RP-HPLC ASSAY METHOD FOR SIMULTANEOUS DETERMINATION OF PERINDOPRIL ERBUMINE AND INDAPAMIDE COMBINATION IN BULK AND TABLET DOSAGE FORM

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ABSTRACT

The present paper deals with the development and validation of a stability indicating reverse phase HPLC method for the Simultaneous Determination of Perindopril Erbumine and Indapamide on Phenomenex Luna C18 column (250mm × 4.6mm, 10ìm). A mobile phase consisting of Acetonitrile : Buffer pH 2.8 (40 : 60 % v/v) was used. The flow rate was 1.2 mL min^{-1}. The separation was performed at room temperature. Detection was carried out at 225 nm by UV detection. Separation was completed within 10 min. The developed method was statistically validated for linearity, accuracy, specificity, Method precision, Intermediate Precision and stability. Calibration curves were linear with correlation coefficient between 0.99 to 1.0 over a concentration range of 70–130% (2.8 to 5.2 ìg mL^{-1}) of Perindopril Erbumine and 70–130% (0.88 to 1.63 ìg mL^{-1}) for Indapamide respectively. The relative standard deviation (R.S.D) was found <2.0%. This method was successfully used for quantification of Perindopril Erbumine and Indapamide combination in Bulk and tablet formulations.

Key words: *Perindopril Erbumine (PE); Indapamide; RP-HPLC; stability; validation; Simultaneous determination*

INTRODUCTION

Perindopril Erbumine (PE), chemically 2-Methylpropan-2-amine(2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate. It is freely soluble in water and in ethanol (96%), sparingly soluble in methylene chloride. Indapamide, chemically Benzamide, 3-(aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl).

It is practically insoluble in water, soluble in ethanol (96%), methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene. PE and Indapamide both the drugs are beneficial in treatment of hypertension. PE, shown in Fig. 1 and indapamide, shown in Fig. 2. PE drug is listed in BP and indapamide drug is listed in BP and USP[1-3].
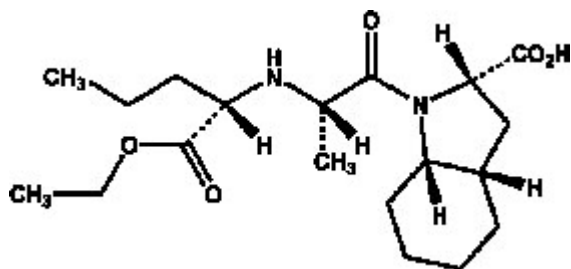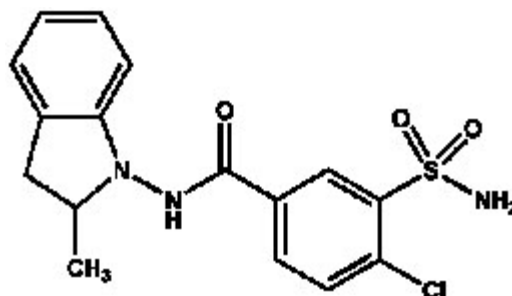

Fig. 2: The chemical structure of indapamide.

Literature survey reveals that few methods have been reported for the estimation of PE and Indapamide in combination and individual method by using UV spectrophotometric[4-5], HPLC[6], Plasma RP-HPLC[7-8] and LC[9]. This paper describes the validation of an analytical method with RP-HPLC analysis for the simultaneous estimation of both the drugs in bulk and combined tablet dosage form as per current ICH[10,11] and FDA [12] guideline.

Stability is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating periods [13]. Stability testing of an active substance or finished product provide evidence on how the quality of a drug substance or drug product varies with time

Fig. 1: Chemical structures of PE

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influenced by a variety of environmental factors such as temperature, humidity and light. Knowledge from stability studies enables understanding of the long-term effects of the environment on drugs. Stability testing provides information about degradation mechanisms, potential degradation products, possible degradation pathways of the drug as well as interaction between the drug and the excipients in drug product. Results are applied in development of manufacturing processes, selecting proper packaging, storage conditions, product's shelf life and expiration dates. Because the distribution environment is highly variable, products must be distributed in a manner that ensures that the product quality will not be adversely affected. The effect of possible temperature and humidity fluctuations, outside of labeled storage conditions, during transportation of drug products, can be evaluated on the basis of the stability analysis for that drug [14-17].

Validation of an analytical method typically involves for linearity, accuracy, specificity, Method precision, Intermediate Precision and stability. A number of papers have been published detailing validation studies for the analytical method [18–22]. The purpose of this study was to develop simple, rapid, precise and accurate RP-HPLC method for the simultaneous estimation of both the drugs in bulk and combined tablet dosage form.

EXPERIMENTAL
Materials
Potassium dihydrogen phosphate, NaOH, both reagent grade, and acetonitrile (HPLC grade) were obtained from Merck Chemicals. Ortho phosphoric acid (AR Grade) was obtained from (LOBA Chemicals). Purified water for chromatography was obtained from a Milli-Q purification unit (Millipore, Milford, MA, USA). Perundopril Ebrumine and indapamide drug was obtained as a gift sample (Mepro Pharmaceuticals Pvt. Ltd., Surendranagar, India).

Instrumentation and chromatographic conditions
The HPLC system used was Shimadzu HPLC system LC-2010CHT Version 3.10 (Shimadzu; Japan) with UV detector, the reversed-phase procedure utilized a Phenomenex Luna C_{18} column (10 ☐m; 250 mm × 4.6 mm i.d.) and UV detection at 225 nm. This wavelength was selected because it is a UV maximum and provides the sensitivity needed for quantitation of the low drug concentration. The column temperature was maintained at 50æ%C. The mobile phase contained acetonitrile, buffer pH 2.8 (40:60, v/v, respectively). The flow rate was 1.2 mL/min for 10 min with an injection volume of 50 µL.

Preparation of stock and working standard solution
Perindopril Erbumine (PE) standard stock solution - A
Weigh accurately 50 mg of Perindopril Erbumine WS and transfer into 500 ml of volumetric flask. Dissolve and make the volume up to the mark with diluting solution. (100 µg/ml).

Indapamide standard stock solution –B
Weighed accurately 25 mg of Indapamide WS and transfer into 250 ml of volumetric flask. Dissolve and make the volume up to the mark with diluting solution. (100 µg/ml)

Perindopril Erbumine (PE) and Indapamide standard solution
The 1.0 ml of standard stock solution A was transferred in 32 ml diluting solution in 50 ml volumetric flask & 1.0 ml of standard stock solution B was transferred to a 10 ml volumetric flask, made the volume up to the mark with diluting solution. So the final concentration of Perindopril Erbumine was 32.0 µg/ml & Indapamide was10.0 µg/ml.

Preparation of sample solution
The 20 tablets were weighed and powdered. The crushed powder equivalent to 1.6 mg of Perindopril Erbumine & 0.5 mg of Indapamide and transferred into a 50 mL volumetric flask. The 35 mL diluting solution added and sonicated for 20 minutes to dissolve. Cooled and the volume made up to the mark with diluting solution, Filtered through 0.45 µ filter paper. From the above filtrate first few mL of filtrate discarded and remaining filtrate for analysis was used. So the concentration of Perindopril Erbumine was 32.0 µg/mL & Indapamide was 10.0 µg/mL.

RESULTS AND DISCUSSION
The method was validated for linearity, accuracy, specificity, Method precision, Intermediate Precision and stability study as per ICH guideline. All the validation studies were carried out by replicate injection of the sample and standard solutions. The chromatogram of PE and indapamide is shown in Fig. 3.
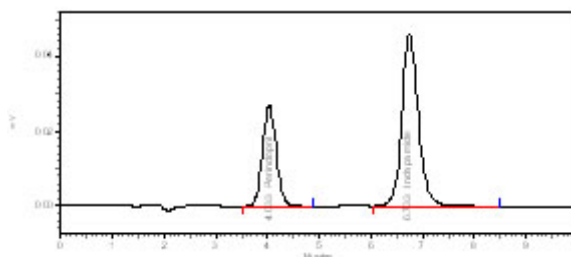

Fig. 3: Chromatogram of Perindopril erbumine and indapamide

Seven different concentrations range 70 % to 130 % of a mixture of all drugs were prepared for linearity studies. The response was measured as peak area. The calibration curve obtained by plotting peak area against concentration showed linearity in the concentration range 70–130% drug concentration of PE (22.4, 25.6, 28.8, 32.0, 35.2, 38.4 and 41.6 µg/mL) and indapamide (7.0, 8.0, 9.0, 10.0, 11.0, 12.0 and 13.0 µg/mL). Fig. 4 shows the best fit for the calibration curve could be achieved by a linear regression equation of PE and indapamide found to be y = 10229x + 61991,

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and y = 48253x + 29019 respectively and the regression coefficient values (R²) were found to be 0.999and 0.998 respectively indicating a high degree of linearity for both drugs.

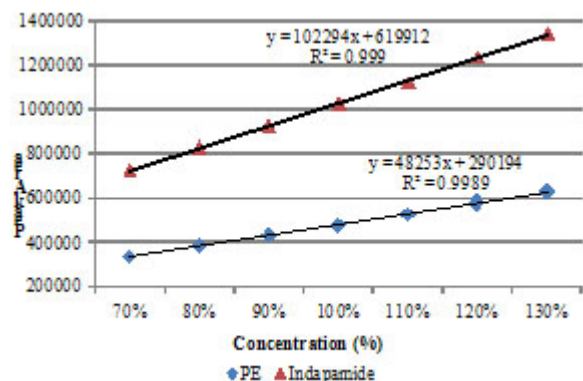**Fig. 4:** *Calibration curve for PE and indapaminde*

Accuracy of developed method was confirmed by doing recovery study as per ICH norms at three different concentration levels 80%, 100% and 120% by replicate analysis (n=3). The result of accuracy study was reported in Table 1. From the recovery study it was clear that the method is very accurate for quantitative estimation of PE and indapamide in tablet dosage form as all the statistical results were within the range of acceptance.

Table 1. *Recovery Studies*

Drug	Amount taken (µgmL⁻¹)	Amount added		% Recovery	%RSD
		%	(µgm L⁻¹) (n=3)		
PE	40.0	80	32.0	100.77	0.12
		100	40.0	100.42	0.07
		120	48.0	100.83	0.04
Indapamide	12.5	80	10.0	100.16	0.26
		100	12.5	100.28	0.43
		120	15.0	100.65	0.23

The specificity of the method was evaluated by injecting an aliquot of the blank (i.e., mobile phase) and the following:

(1) a solution containing the APIs at nominal concentration,

(2) a placebo solution prepared from a synthetic blend of the tablet excipients, and

(3) a sample solution prepared from a synthetic blend of the APIs and tablet excipients. These solutions were prepared in Purified water and sonicate at 37°C for 20 min prior to being injected into the chromatographic system. As shown in Fig. 5, there was no system, filter or excipient-related peak that interfered with the quantitation of either active ingredient. These results demonstrate the specificity of the method.
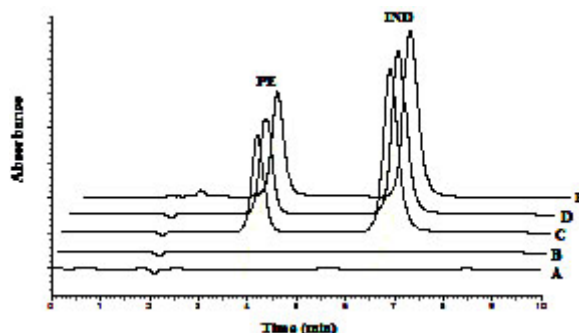

Fig. 5. *Representative of specificity chromatograms: A=blank, B=placebo, C=standard, D= standard + placebo, E=sample, PE=Perindopril Erbumine, IND=indapamide.*

The system precision of the method was evaluated by performing six replicate injections of a sample at the nominal PE (2.0/4.0) and indapamide (0.625/1.25) mg tablets (4 µg/mL PE and 1.25 µg/mL indapamide) standard concentrations. The sample was a synthetic blend of drug and excipients. The peak area R.S.D. (%) of PE was 0.34% and indapamide was 0.21% which was considered acceptable.

The R.S.D. (%) of the sample response factor was calculated for six separate preparations at the nominal standard concentration of the PE (2.0/4.0) and indapamide (0.625/1.25) mg tablets (4 µg/mL PE and 1.25 µg/mL indapamide). The sample was a synthetic blend of drug and excipients. The peak area R.S.D. (%) of PE was 1.09% and indapamide was 0.32%, which was considered acceptable for these low doses drug product formulations. The results are shown in Table 2.

Table 2. *Result of Method Precision and Intermediate Precision of Test Method*

Sample	Assay of PE and Indapamide at % of labeled amount			
	Analyst-1 (Intra-day precision)		Analyst-2 (Inter-day precision)	
	PE	Indapamide	PE	Indapamide
1	99.92	100.57	99.18	100.84
2	100.33	100.54	101.34	100.59
3	98.28	100.95	100.34	99.98
4	97.74	101.17	101.52	100.46
5	97.99	101.15	102.13	100.07
6	98.47	101.31	100.04	99.90
SD	1.07271	0.32572	1.09381	0.37851
%RSD	1.09	0.32	1.09	0.38

The intermediate precision of the method was determined by six replicate analysis of sample, by different analyst using different instruments, different columns, on different days at the nominal standard concentration of the PE (2.0/4.0) and indapamide (0.625/1.25) mg tablets (4 µg/mL PE and 1.25 µg/mL indapamide). Fresh sample and standard solutions were independently prepared on each day of analysis. The peak area R.S.D. (%) of PE was 1.09% and indapamide was 0.38%, which was considered acceptable for drug product formulations. The results are shown in Table 2.

The combined standard solution of PE and indapamide was stored at two different conditions (room temperature and 8°C), unprotected from light, at ambient conditions and assayed after initial, 4, 8, 12, 16, 20 and 24 hours against a initial prepared standard solution. All of the assay results during this time period were within 98–102% of the initial value and % response from initial is NMT 2 therefore no degradation products were observed in any of the chromatograms. The standard solution is therefore considered stable for at least 24 hours under normal laboratory conditions and 8°C conditions. The results are shown in Table 3.

Table 3. Result of Solution Stability

Time (Hours)	Stability at room temperature (% Response from initial)		Stability at 8°C (% Response from initial)	
	PE	Indapamide	PE	Indapamide
Initial	NA	NA	NA	NA
4	1.72	0.03	1.85	0.01
8	0.11	0.73	1.49	-0.08
12	1.04	0.79	1.66	-1.07
16	0.10	0.67	1.05	-0.46
20	1.60	0.36	0.29	-0.26
24	-0.14	-0.04	0.81	-0.54

CONCLUSION

A new, reversed-phase HPLC method has been developed for simultaneous analysis of PE and indapamide in a tablet formulation. The method is linear, accurate, reproducible, repeatable, precise, selective and specific proving the reliability of the method. The run time is relatively short, i.e. 10 min, which enable rapid determination of many samples in routine and quality control analysis of tablet formulations.

This study presents a simple and validated stability-indicating HPLC method for estimation of PE and indapamide in the presence of degradation products. The developed method was specific and stability-indicating. The method could be applied with success even to the analysis of marketed products PE and indapamide formulation, as no interference was observed due to excipients or other components present

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HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECTS OF ALCOHOLIC EXTRACT OF *MIMOSA CATECHU* BARK IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

Herbal medicine has been used for many years by different cultures around the world for the treatment of diabetes and hence the alcoholic bark extract of *Mimosa catechu* **(AEMC)** Wild plant was investigated for its possible antihyperglycemic effect in alloxan induced diabetic rats. The animals were made diabetic by intraperitoneal injection of alloxan monohydrate at a dose of 150mg/kg body weight. The alcoholic extract of *Mimosa catechu*, AEMC (250 and 500mg kg^{-1}) and the standard drug (Glibenclamide 0.5mg/kg) were administered orally. Control group of rats were administered 0.2ml of 10% acacia mucilage (vehicle). The effect of oral administration of AEMC for 7days on the levels of Serum glucose, total cholesterol, and triglycerides, HDL-cholesterol, LDL-cholesterol in normal and diabetic rats were evaluated and compared with that of standard antidiabetic drug, Glibenclamide. Oral administration of 250 and 500mg kg^{-1} body wt of AEMC for 7 days exhibited a significant reduction in serum glucose, total cholesterol, triglycerides, LDL-cholesterol and increase in HDL-cholesterol, Plasma insulin in alloxan induced diabetic rats. The antidiabetic effect of AEMC was similar to Glibenclamide. Hence our study reveals the antidiabetic and Hypolipidemic potential of *Mimosa catechu* bark and the study could be helpful to develop medicinal preparations for diabetes and related symptoms.

Key words: *Mimosa catechu; Hypoglycemic Activity; Hypolipidemic activity; Alloxan; Glibenclamide.*

INTRODUCTION

Diabetes mellitus is a global disease that is a major cause of morbidity in the world. This disorder is basically characterized by high levels of blood glucose caused by defective insulin production and action that are often responsible for severe health problems and death[1]. The commonly encountered acute and late diabetic complications are already responsible for major causes of morbidity, disability and premature death in Asian countries[2]. Hyperglycemic condition causes increased glycosylation leading to biochemical and morphological abnormalities due to altered protein structure which over a period of time develops diabetic complications such as nephropathy, retinopathy, neuropathy and cardiomyopathy[3]. Diabetic patients, particularly those with type II diabetes are at considerable risk of excessive morbidity and mortality from cardiovascular, cerebrovascular and peripheral vascular diseases leading to myocardial infarction, strokes and amputations [4].

Recent decades have shown a resurgent interest in traditional plant treatments for diabetes, which has pervaded nutrition. The pharmaceutical industry and academic research fueled by a growing public interest and awareness of so called complementary and natural types of medicine [5]. Many traditional plant treatments for diabetes exist, wherein lies a hidden wealth of potentially useful natural products for diabetes control [6]. *Mimosa catechu* Wild (Family: Fabaceae and Subfamily: Mimosidaea) known as Black cutch, is a deciduous thorn like tree mainly found in India and also found in deciduous forests around the world. The leaves and heartwood has many nutritional and medicinal uses. The extract of *Mimosa catechu* has been reported to have various pharmacological effects like immunomodulatory[7], antipyretic, hypoglycemic[8], antidiarrhoeal [9], and hepatoprotective activities [10]. However, there are no scientific studies available on the antidiabetic effect of *Mimosa catechu* bark extract. Therefore, the anti-diabetic effect of alcoholic extract of Mimosa catechu (AEMC) bark was investigated in diabetic rats.

MATERIALS AND METHODS

Procurement and identification of plant material

The fresh bark of plant was collected from a village named Punyakshethram, which is about 20km away from Rajahmundry, during October. The plant was

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identified and authenticated as *Mimosa catechu* by the Taxonomist, Dr. T.U.Raghuram.

Preparation of the extract

Bark of Mimosa catechu was dried under shade for two weeks. Dried bark was coarsely powdered and stored in air tight container at room temperature. Dried powder was then extracted repeatedly with alcohol by maceration followed by hot percolation process. The extract was then concentrated by drying and the yield was found to be 17.78%.

Drugs and chemicals

Alloxan monohydrate was procured from Loba Chemie Laboratory Reagents and Fine Chemicals, Mumbai. Glibenclamide (Batch no: G080851) was a gifted sample from Tablets India Ltd, Chennai. Standard Glucose estimation kits were procured from Robonik (India) Pvt.Ltd, Mumbai. Enzymatic kits for the estimation of lipid profile were obtained from Chema Diagnostica (India).

Animals

Albino rats (150–200 g) of both sexes were selected and acclimatized to the experimental room at temperature $23\pm2\text{°C}$, controlled humidity conditions (50–55%) and 12 h light/dark cycle. They were caged with a maximum of three animals in polypropylene cage and were fed with standard food pellets and water *ad libitum*.

Experimental design

Induction of experimental diabetes

Albino rats (n=24) were fasted for 16 to 18hrs. Diabetes was induced by administering freshly prepared alloxan monohydrate in normal saline intraperitoneally at a dose of 150mg/kg body weight as single dose[11]. After 72hrs of alloxan induction, fasting blood was collected and blood sugar was estimated by glucose oxidase method. Only those animals which showed blood glucose levels >250mg/dl were separated and used for the study.

Treatment protocol

All the rats were randomized into four groups comprising of six animals in each group as given below.

Group I   : diabetic control
Group II   : diabetic rats received AEMC - 250mg/kg
Group III : diabetic rats received AEMC -500mg/kg
Group IV : diabetic rats received Glibenclamide -
               0.5mg/kg

Vehicle or AEMC (250 and 500 mg/kg) and Glibenclamide (0.5mg/kg) were administered orally using an intra-gastric tube once daily for 7days and blood glucose levels were monitored at 0, 2, 4 and 24 hrs after the administration of single dose of AEMC or Glibenclamide (for acute study) as well as on the 1st, 3rd, 5th, and 7th day respectively (for prolonged effect). Percentage reduction in serum glucose was calculated with respect to the initial level.

Collection of blood samples and estimation of Biochemical parameters

For the purpose of biochemical estimation, blood samples were collected by snipping the tail vein on day 1 and 7 before the feeding of morning dose of the drugs. Blood samples were allowed to clot for 30 min and serum was separated by centrifugation at 3000rpm[12].

Determination of blood glucose levels

Serum glucose levels were estimated by glucose–oxidase–peroxidase (GOP –POD) method in Prietest touch auto biochemistry analyzer (version 2.6228) using the standard kits obtained from Robonik (India) Pvt.Ltd, Mumbai.

Determination of serum lipid profile

Serum cholesterol[13] and triglycerides[14] were estimated on initial and final days of experiment of each model by CHOD – POD method and enzymatic colorimetric method (GPO which is highly influenced by level of fasting). HDL[15] cholesterol was determined by using standard enzymatic kits obtained from ROBONIK (INDIA) PVT.LTD, Mumbai. While the LDLC[16] was derived from cholesterol and triglyceride values, VLDL cholesterol value was derived from cholesterol and HDL values.

Determination of serum insulin levels

For the estimation of serum insulin, blood samples were collected by snipping the tail vein on day 7 before the feeding of morning dose of the drugs. Blood samples were allowed to clot for 30 min and serum was separated after centrifugation at 3000rpm for 10min. Serum insulin levels were determined by solid phase radioimmunoassay method (INSU – R.I.A) (lab code: 100401889/AND15) and (barcode: 14474773/AND15).

Histopathological study

After collecting blood sample on 7th day, immediately the rats were sacrificed by mild ether anesthesia and pancreas was collected, excised and rinsed in ice-cold 0.9% saline solution. For Histopathological studies the pancreas was blotted, dried and fixed in 10% formalin for 48 h. Thereafter, the tissues were dehydrated in acetone for 1 h and embedded in paraffin wax. Section of pancreatic tissues were then taken through microtome and stained with haematoxylin-eosin for photo microscopic observation[17].

Statistical analysis

All the values of body weight, fasting blood sugar, and biochemical estimations were expressed as mean ± standard error of mean (S.E.M.) and analyzed for ONE WAY ANOVA and post hoc Dunnett's t-test using computerized Graph Pad Prism In Stat version 5.0, Graph Pad software. Differences between groups were considered significant at *P<0.001* and very significant at *P< 0.0001* levels.

RESULTS

There was a significant elevation in serum glucose, total cholesterol, triglycerides while the serum insulin and HDL-C levels significantly decreased in the diabetic control rats after the single i.p injection of alloxan monohydrate at o dose of 150mg/kg.

Changes in the body weight of diabetic and treated rats

As shown in the *Table 1*, diabetic control rats showed a slight but significant reduction in body weight during 7 days which is reversed by the alcoholic extract of *Mimosa catechu* bark after 7 days of treatment.

Table 1: Effect of AEMC bark on body weight (gm) in alloxan induced diabetic rats

GROUP	TREATMENT	AVG BODY WT (gm) ± SEM			
		Day 1	Day 3	Day 6	Day 7
I	Diabetic control (DC)	110±12.65	109.67±14.7	109.33±14.9	107.3±13.76
II	DC + AEMC (250mg/kg)	140±5.4	142.67±7.14	144.3±7.57	151.47±118
III	DC + AEMC (500mg/kg)	163.3±15.32	162.96±14.7	166.67±13.09	174.03±9.6
IV	DC + GLB (0.5mg/kg)	123.3±9.42	124.33±9.4	124.33±9.4	135.9±11.99

Values are expressed as Mean ± SEM

Changes in serum glucose levels

Tables 2 and 3 represent the hypoglycemic effect of the extract on the fasting blood sugar levels of alloxan induced diabetic rats. Administration of alloxan (150mg/kg, i.p) led to 2–3 fold elevation of fasting blood glucose levels, which was maintained over a period of one week and the daily treatment with extract led to a dose-dependent fall in blood sugar levels by 60 – 77%.

Table 2: Effect of AEMC bark on blood glucose level (mg/dl) in alloxan induced diabetic rats on day 1 of the treatment (ACUTE STUDY)

GROUP	TREATMENT	FASTING BLOOD GLUCOSE LEVEL (mg/dl)			
		0hr	2'' hr	4'' hr	24'' hr
I	Diabetic control (DC)	299.7±4.86	273±6.98*	260.33±4.07*	296±3.92
II	DC + AEMC 250mg/kg	365.5±10.54	293.83±8.36***	251.33±7.36***	360±0.46
III	DC + AEMC 500mg/kg	393±10.5	323.83±8.51***	251.83±9.65***	396±9.57
IV	DC + GLB 0.5mg/kg	370.67±15.24	291.33±9.225***	219.5±9.28***	382±14.63

*Values are expressed as Mean ± SEM; *P<0.001; **P<0.001; ***P<0.0001*

Table 3: Effect of AEMC bark on blood glucose level (mg/dl) in alloxan induced diabetic rats

GROUP	TREATMENT	FASTING BLOOD GLUCOSE LEVELS (mg/dl)				
		0 day	1'' day	3'' day	5'' day	7'' day
I	Diabetic control (DC)	299.7±4.86	293.6±9.07	272.33±8.34	268.6±10.97	251.8±10.29*
II	DC + AEMC (250mg/kg)	365.5±10.54	261.3±7.36***	245.5±6.59***	188.8±9.36***	144.5±4.50***
III	DC + AEMC (500mg/kg)	393±10.54	261.8±7.65***	191.5±6.13***	148.16±4.12***	97.33±2.82***
IV	DC + GLB (0.5mg/kg)	370.67±15.24	219.5±9.28***	151.5±6.33***	111.33±4.84***	87±8.15***

*Values are expressed as Mean ± SEM; **P<0.001; ***P<0.0001*

Changes in lipid profile

Alcoholic extract of *Mimosa catechu* bark lowered the triglyceride levels significantly (p<0.0001) from day 1 value of 264mg/dl to 142.5mg/dl and 35mg/dl on day 7 at a dose of 250mg kg⁻¹ and 500mg kg⁻¹ respectively. A slight but significant change was observed in serum cholesterol levels in extract treated group and it was 83mg/dl on day 1 while it was 74.7mg/dl and 68mg/dl on day 7 at a dose of 250mg kg⁻¹ and 500mg kg⁻¹ respectively. A very significant reduction in the VLDL-C levels was observed with the extract treated group of animals. The results were shown in *Table 4*.

Table 4: Effect of AEMC bark on serum lipid profile in alloxan induced diabetic rats after 7 days treatment

GROUP	TREATMENT	TC	TG	HDL	LDL	VLDL	TC:HDL	LDL:HDL
I	Diabetic control (DC)	85±0.41	264±2.12	27.50±0.61	8.1±2.3	52.92±0.89	3.15	0.404
II	DC + AEMC (250mg/kg)	74.7±0.42***	142.5±1.7**	21.9±1.81	24.23±5.0	28.5±0.4***	3.40	1.10
III	DC + AEMC (500mg/kg)	68±0.65***	35±0.95***	22.50±7.36	38.70±6.7***	7.0±0.02***	3.05	1.4
IV	DC + GLB (0.5mg/kg)	65±0.26***	26.1±2.40	20.1±0.45	7.7±2.0	5.1±0.089	3.18	0.35

*TC= total cholesterol; TG= triglycerides; HDL= high density lipoproteins; LDL= low density lipoproteins; and VLDL= very low density lipoproteins. All the values are expressed as Mean ± SEM and are very significant at ***P<0.0001*

Changes in serum insulin levels of diabetic and treated group of animals

After 7 days treatment period, it was observed that the animals treated with alcoholic extract of Mimosa catechu bark (AEMC) showed a significant increase in the serum insulin levels from 2.43µIU/ml to 3.21µIU/ml (32.09%) at a dose of 250mg/kg and 4.12µIU/ml (69.54%) at a dose of 500mg/kg. results were shown in *Table 5*.

Table 5: Effect of AEMC bark on serum insulin levels in alloxan induced diabetic rats after 7 days treatment

| GROUP	TREATMENT	INSULIN LEVELS ± SEM	% INCREASE IN INSULIN LEVELS
I	Diabetic control (DC)	2.43±0.03	-
II	DC + AEMC (250mg/kg)	3.21±0.038***	32.09%
III	DC + AEMC (500mg/kg)	4.12±0.0007***	69.54%
IV	DC + GLB (0.5mg/kg)	4.36±0.016***	64.6%

*Values are expressed as Mean ± SEM; and all the values are very significant at ***P<0.0001. DC= Diabetic control; AEMC-= Alcoholic extract of Mimosa catechu; GLB= Glibenclamide.*

Histopathological changes of pancreas

Photomicrographs (Fig.1) showed normal acini and normal cellular population in the islets of langerhans in pancreas of vehicle-treated rats (A). Extensive damage to the islets of langerhans and reduced dimensions of islets (B), restoration of normal cellular population size of islets with hyperplasia by Glibenclamide (C) was also shown. The partial restoration of normal cellular population and enlarged size of â-cells with hyperplasia was shown by the alcoholic extract of Mimosa catechu bark (Fig. 1C & 1D).
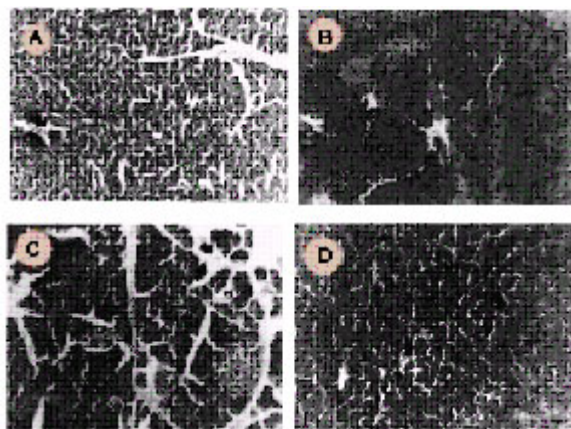
Fig. 1: Photomicrographs rat pancreas stained by haematoxylin and eosin of alloxan-induced diabetic group rats (A) ;effect of glibenclamide (B); effect of AEMC bark at a dose of 250mg/kg (C) and effect of AEMC bark at a dose of 500mg/kg (D). Microscope magnification (400x).

DISCUSSION

The use of ethno botanicals has a long folkloric history for the treatment of blood glucose lowering abnormalities[18]. Therefore the search for more effective and safer antidiabetic or hypoglycemic agents has continued to be an important area of active research. In the present study, *Mimosa catechu* Wild was selected for antidiabetic evaluation owing to its ethno medicinal use in curing diabetes. Therefore the study was undertaken to justify its claimed use. As a result, alcoholic extract of Mimosa catechu bark was prepared and stored. Albino rats were selected as experimental animals for the antidiabetic activity.

The present results showed that the alcoholic extract of *Mimosa catechu* bark(AEMC) significantly decreased serum glucose, triglycerides, cholesterol where as it increased HDL-cholesterol and serum insulin levels in treated diabetic rats as compared with the diabetic control rats.

Models of experimental diabetes that utilizes diabetogenic agents (alloxan and STZ) and induced blood glucose levels higher than 300mg/dl[19] or 400mg/dl[20] have been considered as severe diabetes. In our study, as observed from the values of parameters known to suffer changes in this illness, the alloxan induced diabetic rats presented clear symptoms of diabetes in the diabetic control group. The induction of diabetes by an intraperitoneal injection of alloxan (150mg/kg) was confirmed, as reflected by the hyperglycemia (serum glucose > 300mg/dl), polyphagia, and polydypsia and body weight loss as compared to the normal rats. Experimentally induced diabetes is generally characterized by loss in body weight which may be due to degradation of structural proteins since structural proteins are known to contribute to the body weight. In our study weight loss was observed and treatment with AEMC bark reversed the weight loss, which may be due to the increased secretion of insulin by AEMC bark. Treatment with AEMC bark and Glibenclamide showed the reversal of serum glucose near to normal level which is supported by the elevated level of plasma insulin. The elevated insulin in AEMC bark treatment could be due to increased secretion by regenerated â-cells.

Dyslipidemia is a frequent complication noted in chemical-induced diabetes [21-23] and presents serious risk of vascular disease. The total cholesterol and triglycerides of the diabetic animals treated with the extract were substantially improved, as compared to the diabetic control group. This suggests that the strong hypoglycemic effect of the extract could indirectly be related to beneficial action against the abnormal high concentration of serum lipids observed in diabetic animals.

CONCLUSION

This study demonstrated that the oral administration of alcoholic extract of *Mimosa catechu* bark (AEMC) has beneficial effects in reducing the elevated blood glucose levels and lipid profile of alloxan induced diabetic rats. The extract showed improvement in parameters like body weight, lipid profile as well as regeneration of â-cells of pancreas and resulted in elevation of insulin levels and this might be the possible mechanism contributing to the antidiabetic effect of AEMC bark.

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IN VITRO DISSOLUTION ENHANCEMENT STUDIES ON BINARY SOLID DISPERSIONS OF LORNOXICAM

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ABSTRACT

The poor solubility and wettability of a non steroidal anti-inflammatory drug, Lornoxicam leads to poor dissolution and hence, low bioavailability after oral administration.   The objective of the study was to formulate solid dispersions of Lornoxicam to improve the aqueous solubility and dissolution rate to facilitate faster onset of action. Lornoxicam is a BCS class II drug having low aqueous solubility and therefore low bioavailability. In the present study, solid dispersions of Lornoxicam with three different hydrophilic polymers and one superdisintegrant in 4 drug-carrier ratios were prepared by solvent evaporation and common solvent methods. Solid dispersions were characterized by infrared spectroscopy (IR) and evaluated for drug content, dissolution rate constant, regression coefficient. The dissolution rate and dissolution efficiency of the prepared solid dispersions were evaluated in comparison to the corresponding pure drug. The *in-vitro* dissolution studied showed increased drug release rates compared to that of pure API alone. The increasing order of dissolution rate of solid dispersions Lornoxicam with various polymers was HPMC > PVP > PEG. The solid dispersions in combined carriers gave much higher rates of dissolution than superdisintegrants alone.   Finally*, in-vitro* dissolution studies showed that Lornoxicam release was greatly improved by formation of solid dispersion. A 170.2 fold increase in the dissolution rate of Lornoxicam was observed with solid dispersions prepared using combined carriers such as HPMC, MCC whereas only a 15.78 fold increase was observed with solid dispersions prepared using only MCC. Thus, the solid dispersion technique can be successfully used for enhancement of dissolution rate.

Key words: *Lornoxicam; Solid dispersions; hydrophilic polymers; super disintegrants.*

INTRODUCTION

Lornoxicam (L) (6-Chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2*H*-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide) is a non steroidal anti-inflammatory drug (NSAID) that belongs to the class of oxicams. Lornoxicam is a highly selective COX-2 inhibitor used for a variety of acute and chronic inflammatory diseases[1] and in the management of preoperative and post operative pain associated with gynecological, orthopedic, abdominal and dental surgeries[2]. Its structural formula is given below:
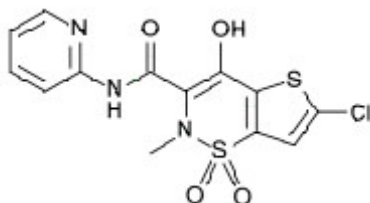
Lornoxicam is insoluble in water and slightly soluble in simulated gastric fluid. Because of its poor aqueous solubility, Lornoxicam has limited dissolution rate[3] and thus delay in onset of action. Being a BCS class II drug,

it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in its solubility and bioavailability[4]. Aqueous solubility of any therapeutically active substance is a key property; it governs dissolution, absorption, and thus the *in vivo* efficacy[5]. To improve the dissolution and bioavailability of poorly water – soluble drugs, various techniques such as hot-melt extrusion[6], common solvent and solvent evaporation[7], cyclodextrin complexation[8], micronization[9], co-grinding[10], solubilization, salt formation, complexation with polymers[11], change in physical form, use of prodrug and drug derivatization, addition of surfactants have been employed. Chiou[12] and Sivert A[13] used the solid-dispersion technique for enhancing dissolution of poorly water soluble drugs. Preparation of solid dispersion is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area

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can be utilized for deposition of the drug on their surfaces[14]. Surface modification and solid-dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials. A number of insoluble drugs have been shown to have improved dissolution character when converted to solid dispersion. Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers[15]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water soluble drug is increasing[16,17]. Various hydrophilic carriers such as polyethylene glycol have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[18].

MATERIALS AND METHODS

Lornoxicam was a gift sample provided by Sun Pharmaceuticals, Vadodara, India and all other materials were of pharmacopoeial grade and procured from commercial sources.

PREPARATION OF SOLID DISPERSIONS

Preparation Employing Superdisintegrants

Solid dispersions of Lornoxicam in superdisintegrants were prepared by solvent evaporation method. The required quantities of drug were dissolved in methanol to get a clear solution in a dry mortar. The superdisintegrants (passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50°C for 4 hours in an oven. The product was crushed, pulverized and sifted through mesh no.100. The different preparations of Lornoxicam were shown in the Table 1.

Sl. No.	Composition		
	Drug	Carriers	SD Code
1.	Lornoxicam (2)	PEG(2), MCC (6)	L-PEG-MCC, 226
2.	Lornoxicam (2)	PVP (2), MCC(6)	L-PVP-MCC, 226
3.	Lornoxicam (2)	HPMC (2), MCC (6)	L-HPMC-MCC, 226
4.	Lornoxicam (1)	MCC(4)	L-MCC, 14

Table 1: Lornoxicam Content of various Solid dispersions

Estimation of Lornoxicam

A spectrophotometric method based on the measurement of absorbance at 376 nm in 0.1 N HCl, pH 1.2 was used in the present study for the estimation of Lornoxicam. The stock solution of Lornoxicam was subsequently diluted to a series of dilutions containing 2,4,6,8 and 10 mg/ml of solution, using 0.1 N HCl. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL - 159) at 376 nm against same dilution as blank[19]. The absorbances relating to different concentrations of Lornoxicam in 0.1 N HCl, .The present analytical method obeyed Beer's law in the concentration range of 2-10 mg/ml and is suitable for the estimation of Lornoxicam from different solutions.

Estimation of Lornoxicam in solid dispersions

From each batch, 4 samples of 50 mg were taken and analyzed for Lornoxicam. 50 mg of dispersion was weighed and transferred into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100 ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with 0.1 N HCl of pH 1.2 and assayed at 376 nm for Lornoxicam.

Fourier-transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FT-IR) has been used to assess the interaction between Lornoxicam and polymers in the solid state. The samples were scanned over the frequency range of 4000-500 cm^{-1}. The chemical interaction between the drug and the carrier often leads to identifiable changes in the infrared (IR) profile of the solid complexes[20]. The principal peaks corresponded to the structural features of Lornoxicam are found due to O-H stretching at 3215.39 cm^{-1}, N-H stretching at 3061 cm^{-1}, Aromatic C-H stretching at 2814 cm^{-1}, secondary amide stretching at 1590 cm^{-1}, 1532 cm^{-1}, R-SO$_2$-R stretching at 1144 cm^{-1}, 1322 cm^{-1}, 1377 cm^{-1}, stretching at 827 cm^{-1} due to C-H aromatic ring bending and –CCl stretching at 785 cm^{-1}. Any sign of interaction would be reflected by changes in the characteristic peaks of Lornoxicam depending on the extent of interaction. In IR study solid dispersions showed combination of the peaks of Lornoxicam and carrier. The overlays of IR spectra are presented in Fig. 1. The FT-IR spectra of solid dispersions were compared to the Lornoxicam. In all the cases the characteristic bands of Lornoxicam confirm the existence of the drug in its unaltered form. The FT-IR spectra of solid dispersions of Lornoxicam showed almost all the bands of Lornoxicam, without affecting its peak position and trends, which indicated the absence of well defined interactions between Lornoxicam, HPMC and MCC.

Dissolution Rate Study

Dissolution rate of Lornoxicam solid dispersions were studied using an USP XXIII six station dissolution rate test type II apparatus (Electro Lab). The dissolution rate was studied in 900 ml of simulated gastric fluid without enzyme pH 1.2 at a paddle speed of 100 rpm and a temperature of 37° ± 1°C [21]. Lornoxicam or solid dispersion of Lornoxicam equivalent to 8 mg of drug was used in each dissolution rate test. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for Lornoxicam. The dissolution experiments were conducted in triplicate and their results are given in Table 2. Dissolution rates of Lornoxicam and its solid dispersions followed first order kinetics. The dissolution profiles of various solid

dispersions are shown in Figure 2. Dissolution parameters such as T_{50}, DE_{30} and K_1 are given in Table 3.
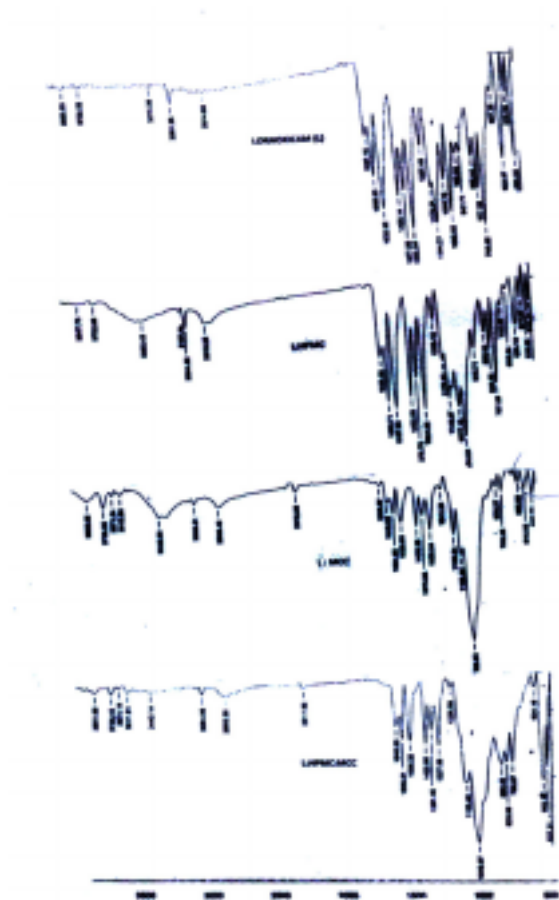

Fig. 1 : *FTIR Spectra of (i) Lornoxicam (ii) Lornoxicam : HPMC (iii) Lornoxicam : MCC (iv) Lornoxicam : HPMC : MCC*

Table 2: *Dissolution Profiles of Lornoxicam Solid Dispersions*

Time (min)	Percent Lornoxicam Dissolved ($\bar{x} \pm s.d.$)				
	L	L-P EG-MCC 226	L-PVP-MCC 226	L-HPMC-MCC 226	L- MCC 14
5	1.32±0.3	40.9±0.5	65.3±0.67	85.9±0.88	35.9±0.67
10	1.73±0.8	42.2±0.6	68.7±0.65	88.3±0.86	37.9±0.65
20	2.12±0.6	43.3±0.46	70.1±0.89	94.5±0.87	39.5±0.67
30	2.31±0.7	55.6±0.89	70.3±0.99	95.3±0.76	40.1±0.78
45	3.14±0.3	57.6±0.77	70.6±0.76	96.4±0.76	40.2±0.75
60	5.21±0.4	60.2±0.65	70.8±0.65	97.3±0.88	40.3±0.76
90	6.13±0.5	62.3±0.86	70.8±0.49	98.5±0.48	40.6±0.76
120	8.24±0.3	63.5±0.76	70.8±0.89	99.2±0.78	40.9±0.77

RESULTS AND DISCUSSION

All the estimated dissolution parameters indicate rapid and higher dissolution of Lornoxicam from all solid dispersions when compared to Lornoxicam. pure drug. The dissolution profiles of various solid dispersions are shown in Fig 2. L-HPMC-MCC (2:2:6) solid dispersion gave rapid and higher dissolution than the pure drug. Combined carriers gave much higher enhancement in the dissolution rate of than water dispersible carriers
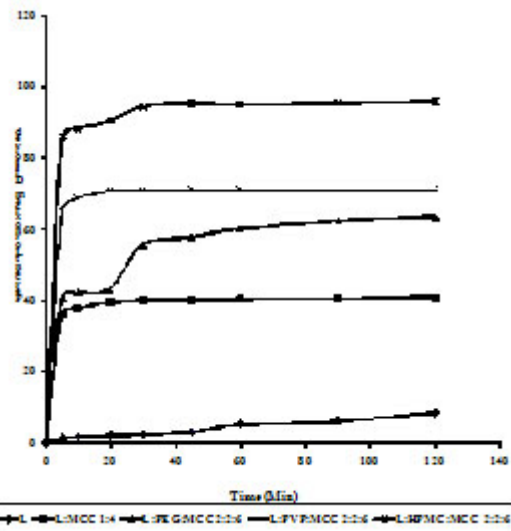

Fig. 2 : *Dissolution Profiles of Lornoxicam and its solid dispersions*

Table 3: *Dissolution Parameters of Lornoxicam and its Solid Dispersions in Superdisintegrants*

Sl. No.	Solid Dispersion	Dissolution Parameter			No. of folds increase in K_1
		T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	
1.	Lornoxicam	>120	1.74	0.00076	-
2.	L-PEG-MCC, 226	25	41.06	0.021	27.63
3.	L-PVP-MCC, 226	4.3	63.14	0.051	67.53
4.	L-HPMC-MCC, 226	03	83.77	0.129	170.2
5.	L-MCC, 14	>120	35.31	0.012	15.78

alone. Solid dispersions of superdisintegrants and combined carriers gave rapid and higher dissolution of Lornoxicam. when compared to pure drug. In each case, the K_1 and DE_{30} values were increased. All the solid dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. L-HPMC-MCC 226 solid dispersion gave a 170.2 fold increase in the dissolution rate of Lornoxicam whereas solid dispersion of Lornoxicam in MCC alone (L-MCC 14 solid dispersion) gave only 15.78 fold increase. Thus combination of superdisintegrants with water soluble carriers PEG, PVP, HPMC resulted in a greater enhancement in the dissolution rate of Lornoxicam.

The dissolution data were fitted into zero order, first order, and Hixson-crowell models to assess the kinetics and mechanism of dissolution. The kinetic model that best fits the dissolution data was evaluated by comparing the correlation coefficient (r) values obtained in various models. The model that gave higher 'r' value is considered as the best fit model. The correlation coefficient (r) values obtained in the analysis of dissolution data as per different models are given in Table 4. The 'r' values were higher in the first order model than those in the zero order models with all the solid dispersions of Lornoxicam, indicating that the dissolution of Lornoxicam from all the solid dispersions

followed first order kinetics. Dissolution of Lornoxicam from all the solid dispersions followed first order kinetics with correlation coefficient 'r' above 0.8 (Table 4).

The first order dissolution plots of various solid dispersions are shown in Fig. 3. The dissolution parameters (K_1, DE_{30} and T_{50}) indicated rapid and higher dissolution of Lornoxicam from solid dispersions when compared to plain drug. The increasing order of dissolution rate of Lornoxicam from solid dispersions observed with various hydrophilic polymers was HPMC>PVP>PEG. The dissolution data of Lornoxicam

Table 4: *The Correlation Coefficient (r) values in the Analysis of Dissolution Data of Lornoxicam Solid Dispersions as per Zero order, First Order and Hixson-Crowell Cube Root Models*

Sl. No.	Solid Dispersion	Correlation coefficient (r) value		
		Zero order	First order	Hixson-Crowell
1.	Lornoxicam	0.935	0.988	0.987
2.	L-PEG-MCC, 2:2:6	0.778	0.837	0.885
3.	L-PVP-MCC, 2:2:6	0.721	0.755	0.741
4.	L-HPMC-MCC, 2:2:6	0.739	0.862	0.825
5.	L-MCC, 1:4	0.465	0.691	0.892

and their solid dispersions were also analyzed as per Hixson-Crowell's[22] cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the cube-root law to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell plots of the dissolution data were found to be linear (Fig. 4) with all solid dispersions. The increasing order of dissolution rates of solid dispersions of Lornoxicam are comparable with solid dispersions of raloxifene-crospovidone[23] atorvastatin-beta cyclodextrin[24] complexation curcumin-cellulose acetate solid dispersion[25] Etodolac solid dispersion with cyclodextrin[26] Etodolac-PEG solid dispersion[27]. The solid dispersions of Lornoxicam
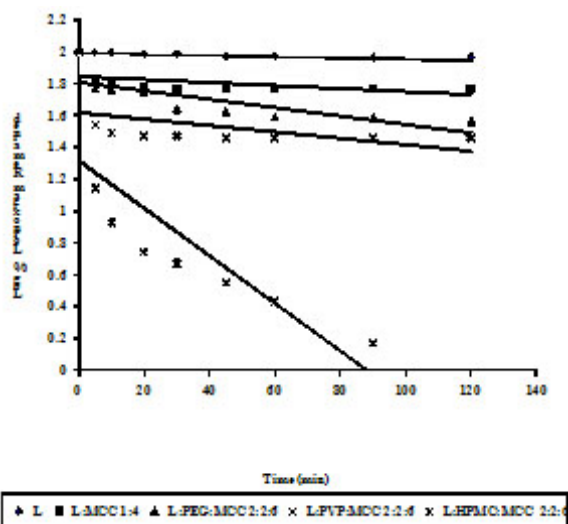
Fig. 3 : *First Order dissolution plots of Lornoxicam and its solid dispersions*

provide rapid dissolution rate by one or more of the following mechanisms :
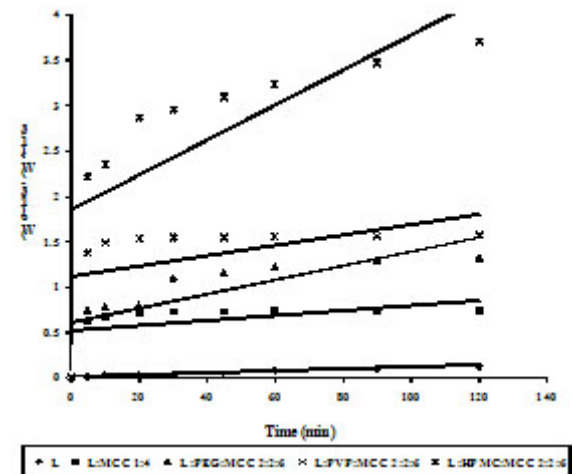
Fig. 4 : *Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions*

(i) **Particle size reduction**: Solid dispersions achieve faster dissolution rates as the drug undergoes micronization while depositing over the surface of the excipient. As Lornoxicam and carriers (MCC) are dispersed at molecular level in a solid dispersion it releases very fine particles of the drug when the carrier molecules readily dissolve in the aqueous fluids.

(ii) **Improving the wettability of the particles**: Wetting of powders is the primary condition for them to disperse and dissolve in body fluids [28]. The presence of water soluble carriers (HPMC, PVP, PEG) improves the wettability of hydrophobic drug particles.

(iii) **Conversion of crystalline drugs into amorphous form**: Solid dispersions of Lornoxicam may convert a crystalline drug into amorphous form. Since the amorphous form is the highest energy form of a pure compound it produces faster dissolution.

(iv) **Solubilizing effect** of the carriers (PVP, HPMC, PEG, DCP) by promoting wetting through increase in effective surface area.

CONCLUSION

The dissolution rate and dissolution efficiency of Lornoxicam could be enhanced several times by their solid dispersion in superdisintegrants alone and in combination with hydrophilic polymers such as PEG, PVP and HPMC. Superdisintegrants particularly microcrystalline cellulose (MCC) was found to be good carrier giving solid dispersions with enhanced dissolution rate and efficiency, several times higher than those of pure drug. Thus, solid dispersion in

superdisintegrants is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of Lornoxicam. Super-disintegrants are inert, safe and non-toxic excipients that are currently used in compressed tablet formulations as disintegrants. These can be used as efficient carriers in solid dispersion techniques to enhance the dissolution rate of insoluble and poorly soluble drugs.

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FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF TELMISARTAN

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Present investigation was undertaken with a view to develop fast dissolving tablets of Telmisartan which offers a new range of product having desired characteristics and intended benefits. Fast dissolving tablets of Telmisartan using various superdisintegrants such as Sodium Starch Glycolate (SSG), Crosspovidone (CP) and Crosscarmellose sodium (CCS) were formulated by direct compression method and evaluated for physicochemical parameters, content uniformity, in vitro release and stability studies. All the formulation batches showed drug release in the range of 98.6% - 100.6% within 20 min. Disintegration time of all batches was less than 1 min. The best formulation F6 containing 5% CP and 2.5% â-cyclodextrin exhibited 98.8% drug release within 15 min and disintegration time of 13 sec. The formulation F6 was found to be stable at accelerated conditions of temperature and humidity (40°C and 75% RH). Fast dissolving tablets containing crosspovidone (5%) was found to give best results for in vitro disintegration and dissolution. Moreover, addition of â-cyclodextrin (2.5% w/w) might have enhanced swelling of tablet, thereby decreasing the disintegration time and increased wettability and dispersability of tablets leading to improved dissolution.

Key words: Crosscarmellose sodium; Crosspovidone; sodium starch Glycolate; â-Cyclodextrin; direct compression.

INTRODUCTION

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms particularly tablets have not been eclipsed, because of its numerous advantages[1]. Two widely faced drawbacks in oral drug delivery are dysphagia and delivery of unpalatable drugs, which may be a problem for mainly geriatric, pediatric, bedridden, nauseous or non-compliant patients[2]. Therefore, emphasis is laid on the development of viable dosage alternatives that has led to exploration of oral mucosal route as a substitute delivery approach for systemic action. The highly vascularised nature and rich blood supply in oral mucosa provide faster onset of action of drugs. Moreover several constraints such as difficulty in swallowing in case of paediatrics and geriatrics patients, nausea and vomiting experienced with certain drugs when released in stomach, degradation and metabolism of susceptible drugs in GIT are avoided through oromucosal delivery of drugs[3]. It is estimated that 50% of the population is affected by this problem which results in a high incidence of noncompliance and ineffective therapy[2]. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such population. Hence, fast dissolving/disintegrating tablets (FDDTs) are a perfect fit for them. FDDTs dissolves or more commonly disintegrate rapidly in the saliva without the aid of water[4]. For this reason the development of mouth dissolving or rapidly disintegrating tablets (RDT) with proper taste masking are among recent trends in pharmaceutical market[2]. The fast dissolving/disintegrating dosage forms are well established in the management of pain, inflammation, vomiting, headache and hypertension. Valuable research reports for formulation of rapidly disintegrating tablets are available; also various technologies for improving dissolution property of poorly water soluble drugs have been documented to enhance bioavailability following oral absorption[5]. Telmisartan is a promising drug candidate to formulate fast dissolving tablet (FDT). Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension with half-life of approximately 24 hours. The bioavailability of Telmisartan is poor (about 45 to 60%) which is due to extensive first pass metabolism. Conventional Telmisartan tablet available in market are not suitable where quick onset of action is required[6]. Present work reports preparation of fast dissolving tablets of Telmisartan using superdisintegrants such as Crosscarmellose sodium, Crosspovidone and Sodium starch glycolate and evaluated for their physiochemical parameters, in vitro dissolution and content uniformity and stability studies.

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MATERIALS AND METHODS

Telmisartan was procured from Sequel Pharmaceuticals Ltd. India. Avicel 112, Mannitol 400DC, Crosscaromellose Sodium, Crosspovidone and Sodium Starch Glycolate were purchased from Signet Chemical Corporation, Mumbai, India. â-cyclodextrin and Aspartame was kindly gifted by Ontop Pharmaceutical Pvt. Ltd. Bangalore. All other chemical used were of analytical grade.

METHODS
Preformulation studies
Melting point of drug
Melting point of drug was done by the capillary tube method using melting point apparatus (Servewell Instrument Pvt. Ltd.). Pure drug was filled into the capillary tube and capillary tube was kept in apparatus melting point seat at 260ÚÆC and capillary tube was observed till drug was melted. The temperature at this point was noted as melting point of drug.

FTIR of drug & excipient
FTIR spectrum was recorded of pure drug and excipients. The samples were analyzed by KBr pellet method using FTIR spectroscopy.

Drug Excipient compatibility
Pure drug and various excipients were mixed in equal amounts and the mixtures were kept for 3 days and then analyzed by FTIR spectroscopy for any interaction between drug and excipient.

Preparation of Fast Dissolving Tablets by Direct Compression Method
The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrant and optimization of concentration of superdisintegrant. Fast dissolving tablet of Telmisartan were prepared by direct compression method using different superdisintegrants like Sodium Starch Glycolate, Crosscarmellose Sodium, Crosspovidone. Telmisartan (pure drug) was first converted into granulated form by adding PVP K-30 as binder using isopropyl alcohol as solvent and mixing by mechanical stirrer. The pure wet drug mass was sieved through # 12mm mesh and dried in hot air oven at a temperature of 45-55°C for 2h, till the moisture content of dried mass of drug was 1-2%. High temperatures lead to change in color of drug, so low temperature range and longer period was preferred. The dried drug mass was further sieved through # 60 mesh. The granular drug was mixed with other ingredients (Sodium Starch Glycolate, Crosscarmellose Sodium, Crosspovidone, Avicel 112, Mannitol, â-cyclodextrin) and the active mass blend was passed through # 60 mesh (to get uniform size powder blend) and again mixed for 15 min in poly bag. Lubricating agent like talc, magnesium stearate and Aerosil, Raspberry flavour (passed through # 60 mesh) were added at last to the mixture and thoroughly mixed just before compression. The active drug blend was

evaluated for flow properties and tablets were then compressed using 8mm flat punches in 8 station tablet machine. The composition of various batches is shown in Table 1.

Table 1: *Composition of various formulation batches (F1-F12)*

Formulation Code/ Ingredient?	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Telmisartan	20	20	20	20	20	20	20	20	20	20	20	20
Sodium Starch Glycolate	10	-	-	10	-	-	10	-	-	10	10	-
Cross Carmellose Sodium	-	10	-	-	10	-	-	10	-	10	-	10
Cross Povidone	-	-	10	-	-	10	-	-	10	-	10	10
β-Cyclodextrin	-	-	-	5	5	5	20	20	20	-	-	-
Avicel 112	102	102	102	97	97	97	82	82	82	92	92	92
Mannitol 400DC	55	55	55	55	55	55	55	55	55	55	55	55
Aspartame	6	6	6	6	6	6	6	6	6	6	6	6
Raspberry flavor	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
PVP K30	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

*all quantities are expressed in mg.

Evaluation of pre-compression parameters
Bulk Density
It was determined by Tap density tester (Electrolab-ETD-1020) by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight[7].

BD = Weight of the powder / initial Volume

Tapped Density
It was determined by Tap density tester (Electrolab-ETD-1020) by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

TBD = weight of the powder / volume of the tapped packing

Angle of Repose
Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend was allowed to flow through the funnel freely on to the surface[7]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Tan θ = h/r

Where h and r are the height and radius of the powder cone.

Hausner's Ratio
Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula:

Hausner's ratio = D_t / D_b

Where, D_t is the tapped density; D_b is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties.

Carr's Index
It indicates compressibility characteristics of powder. It is expressed in percentage and is given by

$I = \{(D_t - D_b)/ D_t\} * 100$

Where, D_t is the tapped density and D_b is the bulk density of the powder.

Evaluation of post compression parameters:
Weight variation

Twenty tablets were randomly selected from each formulation and weighed using a Shimadzu digital balance (AX200). The mean SD values were calculated[8].

Hardness

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester[5]. It is expressed in kg/cm^2.

Tablet Thickness

Ten tablets from each formulation were taken randomly and their thickness was measured with Vernier Calipers[8]. The mean SD values were calculated.

Tablet Diameter

Diameter of tablet was measured by using Vernier Calipers. Three tablets were selected at random from each batch [8]. It is expressed in mm.

Friability test

The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator (Electro Lab Ef- 2 USP). Preweighed tablets were placed in a plastic chambered friabilator attached to a motor evolving at a speed of 25 rpm for 4 minutes[9]. The tablets were then dedusted, reweighed, and percentage weight loss (friability) was calculated.

% Friability = $[(W_1-W_2)*100]/W_1$

Where, W_1 is the weight of tablet before test; W_2 is the weight of tablet after test.

Wetting Time

Five circular tissue papers were placed in a petri dish of 10-cm diameter. Ten milliliters of water containing 0.5% eosin, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch [10].

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and the time required for complete wetting of the tablet was measured[11]. The wetting tablet was then weighed. Water absorption ratio "R" was determined using the equation as follows:

$R = (W_a/W_b) \times 100$

Where W_b is weight of tablet before water absorption & W_a is weight of tablet after water absorption.

In vitro disintegration test

The USP disintegration test apparatus was used to determine disintegration time. 6 tablets from each formulation were tested in 900 ml water at 37°C. The study was done in triplicate.

In vitro dissolution studies

In vitro drug release from all formulation batches (F1-F12) was carried out using USP II dissolution apparatus. All the formulations were subjected to *in vitro* dissolution studies by using 900 ml of 0.1N HCl kept at 37°C and rotated at a speed of 75rpm. The aliquots were collected at specified time intervals (5, 10, 15, 20, 25 min) and analyzed by liquid chromatography. Percent drug release was then calculated. The study was done in triplicate. *In vitro* drug release was also determined for marketed formulation and compared with that of optimum batch. HPLC conditions followed were as specified in official standards[12].

Column: Stainless steel column 15 cm x 4.6mm, packed with octadecylsilane bonded to porous silica (5 ì m) (Such as Inertsil ODS-3); Mobile phase: a mixture of 60 volumes of buffer solution prepared by dissolving 2.72 g of potassium dihydrogen phosphate in 1000ml of water, add 2ml with orthophosphoric acid and 40 volume of acetonitrile; Flow rate: 1ml per minute; Detector: UV detector at absorption maxima of 298 nm; Injection volume: 20 ì l.

Drug Content Uniformity

Drug Content was determined by the assay method as specified in IP 2010[12].

Accelerated Stability Testing

The accelerated stability studies of selected tablet batch F6 were carried out in stability chamber (Thermo Lab) kept at 40°C and 75% RH conditions for three months. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The tablets were examined for their physical changes, drug content and *in vitro* dissolution after interval of 15 days, 1 month, 2 month and 3 months.

RESULTS AND DISCUSSION
Preformulation studies
Melting point:

The melting point of pure drug was in the range of 260°C to 262°C.

FTIR of drug & excipient

The FTIR spectra of pure drug and various excipients are shown in Figure (1 - 8). The IR spectra of drug showed characteristic peaks of drug as given in Table 2.
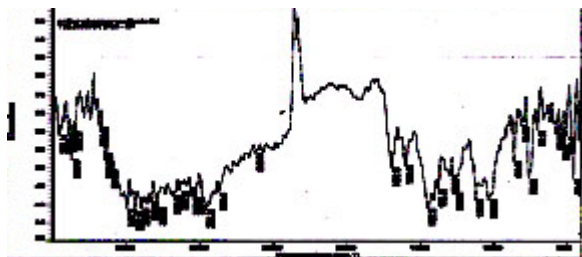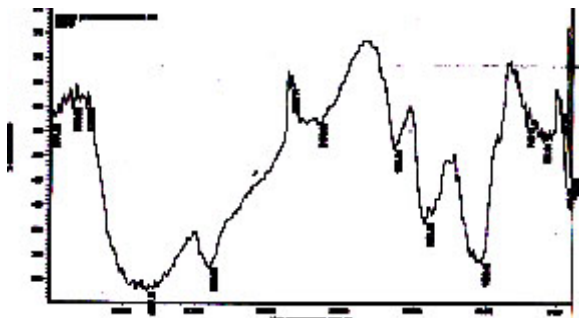
Fig. 1: FTIR Spectra of pure drug Telmisartan

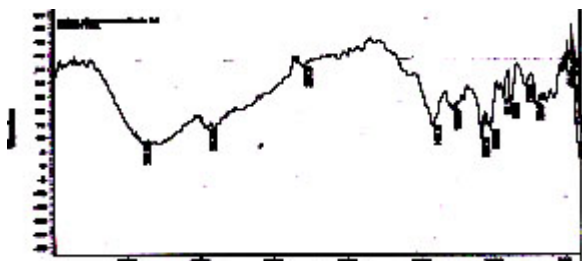*Fig. 2: FTIR Spectra of Avicel -112*
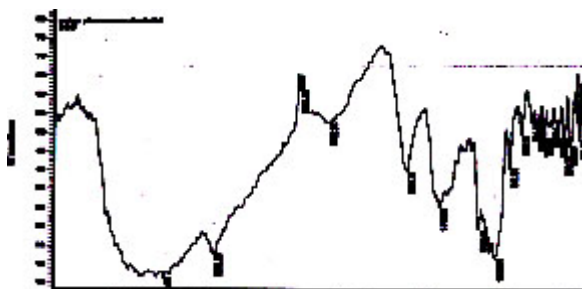

Fig. 3: FTIR Spectra of Mannitol

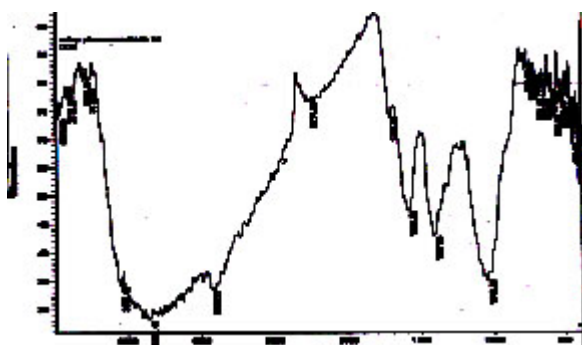*Fig. 4: FTIR Spectra of ▢-Cyclodextrin*

Fig. 5: FTIR Spectra of Crosscarmellose Sodium
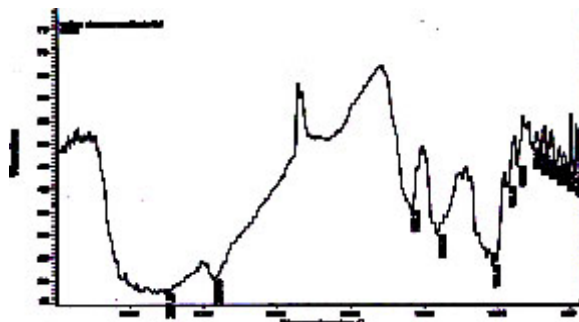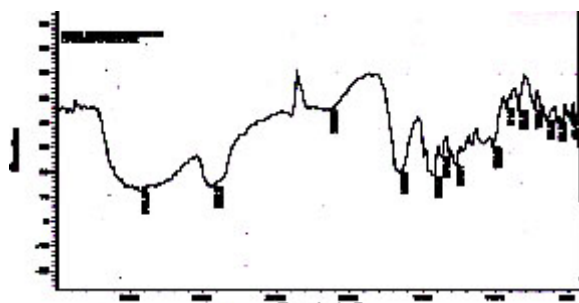

Fig. 6: FTIR Spectra of Sodium Starch Glycolate

Fig. 7: FTIR Spectra of Crosspovidone
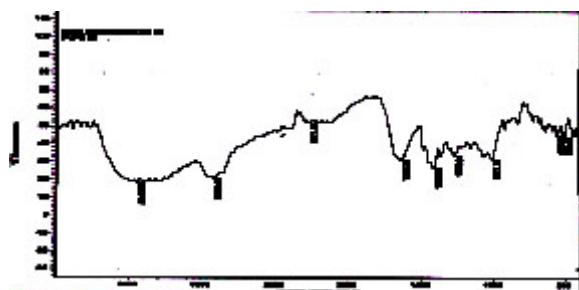

Fig. 8: FTIR Spectra of PVP-K30

Table 2: Standard band frequency of drug Telmisartan

Wave Number (cm⁻¹)	Fuctional group
3392	O-H (H- Bonded)
3680	O-H Free
1640	C=N(imines and Oximes)
1453	C-H(CH₃bend)
639	C-H(Alkenes out of plane bent)

Drug - excipient compatibility study

The IR spectrum of various mixtures (drug with various excipients) is shown in Figure 9-15. Presence of characteristic peaks of drug in IR spectra indicates no interaction of drug with excipients was observed.
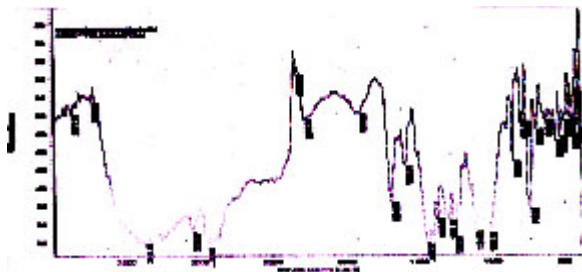
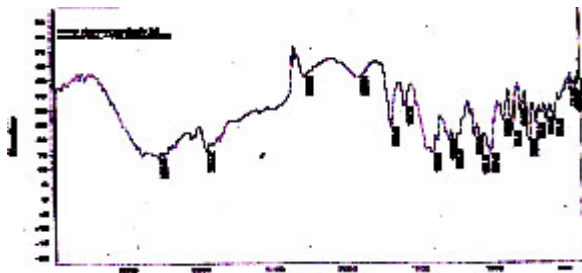**Fig. 9:** *FTIR Spectra of mixture of Avicel 112- Telmisartan*

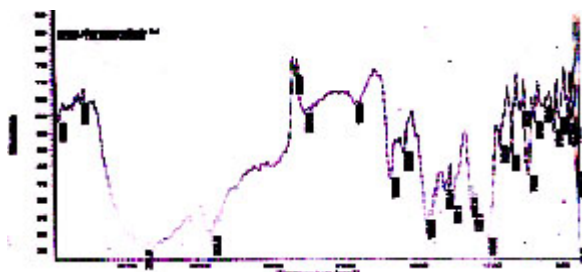**Fig. 10:** *FTIR Spectra of mixture of Mannitol- Telmisartan*

Fig. 11: *FTIR Spectra of mixture of □-Cyclodextrin and Telmisartan*
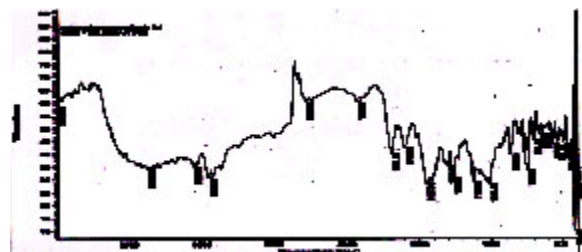

Fig. 12: *FTIR Spectra of mixture of CCS and Telmisartan*
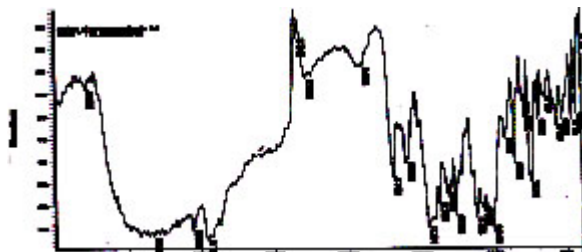

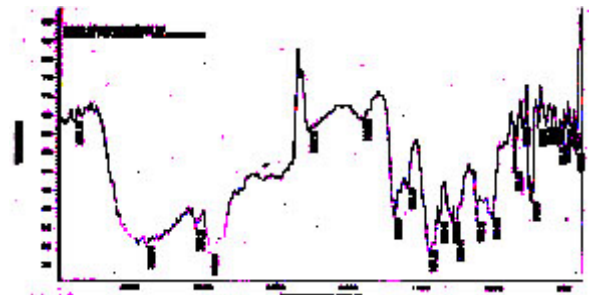**Fig. 13:** *FTIR Spectra of mixture of SSG and Telmisartan*

Fig. 14: *FTIR Spectra of mixture of Crospovidone and Telmisartan*
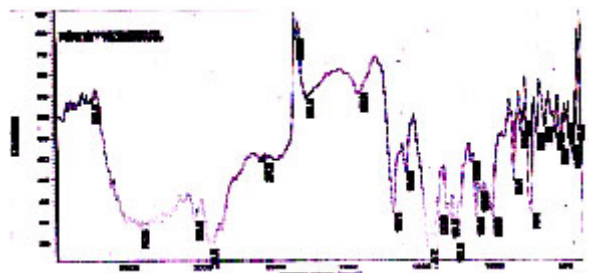

Fig. 15: *FTIR Spectra of mixture of PVP k-30 and Telmisartan*

Evaluation of Precompression Parameters
The results of precompression studies are given in Table 3. The results of bulk density and tapped density ranged from (0.475±0.024 to 0.556±0.043) and (0.545 ±0.021 to 0 .632 ±0.019) respectively. The results of angle of repose (23.34 ±0.24 to 29.17 ±0.25) indicated good flow properties which were further supported by Carr's index values (12.02 to 16.09) and Hausner's ratio data (1.13 to 1.19).

Table 3: *Evaluation of Precompression parameters of various batches (F1-F12)*

Formu lation Code	Bulk density (g/ml)	Tapped density(g/ml)	Angle of repose	Hausner's ratio	Carr's Index (%)
F1	0.496 ±0.023	0.588 ±0.013	27.23 ±0.31	1.18	15.65
F2	0.478 ±0.014	0.545 ±0.021	23.42 ±0.13	1.14	12.29
F3	0.475 ±0.024	0.556 ±0.000	25.35 ±0.25	1.17	14.57
F4	0.503 ±0.028	0.596 ±0.009	28.75 ±0.32	1.19	15.89
F5	0.498 ±0.031	0.586 ±0.018	27.13 ±0.08	1.18	15.02
F6	0.501 ±0.029	0.583 ±0.021	24.75 ±0.15	1.16	14.06
F7	0.497 ±0.025	0.588 ±0.015	27.45 ±0.22	1.18	15.48
F8	0.556 ±0.043	0.632 ±0.019	23.34 ±0.24	1.13	12.02
F9	0.521 ±0.009	0.613 ±0.023	28.23 ±0.09	1.18	15.01
F10	0.527 ±0.021	0.621 ±0.026	27.72 ±0.32	1.18	15.14
F11	0.511 ±0.032	0.609 ±0.031	29.17 ±0.25	1.19	16.09
F12	0.507 ±0.017	0.601 ±0.031	27.68 ±0.09	1.18	15.64

Evaluation of Post Compression Parameters
The physical properties of different formulation batches are given in Table 4. Tablet mean thickness was almost uniform in all formulations. All tablet batches passed weight variation test as % weight variation was within pharmacopoeial limits of (±7.5%) of weight. The prepared tablets from all formulations possessed good mechanical strength with sufficient hardness in the range of (2.5 ±0.4 to 2.8 ±0.4). Friability values below 1% are good indication of good mechanical resistance of tablets. The wetting time values for all the batches

lie between (23 ±3 sec to 66 ±2 sec). A significant low value of wetting time (23 and 25 sec) was observed in batches containing crosspovidone (F3 and F6) indicating porous nature of superdisintegrant. Wetting time was also less (35 sec) in batches F11 and F12 (Containing combination of CP with SSG and CCS respectively). Comparatively higher values in F11 and F12 batches may be due to higher viscosity due to higher concentration of superdisintegrants (5% + 5%) in these batches. Water absorption ratio was more than 100% for all formulations. The *in vitro* dispersion time for all the twelve formulations ranged between (38 ±2 to 66 ±4 sec) with the least value (38 sec) observed in batch F6. All the formulation batches showed disintegration time (DT) value of less than 1 min. Significant decrease in DT was observed in batch F3 containing crosspovidone which was further decreased (slight) by addition of â-Cyclodextrin 2.5% (F6 batch) whereas higher concentration of â-Cyclodextrin (10%) enhanced DT value (F9 batch). The wetting time, *in vitro* dispersion time and disintegration time of the tablets were significantly reduced in tablets containing crospovidone which may be attributed due to the wicking type of disintegrants (crospovidone) formed thus facilitating faster disintegration. Due to porous network of tablet, water uptake was increased and disintegration facilitate. Moreover, addition of â-Cyclodextrin also leads to increased disintegration characteristics (F6 batch) which may be due to increased swelling of tablet due to increased absorption of medium in which studies are carried out. However, higher concentrations of â-Cyclodextrin (F9 batch) rather increase the disintegration time which may due to formation of viscous plugs at higher concentrations. Thus porous structure of tablet, wicking and swelling effects in combination made the tablets more rapidly disintegrating as supported by literature[13,14].

Drug Content Uniformity
The percentage drug content of all the batches was found to be between 99.1 to 100.5% of Telmisartan which was within acceptable limits.

In vitro **drug release studies**
All the formulation batches exhibited 100% release within 20 min (Figure 16). More than 85% drug release within 15 min was observed in all formulation batches (F1-F12) with maximum dissolution rate (98.8% in first 15 min) in batch F6 which may be attributed to highly porous network, rapid capillary activity (achieved with crosspovidone) which leads to pronounced hydration thereby enhancing drug dissolution (also supported by disintegration data). Moreover, addition of â-Cyclodextrin enhanced the dissolution characteristics which may be due to increased wettability which is attributed to increased surface area available for dissolution due to reduction in interfacial tension between drug and dissolution media. Higher concentrations of â-Cyclodextrin did not retard dissolution behavior as the case with disintegration studies. Figure 17 indicated comparative release profile of best batch F6 with that of marketed product. Drug release of 7.6% was observed within first 5 min in case of marketed conventional tablet which is significantly less than that of batch F6 (92.1%).
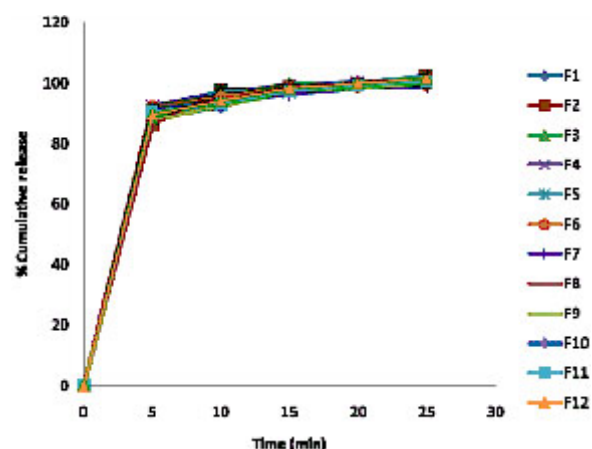

Fig. 16: *Comparative in vitro dissolution profile of various batches (F1-F12)*

Table 4: *Evaluation of post compression parameters of various formulation batches (F1-F12)*

| Code	Weight variation (mg)	Tablet Thickness (mm)	Tablet diameter (mm)	Hardness (Kg/cm^2)	Wetting time (Sec)	Water absorption ratio (%)	Friability (%)	Disintegration time (Sec)	Dispersion time (Sec)
F1	200.19	3.45±0.04	8.08±0.02	2.80±0.3	49±2	134.23	0.5±0.03	32 ±2	54±2
F2	199.75	3.53±0.04	8.08±0.02	2.80±0.4	41±2	162.72	0.13 ±0.04	34 ±3	52 ±2
F3	200.46	3.59±0.03	8.08±0.01	2.85±0.2	23 ±3	117.11	0.64±0.03	18 ±2	44±3
F4	198.86	3.47±0.03	8.07±0.02	2.76±0.3	54 ±3	134.23	0.19±0.03	38 ±2	53 ±2
F5	200.37	3.46±0.04	8.07±0.02	2.74±0.3	57 ±2	127.45	0.21±0.04	36 ±2	57 ±2
F6	199.26	3.52±0.03	8.05±0.02	2.80±0.3	25 ±2	106.85	0.27±0.03	13 ±2	38 ±2
F7	197.47	3.34±0.04	8.07±0.02	2.80±0.3	66 ±2	104.49	0.19±0.03	44±3	52 ±3
F8	199.47	3.47±0.03	8.07±0.01	2.5 ±0.4	48 ±3	129.90	0.13±0.04	54 ±2	57 ±3
F9	199.6	3.50±0.03	8.07±0.02	2.6 ±0.3	51 ±3	102.60	0.07 ±0.03	19 ±2	46 ±2
F10	199.01	3.47±0.4	8.07±0.02	2.6 ±0.4	43 ±2	177.48	0.06 ±0.04	38 ±2	66 ±4
F11	199.70	3.55±0.03	8.07±0.02	2.5±0.3	35±4	137.79	0.1±0.05	29±2	46±3
F12	199.07	3.54±0.03	8.08±0.01	2.6±0.4	35±3	177.22	0.093±0.05	33 ±2	50 ±3
Telma -20	136.02	2.86±0.03	7.04±0.02	1.81±0.2	115± 5	7.7	0.58 ±0.04	240± 0.5	352 ±4
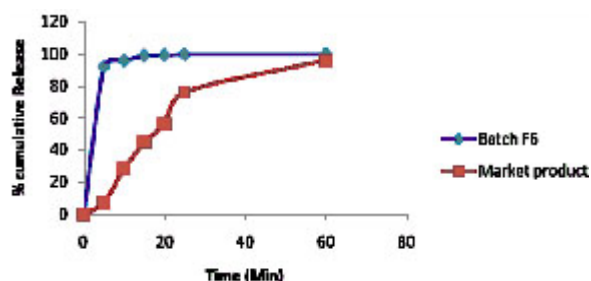
Fig. 17: Comparison of dissolution profile of optimum batch F6 with marketed product

Accelerated stability studies

Stability studies performed on batch F6 as per ICH guidelines for 90 days at 40°C / 75% RH. The results showed no remarkable changes in the physical properties of the tablets as well as no remarkable changes in the drug content (Table 5) and the release profile (Figure 18) indicated good stability of the formulation even after stressed conditions.
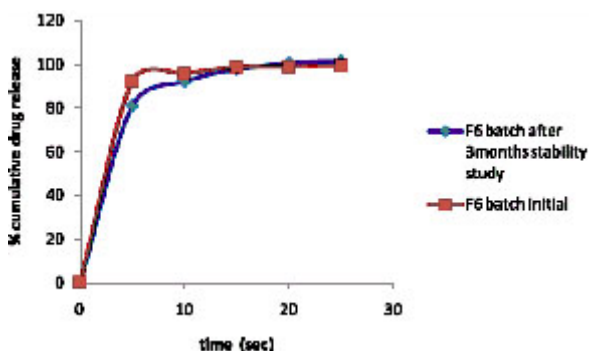

Fig. 18: Comparative release profile of batch F6 before and after stability studies

CONCLUSION

Faster disintegration characteristics of crosspovidone as compared to other superdisintegrants can be exploited to formulate FDT of various drugs which can lead to better management of various diseased conditions. It can be concluded that fast dissolving tablets of telmisartan containing crosspovidone and â-Cyclodextrin can be prepared to obtain faster action of the drug with enhanced solubility characteristics for the effective treatment of hypertension. This approach is effective, economical and industry feasible compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets.

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Table 5: Physicochemical parameters of formulation F6 stored at Accelerated Condition (40°C and 75% RH)

Parameter → / Time ↓	Weight variation (mg)	Tablet Thickness (mm)	Tablet diameter (mm)	Hardness (Kg/cm²)	Wetting time (Sec)	Friability (%)	Disintegration time (Sec)	Dispersion time (Sec)	Assay %
15 days	199.46	3.54±0.03	8.07±0.02	2.51±0.3	26±2	0.13±0.07	13±2	34±2	99.5
30 days	199.51	3.56±0.04	8.08±0.02	2.47±0.3	25±2	0.27±0.04	12±3	37±2	99.1
60 days	199.76	3.66±0.06	8.14±0.014	2.45±0.3	26±3	0.65±0.04	12±2	37±3	98.9
90 days	200.00	3.69±0.03	8.14±0.02	2.42±0.2	24±3	0.19±0.03	12±2	36±2	98.8

FAST DISSOLVING TABLETS OF TELMISARTAN

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DESIGN AND OPTIMIZATION OF VENLAFAXINE HYDROCHLORIDE CONTROLLED RELEASE TABLETS USING HPMC K$_{15}$M

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ABSTRACT

Venlafaxine hydrochloride was formulated as oral controlled release matrix tablets using hydrophilic polymer such as hydroxypropyl methyl cellulose (HPMC K$_{15}$ M) along with electrolytes. In this work a new attempt was made for *in situ* interactions between drug and electrolytes were devised to control the release of highly water soluble drugs from oral hydrophilic monolithic systems. Electrolytes such as Calcium carbonate, magnesium trisilicate, sodium bicarbonate were used at different concentrations in various formulations, while drug and polymer concentrations were maintained constantly at 1:1 ratios in all the formulations. These electrolytes were used to monitor matrix swelling and gel properties. These findings indicated that the swelling and gel formation in the presence of ionizable species within the hydrophilic matrices provide an attractive alternative for controlled drug delivery from a simple monolithic system. FTIR studies were carried out for some selected formulations, which indicated that there were no interactions between drug and excipients used.

Key words: *Venlafaxine Hydrochloride; HPMC K$_{15}$M; Electrolytes; Controlled release; Matrix tablets.*

INTRODUCTION

Recently numerous hydrophilic polymers have been investigated and are currently used in design of complex controlled release systems.[1-3] The polymers that are most widely used in the design of controlled release of drug include nonionic hydroxypropyl methylcellulose (HPMC) and polyethylene oxides (PEO's). The major challenge in the development of new controlled release devices is to achieve optimal drug concentration at the site of action. To achieve optimal drug concentration at the site of action, liberation of the drug from the device must be controlled accurately as possible.[4] The dissolution in a monolithic matrix for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. The limitation of hydrophilic polymer may be circumvented through modification of physical and chemical infrastructure of the polymeric gel system by using electrolytes.

In the present investigation, studies were under taken for design and development of oral controlled release drug delivery system of venlafaxine HCI tablets by matrix diffusion technique. Venlafaxine a phenyl ethyl amine derivative, is an anti-depressant (Serotonin-norepinephrine reuptake inhibitor) used in the treatment of depression.[5] It also weakly inhibits dopamine reuptake. It is freely soluble in water and methanol. Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first pass metabolism in the liver mainly to the active metabolite O-desmethyl venlafaxine. The mean elimination half life of venlafaxine and O-desmethyl venlafaxine is about 5 and 10 hrs respectively. Based on these physicochemical and biopharmaceutical properties, Venlafaxine HCI was selected as a drug candidate for developing controlled release matrix tablet formulations.[6] In the present work, a reliable process has been established for inducing insitu reactions between pharmaceutically acceptable electrolytes and drug which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix structure. Furthermore, that may produce heterogenous domains within the swollen gel boundary. In the past, alkaline compounds (or) buffers have been included in solid oral formulations for several acidic drugs that undergo dissolution rate limited absorption.[7] The same principle of addition of buffers, osmotically active agents, surfactants (or) combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques.[8] However more specific strategy has been employed to apply the same principle to design a simple directly compressible, monolithic controlled release system. In general the application of buffers and ionizable compounds in dosage form design has essentially been limited to the minimization of localized GIT adverse effects and the solubility dependency of poorly soluble compounds.[9,10] The aim of this work was to provide and expand on a means to design , formulate and develop a novel oral monolithic, controlled release tablet dosage form of a drug that may be tailored to provide quasi study state drug release over an

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extended period of time.[11] The rationale behind the mechanism and dynamics of electrolytes induced matrix stiffening and structural changes to the gel is the basis of controlled drug release which also been elucidated.

MATERIALS AND METHODS
Materials
Venlafaxine HCl (gift sample from M/S Dr. Reddy labs, Hyderabad). Hydroxy Propyl methyl cellulose $K_{15}M$ (gift sample from Dow Chemicals Asia pvt., Ltd., Mumbai). Microcrystalline Cellulose (commercially procured from Colorcon Chemicals Asia pvt., Ltd., Mumbai). Sodium Bicarbonate (commercially procured from Qualigens Fine Chemicals, Mumbai). Calcium Carbonate (commercially procured from Thermo Fischer Scientific India Ltd., Mumbai). Magnesium Trisilicate (commercially procured from Loba Chemie Pvt., Ltd., Mumbai). All chemicals used in this investigation were of analytical grade.

Preparation of matrix tablets
Venlafaxine HCl controlled release matrix tablets were prepared by direct compression process. The controlled release matrix tablet formulations consisted of drug, polymer, diluent and electrolytes. The ratio of drug and polymer were maintained constant while the electrolyte concentration was varied. The weight of all the tablet formulations was maintained uniformly by using MCC as diluent. The compositions of various tablet formulations were given in table 1. The materials were individually weighed, passed through sieve no: 60 and blended for 15 minutes by using double cone blender. The powder mixture was then lubricated with 1% talc and magnesium stearate and blended for 5 minutes. Then the powder blends were directly compressed into matrix tablets using Clit 10 station mini press. To minimize the processing variables all batches of tablets were compressed, under identical condition. The powder blends were evaluated for flow properties such as angle of repose and compressibility index.

Table 1: Composition of various controlled release matrix tablets of Venlafaxine HCl

Ingredients mg/ Tablet	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
Venlafaxine HCl	75	75	75	75	75	75	75	75	75	75	75
HPMC K15M	75	112.5	75	75	75	75	75	75	75	75	75
Sodium bicarbonate	--	--	20	30	40	--	--	--	--	--	--
Calcium Carbonate	--	--	--	--	--	20	30	40	--	--	--
Magnesium Trisilicate	--	--	--	--	--	--	--	--	20	30	40
MCC	148	111	128	118	108	128	118	108	128	118	108
Talc	1.5	1.5	2	2	2	2	2	2	2	2	2
Total Tablet wt (mg)	300	300	300	300	300	300	300	300	300	300	300

Evaluation of physical properties
The physical parameters such as weight uniformity, friability, hardness and drug content were evaluated for the prepared matrix tablets as per the standards of official compendium[12].

Determination of swelling index
The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N HCl at 37±0.5˚C. After 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hrs, tablet from each dissolution basket was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.[13] The swelling index for various selected formulations of matrix tablets were shown in Table 2.

Table 2: Swelling Index of Controlled Release Matrix Tablets of Venlafaxine HCl

S.No	Formulation	Swelling Index (%)		
		1 hr	6hr	10hr
1	F-5	66.6	92.0	153.3
2	F-8	73.3	96.3	142.6
3	F-11	116.6	100.0	137.6

Swelling index = (Wet weight of tablet - Dry weight of tablet) / Dry weight of tablet

Drug release studies
Dissolution studies on all the formulation were performed in a calibrated 8 station dissolution apparatus equipped with paddles employing 900 ml of distilled water as a medium.[14]

The paddles were operated to rotate at 75 rpm and the temperature was maintained at 37±1⁰C throughout the studies. Samples were withdrawn at regular intervals up to 12 hrs and each time samples were replaced with equal volume of fresh medium to maintain the volume of dissolution medium constant throughout the experiment. Drug content of the samples were determined by ELICO double beam UV spectrophotometer at 225nm, after suitable dilution. To analyze the mechanism of drug release from the obtained data, various calculations were analyzed based on the equation like first order constant, Higuchi constant and the koresmeyer peppas constant respectively.

The following are the equations used:

$$lnQ = k.t \quad \ldots\ldots\ldots\ldots 1$$
$$Q = k.t \quad \ldots\ldots\ldots\ldots 2$$
$$M_t/M_\infty = kt^n \quad \ldots\ldots\ldots 3$$

Where Q in the equation 1 is cumulative percent drug remained, while Q in the equation 2 is cumulative amount of drug released, M_t/M_∞ is the fraction of drug released, t is the release time and k is the constant incorporating the structural and geometrical characteristics of the release device. If the value of n= 0.45 indicates Case I (Fickian) diffusion or square root of time kinetics, 0.45 < n < 0.89 indicates anomalous (Non-Fickian drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, n= 0.89 indicates case II transport and n>0.89 indicates super case II transport. Linear regression analysis was performed for all these

equations and regression coefficients (r) are determined.

The dissolution profiles of all the prepared matrix tablet formulations for venlafaxine hydrochloride were compared with the marketed extended release tablet formulation of venlafaxine hydrochloride by using a model independent approach of similarity factor *f2,* with all time points included in the *in vitro* dissolution studies [15-16]. The equation for calculating similarity factor is

$$f_2 = 50 + \log \{[1 + (1/n) \sum_{t=1} n (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where 'n' is the number of dissolution time and R_t and T_t are the reference (theoretical) and test dissolution values at time 't'. Dissolution profile was considered satisfactory if f_2 value lies more than 50. Two dissolution profiles are considered similar when the *f*2 value is 50 to 100.

RESULTS AND DISCUSSION

The present study was under taken for design and evaluation of the controlled release matrix tablets of venlafaxine hydrochloride with HPMC $K_{15}M$, by employing various pharmaceutically acceptable electrolytes as drug release retardants. All batches of tablets were produced under similar conditions to avoid processing variables. The compositions of various matrix tablets were given in Table 1. These tablets were preliminarily evaluated for various physical parameters such as weight uniformity, hardness, friability and for drug content. All batches of tablets with different electrolyte composition were within the weight range of 299-301 mg. Hardness of the matrix tablet formulations were constant for all batches and were maintained at 5-6 kg/cm². Friability loss of formulations was negligible and was less than 0.2% for all the batches. Drug content was uniform in all the batches of matrix tablet formulations and was within the range. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets are given in Table 3.

Table 3: Physical parameters of Venlafaxine HCl Controlled release Matrix Tablets

| S. No	Formulation	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%)	Drug content (mg/tablet)
1	F-1	302±2.0	6.5±0.3	0.12	74.3±0.5
2	F-2	301±3.0	6.0±0.3	0.12	74.2±0.5
3	F-3	296±3.0	6.5±0.3	0.18	75.4±0.5
4	F-4	302±3.0	6.0±0.3	0.16	74.6±0.5
5	F-5	300±3.0	6.5±0.3	0.18	74.8±0.3
6	F-6	301±2.0	6.5±0.3	0.14	75.2±0.5
7	F-7	302±2.0	6.5±0.3	0.15	75.5±0.2
8	F-8	303±3.0	6.5±0.3	0.13	75.4±0.3
9	F-9	302±3.0	6.0±0.3	0.16	74.3±0.2
10	F-10	300±3.0	6.5±0.3	0.18	75.4±0.2
11	F-11	296±3.0	6.0±0.3	0.19	74.7±0.5

From the *in vitro* dissolution studies, it was observed that formulations F5, F8 & F11 showed greater inhibition of release rate of venlafaxine from the tablet matrix. The dissolution profiles of various matrix tablets were shown in figures 1-4 and their corresponding kinetic data was shown in table 4.
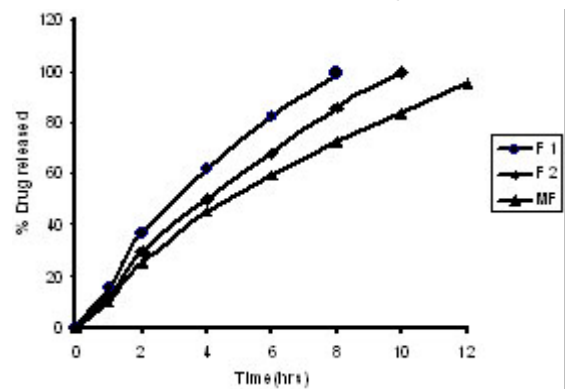
Fig. 1: Drug release profile for controlled release matrix tablets of Venlafaxine hydrochloride
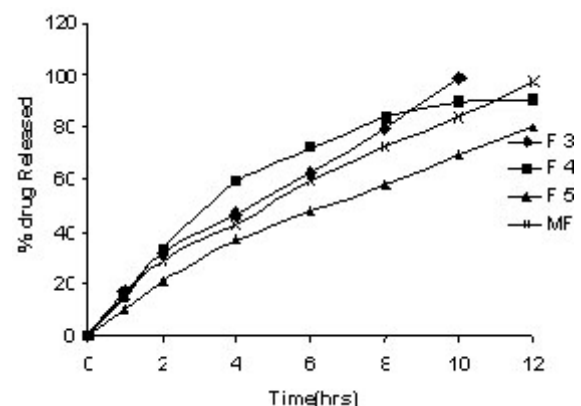
Fig. 2: Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Sodium Bicarbonate
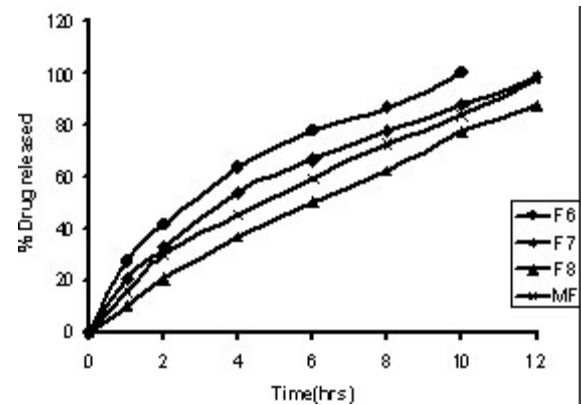
Fig. 3: Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Calcium carbonate

By the addition of electrolytes into the matrix tablet formulations, it was possible to reduce the release rate of drug over an extended period of time. The inclusion of electrolyte within the matrix tablet for controlling the release rate of venlafaxine hydrochloride might lead to the formation of free base of venlafaxine and fundamental structural changes in gel boundary, thus
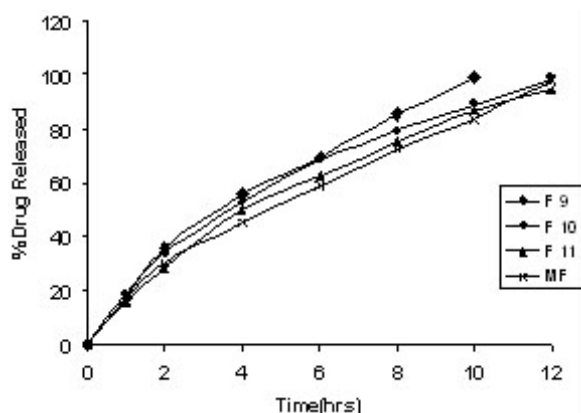
Fig. 4: *Drug release profiles of various controlled release formulations of Venlafaxine hydrochloride with Magnesium Trisilicate*

Table 4: *In Vitro Pharmacokinetic parameters of controlled release matrix tablets of Venlafaxine HCl*

Formulation	Zero Order Constant		First Order Constant		Higuchi Constants		Peppas Constant	
	K	R²	K (mg.h)	R²	K (h⁻¹)	R²	n value	R
Marketed	14.35	0.89	0.21	0.96	35.42	0.98	0.60	0.986
F-1	15.24	0.97	0.31	0.99	33.02	0.99	0.50	0.978
F-2	14.38	0.89	0.18	0.93	30.68	0.98	0.55	0.996
F-3	14.70	0.89	0.22	0.95	29.21	0.99	0.60	0.998
F-4	15.23	0.91	0.19	0.98	26.76	0.99	0.62	0.997
F-5	13.33	0.92	0.16	0.99	25.68	0.99	0.62	0.997
F-6	11.83	0.84	0.11	0.97	32.73	0.98	0.70	0.995
F-7	12.70	0.89	0.24	0.86	30.13	0.98	0.62	0.989
F-8	11.38	0.93	0.18	0.97	29.22	0.99	0.62	0.992
F-9	15.53	0.93	0.15	0.95	33.73	0.99	0.70	0.992
F-10	9.58	0.85	0.230	0.84	30.75	0.99	0.58	0.997
F-11	878	0.85	0.202	0.99	28.29	0.99	0.58	0.994

including the textural variations in the swollen matrix. Further it may be due to higher pKa values of electrolytes, which can display higher buffer threshold for maintaining suitable pH inside the matrix. Electrolytes such as sodium bicarbonate with pH values greater than 7.0 might exert a better and desired control on drug release from matrix tablet. As the dissolution medium enters the periphery of the tablet, there is a rapid electrolyte water interaction with significant chemical reaction through electrolyte solubilization and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process, the electrolyte present in the gel boundary could have been converted to bicarbonate form (for example sodium bicarbonate) due to which the hydrochloride form of venlafaxine hydrochloride leads to the formation of free base of venlafaxine. The passive and actively formed electrolytes within the gel matrix would compete for water leading to dehydration of polymer molecules, thus leading to dehydration of polymer molecules, thus leading to suppression of initial swelling which was seen up to 2 to 3 hours within formulations containing high concentration of electrolytes. After 3 hour the water attracted by electrolytes into the polymer matrix could result in solubilising the drug molecules which would diffuse by penetration of water leading to enhancement of swelling. The swelling index characteristics of various

matrix tablets were given in Table 3. From these alterations and mechanisms of intragel changes, it appears possible to inhibit drug dissolution rate. This inhibition in dissolution rate appears to be time-dependent phenomenon. Since, as more water enters the gel matrix layer–by-layer, the electrolytes and their by products are diluted and any drug base may be revert to its hydrochloride form, which is subsequently released [17]. The dissolution profiles of venlafaxine hydrochloride matrix tablet formulations were compared with marketed controlled release formulation of venlafaxine hydrochloride extended release tablets. The similarity factors were calculated for these matrix tablet formulations. The similarity factor f_2 values were in the range of 19–89. The formulations F7, F10 and F11 showed the similarity factor values above 50 indicated that the release profiles for these formulations were similar to that of marketed formulation. The FTIR spectra of venlafaxine hydrochloride exhibited principle peaks at wave numbers 3350 cm⁻¹ [CH stretch], 1438 cm⁻¹ [N-$(CH_3)_2$] and 2935 cm⁻¹ [OH] shown in figures 5-8. The FTIR spectra of matrix tablet formulations F5, F8 & F11 exhibited all the principle peaks present in the venlafaxine hydrochloride pure drug. The results revealed that there were no major interaction between the drug and the excipients.
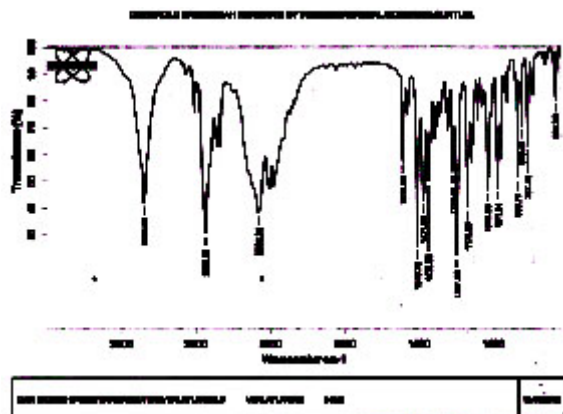

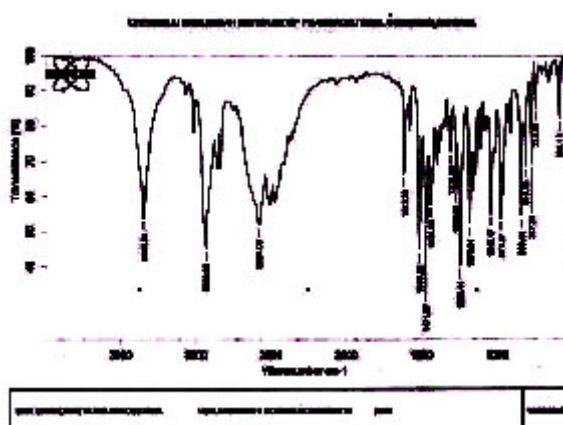**Fig. 5:** *FT IR spectra of Venlafaxine HCl Pure Drug*

Fig. 6: *FT IR spectra of Venlafaxine HCl (F 5)*
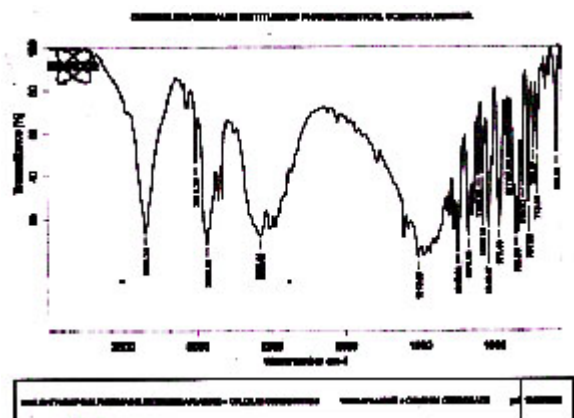
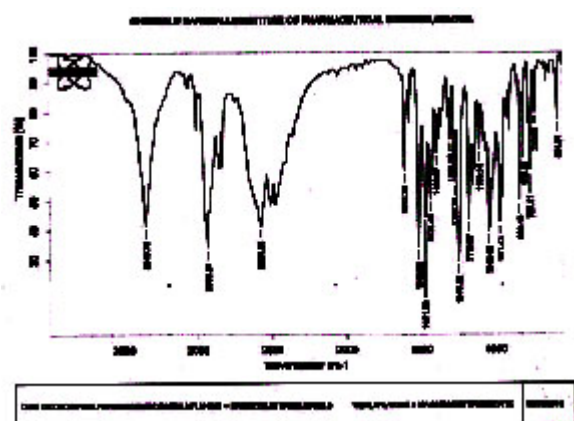**Fig. 7:** *FT IR spectra of Venlafaxine HCl (F 8)*

Fig. 8: *FT IR spectra of Venlafaxine HCl (F 11)*

CONCLUSION

This work has provided a novel and a simple approach to formulate an oral controlled release drug delivery system designed for delivery of venlafaxine HCl over an extended time period. An important feature of this system is the potential for generating constant drug release. The formulations F5, F8 & F11 were found to extend the drug release over an extended period of time. Hence these formulations were found to be suitable for once a day matrix tablet administration for treating the depression patients. Their physical parameters were within Indian pharmacopoeial specified limits.

ACKNOWLEDGEMENTS

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