.25%)
AIDS	11 (68.75%)

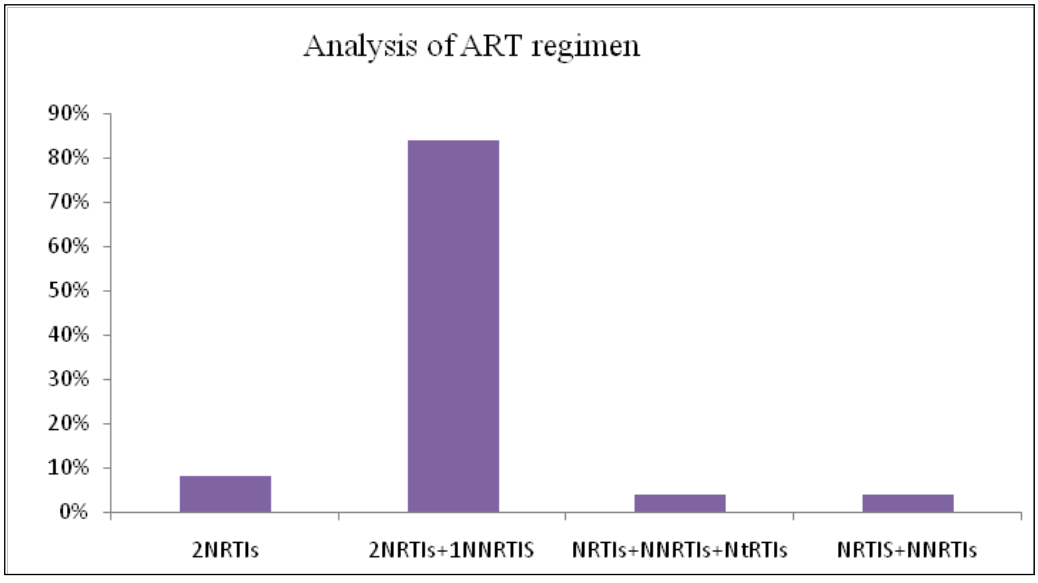
Table 6

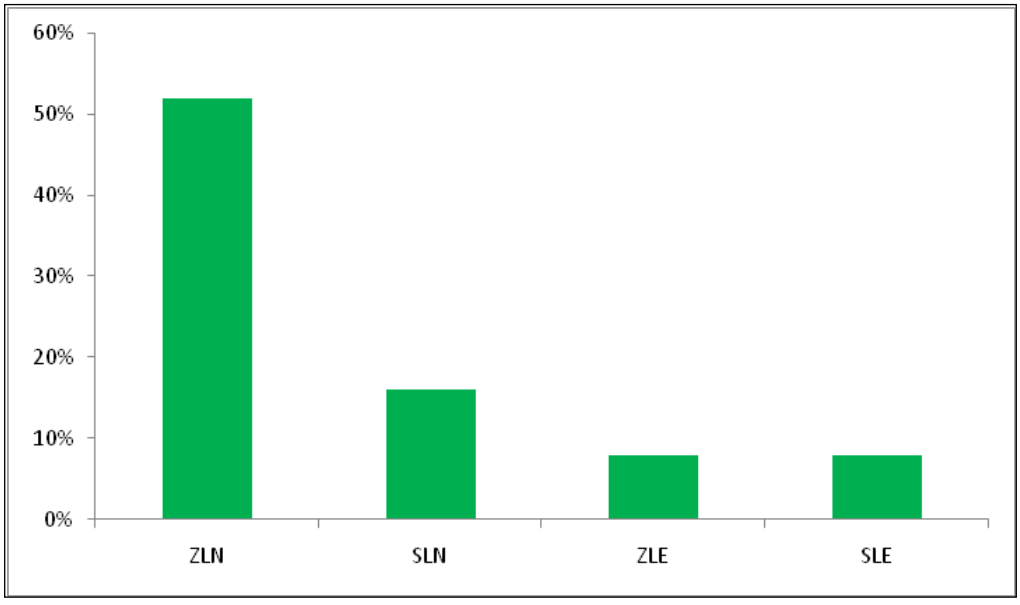
Co-trimoxazole prophylaxis therapy

Co-trimoxazole	No of patients (%)
Yes	31.25%
No	68.75%

Drug regimen	No.of prescriptions
2 NRTIs Zidovudine+ Lamivudine(3TC)	2(8%)
2NRTIs +1NNRTIs Zidovudine(ZDV) + Lamivudin+Nevirapine(NVP) - ZLN Stavudine(d4T) + Lamivudine + Nevirapine - SLN Azidothymidine +Lamivudine + Efavirenz - ZLE Stavudine(d4T)+ Lamivudine + Efavirenz - SLE	13(52%) 4(16%) 2(8%) 2(8%)
NRTIs +NNRTIs+ NtRTIs Lamivudine+ Nevirapine+ Tenofovir Disoproxil fumarate	1(4%)
NRTIs + NNRT Lamivudine+Efavirenz	1(4%)

Table 7 : Antiretroviral drug regimen prescribed[2]





Discussion

Sample demographics reveals that male patients of 45.4% between the age of 36-45 and female patients of 40% between the ages of 31-40 were mostly diagnosed as HIV+, female patients were less compared to males this may be due to social out casting. Among 16 patients 31.25% were HIV+ and remaining 68.75% were having AIDS, this is due to that the three patients were diagnosed recently as seropositive with no opportunistic infections and the remaining patient were having opportunistic infections such as TB meningitis, pulmonary TB etc,.

This study was conducted to evaluate ART dosage regimen. Alternatives therapy was given in response to adverse drug reactions of ART[14]. The hospitalized patients were monitored for co-morbid conditions.

We found more number of HAART prescription in patients taking ART[15]. HAART constituted 76% of the prescribed regimen[16]. HAART preferred over protease inhibitors (PI/r) based regimens considering similar potency, convenience, lesser expense and lower prevalence of primary resistance in the population[7,16].

Before initiation of ART, Co-trimoxazole prophylaxis therapy should be prescribed according to NACO guidelines[11,12]. Co-trimoxazole therapy of (31.25%) was observed, which indicates that following of poor guidelines regarding prophylaxis therapy.

The data collected regarding co-morbid conditions showed that the more number of patients are associated with anemia (25%) compared to the other co-morbid conditions. Anemia is mostly observed because infections like B19 parvovirus, Mycobacterium avium complex, Mycobacterium tuberculosis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans,Pneumocystis carinii infections due to the weakening of the immune system[17]. ART was not changed in these patients zidovudine therapy is continued as such.

The second most observed co morbid conditions include TB meningitis and malaria the former may be due to as the immunity declines in HIV, the clinical presentation of TB also changes because the body is not able to prevent the growth and spread of *Mycobacterium tuberculosis.* Therefore, disseminated and/or extra pulmonary TB occurs more commonly, although pulmonary tuberculosis (PTB) is still the most common form of TB disease and malaria.

ART induced condition's such as anemia and peripheral neuropathy were observed, anemia is caused due to Zidovudin in the dosage regimen this is due to bone marrow toxicity,[17] where as peripheral neuropathy is caused due to Stavudine therapy this is due to nerve damage in feet, legs, hands. In the former condition ART was stopped where as in later therapy was changed to zidovudine therapy.

Conclusion

The mostly prescribed ART is zidovudine combination therapy and then stavudine therapy,this therapy is appropriate according to the guidelines given[15]. Before starting the ART prophylaxis therapy with co trimoxazle is found to be very essential. Co trimoxazole therapy is prescribed to treat the opputunistic infections[5,15],[17]. Adverse effects of ARV medicines are evident in patients taking first-line ARV regimens.Hence in ART, alternative dosage regimen were followed to minimize the ART adverse reactions.

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Development and Validation of HPLC Method for Quantification of Nizatidine in Bulk and Microparticulate Dosage Form

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ABSTRACT

A simple and rapid HPLC method for quantification of nizatidine in bulk and microparticulate dosage form has been developed and validated. The standard and sample solutions were injected at 37°C into a C18 column. The elution was made in 3.6 min in isocratic mode with an UV detection at 314nm, using a mixture of methanol and water (70:30 v/v) as mobile phase. The linearity domain was established between 25 to 150 µg/ml with a correlation coefficient of 0.9994. The system suitability parameters were found to be within the acceptance limits. The limit of detection and limit of quantification were determined as 0.10µg/ml and 0.333 µg/ml. The %RSD values of method precision, intra-day and inter-day assay were found to be in the range of 0.48 – 2.39, 0.37 – 1.49 and 0.37 – 1.41 respectively. The recovery ranged between 88 - 95%. All the above mentioned findings indicated that the proposed method was proved to be specific, simple and fast and hence the validated method can be successfully applied for the estimation of nizatidine in microparticulate dosage form.

Key words: Nizatidine, Microparticles, HPLC, Validation.

Introduction

Nizatidine is a histamine H_2 antagonist and is chemically known as dimethyl[(4-{[(2-{[1-(methyl amino)-2-nitroethenyl] amino} ethyl)sulfonyl] methyl}-1, 3-thiazol-2-yl) methyl]amine (Fig.1). The compound belongs to the class of 2,4-disubstituted thiazoles. It inhibits the action of histamine mediated H2 receptors such as gastric acid and pepsin output and the drug is used for the treatment of duodenal ulcers [1,2].

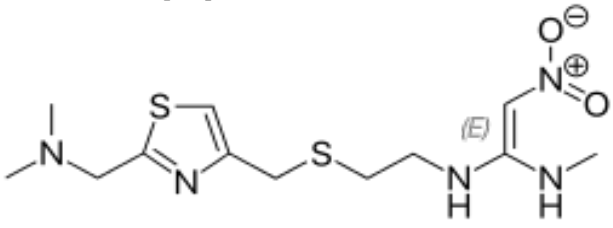

Fig. 1: Structure of Nizatidine

Nizatidine is an official drug of United States Pharmacopoeia (USP) [3], the HPLC procedures are described for the assay of bulk powder and dosage forms i.e, capsules. The literature survey regarding analytical methods for nizatidine estimation describes methods for estimation of nizatidine in bulk, pharmaceutical dosage forms and biological fluids, which includes liquid chromatography [4], UV spectrophotometry [5], stability indicating RP-HPLC method development and its validation [6], titrimetric method [7], RP-HPLC method for Nizatidine and its derivatives [8], kinetic spectrophotometric method [9], capillary zone electrophoresis [10] and head-column field-amplified sample stacking in capillary electrophoresis [11].

The aim of the study was to develop a new HPLC method and to exhibit validation strategies for the analysis of nizatidine in bulk powder and microparticles as per ICH guidelines.

Materials and Methods

Materials

Nizatidine drug sample was obtained as gift sample from Strides Shasun, Bangalore and Cuddalore, India. Analytical grade internal standard phenol was obtained from Himedia laboratory, Mumbai, India. HPLC grade methanol was obtained from Himedia laboratory, Mumbai, India. HPLC grade water was prepared using Milli-Q water purification system. Class A glassware was used throughout the experiment.

Instrumentation

The method was developed using Shimadzu HPLC system which consisted of RP-C18 Phenomenex column,

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operated in isocratic pump mode with the flow rate of 1mL/min, UV detection at 314nm and the injection volume of 5µL. The mobile phase consisted of water and methanol in the ratio of 70:30. The column oven temperature was maintained at 35°C. All the solutions were degassed by ultra-sonication. Mobile phase was filtered through 0.45µm membrane filter.

Preparation of standard and sample solutions

Standard solution: Accurately weighed about 100 mg of nizatidine working standard and transferred into 100mL clean, dry volumetric flask, about 10 mL of water was added and sonicated to dissolve. The volume was diluted with 30ml of methanol and the volume was made up using HPLC grade water to 100mL and mixed well to get a concentration of 1mg/ml (Stock I). Aliquots of 0.25 mL, 0.5 mL, 0.75 mL, 1.0 mL, 1.25 mL and 1.5 mL was transferred to 10 mL volumetric flask and diluted with mobile phase and mixed well to get a concentration ranging between 25 and 150 µg/ml.

Internal standard preparation: Internal standard used was phenol solution prepared using mobile phase methanol and water in the ratio of 70:30(v/v) to attain a concentration of 100 µg/mL[12].

Mobile phase: Mixture of water and methanol in the ratio of 70:30(v/v) was degassed and the solution was filtered through 0.45µm membrane filter.

Sample preparation: Microparticles equivalent to 100 mg of nizatidine was extracted into 25 mL methanol with the aid of sonication for 30 min then filtered into a 100 mL volumetric flask. The residue was washed with two 10 mL portions of methanol and washings were added to the filtrate. The filtrate was diluted to volume to get a final concentration of 1 mg/mL. From the above dilution 7.5 mL of sample solution was diluted to 100 mL using methanol to get the concentration of 75 µg/ml and the solution was filtered through 0.45 µm membrane filter. The sample solution was injected into the column and the chromatogram was recorded.

RESULTS AND DISCUSSION

Method development and optimization

Manipulation of mobile phase is an important factor for optimizing the seperation and elution of the analyte in HPLC. Taking into consideration, different parameters like resolution, peak shape *etc,* best results were obtained by varying the methanol concentration. To increase the sensitivity of the method, detection wavelength was selected at 314 nm at which nizatidine showed maximum absorption. Run time was set as 7 min and the retention time of nizatidine was found to be 3.6 min.

METHOD VALIDATION:

Validation of the proposed method was performed with respect to specificity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision and robustness according to ICH guidelines [13, 14].

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc. It was evaluated by injecting analytical placebo which was prepared in the same manner as that of sample preparation. The placebo (mixture of inactive ingredients) was spiked with standard and internal standard substances to check the interference by excipients used in the preparation. Specificity of the method was described by its ability to separate nizatidine peak from internal standard substance phenol and the proposed method showed that the excipients from formulation and the diluents do not interfere with the drug peak as shown in fig.2.

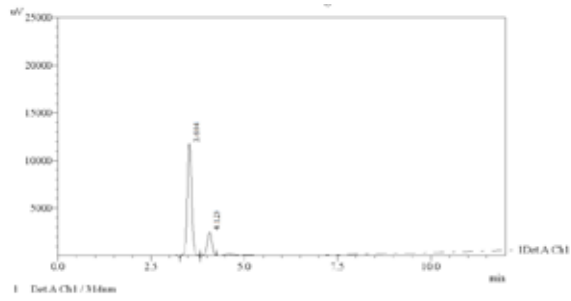

Fig. 2: Chromatogram obtained for blank spiked with nizatidine and internal standard substance

Linearity

The various concentrations of standard solutions of nizatidine were prepared by taking aliquots of 0.25 mL, 0.5 mL, 0.75 mL, 1.0 mL, 1.25 mL and 1.5 mL from SS-I and further diluting to 10 mL in a volumetric flask using mobile phase and mixed well to get a concentration range of 25-150 µg/ml. About 5 µl of each of these working standard solutions were injected into the chromatograph at a flow rate of 1ml/min. Retention time and peak area obtained were recorded and standard curve was plotted (Fig. 3) and linearity curve was defined by the following equation y = 15907x+12547, r = 0.9994, where y is the area and x is the concentration expressed in µg/ml (n = 3). The equation of linear regression and statistical data for nizatidine is presented in table 1. The linearity of the calibration curve for the drug was validated by the high value of correlation coefficient.

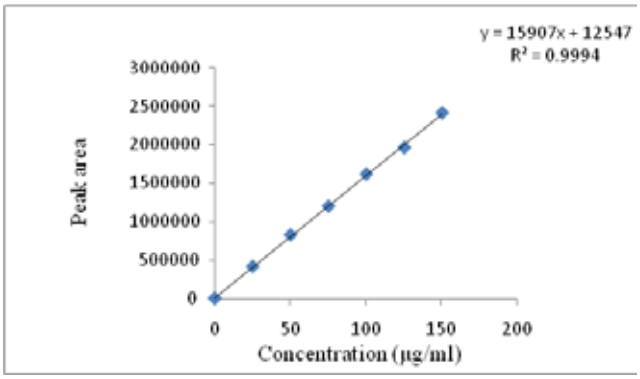

Fig. 3: Calibration curve of nizatidine

Table 1:
Statistical data of calibration curve of nizatidine

Parameters	Nizatidine
Linearity	25-150µg/ml
Regression equation	y = 15907x + 12547
Correlation coefficient (r^2)	0.9994
Limit of detection (LOD) (µg/ml)	0.10
Limit of quantification (LOQ) (µg/ml)	0.333

LOD and LOQ

The LOD and LOQ were determined by visualization method. In this method the dilutions containing very low drug concentration was successively prepared and injected into the chromatograph and the responses obtained were further recorded. Both LOD and LOQ values confirms the sensitivity of the proposed HPLC method. Results are presented in the table 1.

Precision

The method was investigated for system suitability test, method precision and intermediate precision. System suitability test ensures that the analytical system is working properly and can give accurate and precise results. System suitability test and method precision was carried out to monitor repeatability and reproducibility. Method precision was performed by injecting the standard solutions into the column in triplicate, the peak area and chromatograms were recorded. The standard deviation and % RSD for peak areas were also calculated and are shown in the table 2. System suitability parameters determined were well within the acceptable limits and indicated suitability of the method (Table 3).

Table 2:
Method Precision (N=3)

Working standard dilutions (µg/ml)	Mean	SD	% RSD
25	409987	9808	2.39
50	754026	3661	0.48
75	1171702	18914	1.61

Table 3:
System suitability parameters

System suitability factor	Nizatidine			Acceptance criteria
	25 µg/ml	50 µg/ml	75 µg/ml	
Theoretical plates	5258	5235	5214	>2000
HETP (mm)	27.99	28.65	29.33	-
Tailing factor	1.17	1.09	1.09	< 2

Intermediate precision was determined by the assay of sample sets in three cycles within day (intra-day) and three successive days (inter-day). In every cycle the sample was injected in triplicates, results are depicted in table 4. The calculated % RSD values of method precision, intra-day and inter-day precision were found within the limits specified.

Table 4:
Results of intermediate precision

	Taken (µg/ml)	Found ±SD (µg/ml))	RSD %
INTRA-DAY	25	25.92±0.3	1.49
	50	47.53±0.27	0.56
	75	74.28±0.27	0.37
INTER-DAY	25	25.63±0.36	1.41
	50	47.26±0.07	0.15
	75	74.07±0.32	0.37

Accuracy

It is used to determine the amount of drug recovered from the formulation. Recovery experiments were performed spiking the sample with analyte concentrations at 3 different levels i.e, 80%, 100% and 120%. The samples were injected and chromatograms were recorded. The recovery was found to be between 88 – 95% which depicts the accuracy of method for analysis (Table 5).

Robustness

Robustness was determined by carrying out estimation with small but deliberate variations in methanol content in the mobile phase (+2 mL), flow rate (+0.05 mL/min) and working wavelength (+2 nm). The robustness of the method

Table 5

Results of Accuracy (Recovery studies) (N=3)

Level	Amount of standard (μg/ml)	Amount of sample (μg/ml)	Total Conc. (μg/ml)	Amount found (μg/ml)±SD	Recovery (%)	%RSD
80%	22.5	37.5	60	42.38±0.18	88.35	0.42
100%	37.5	37.5	75	69.88±0.43	86.34	0.61
120%	52.5	37.5	90	102.21±0.28	94.68	0.27

Table 6:

Results of robustness

Chromatographic parameters	Peak area	Retention time (min)
Mobile phase, Methanol: Water (30:70)		
28:72	1060874	3.82
30:70	1165106	3.6
32:68	1115077	3.4
Recovery %	88.78	-
Flow rate (mL/min)		
0.95	1140532	3.9
1.0	1176896	3.6
1.05	1062915	3.54
Recovery %	86.50	3.6
Detection Wavelength (nm)		
312	1071882	3.76
314	1169872	3.6
316	1140532	3.69
Recovery %	89.53	-

was validated based on the % recovery of nizatidine. The results are shown in table 6.

Conclusion

A simple, rapid and sensitive HPLC method was developed for the analysis of nizatidine in bulk and microparticles. The established concentration range showed linearity with correlation coefficient of 0.999 and recovery within the range of 88-95 %. The % RSD values of method precision, inter-day and intra-day and accuracy were found to be less than 2.4 %, which indicates that the measurement of nizatidine in different prevailing conditions is precise and accurate. The method is comparatively advantageous as it is economical, involves simple instrumentation and sample preparation, low injection volume and short run time making the method appropriate for handling multiple samples. The proposed method is sensitive enough to determine low concentration of nizatidine as LOD and LOQ were found to be 0.10 and 0.33 μg/ml respectively. Hence, it can be concluded that this method can be successfully employed to determine nizatidine in bulk and microparticulate based formulation, since the method is simple, accurate, quick, specific and reproducible.

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