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DEVELOPMENT AND CHARACTERIZATION OF GASTRO-RETENTIVE SOLID DOSAGE FORM OF ANTI-HYPERTENSIVE DRUG

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ABSTARCT

In the present research work gastro retentive floating matrix formulation of Captopril by using various hydrophilic polymers were developed. Initially analytical method development was done for the drug molecule. Absorption maximum was determined based on which calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Methocel and Guar gum as polymeric substances. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations, the formulations of Methocel K15M as polymer were retarded the drug release up to desired time period of 12 hours in the concentration of 180 mg (F3 Formulation, 98.66% Drug release), whereas in low concentrations the polymer was unable to produce the desired action. The formulations prepared with Methocel K100M were also retarded the drug release for more than 12 hours. Hence they were not considered. From the FT-IR spectrum, it was revealed that there was no drug-excipient incompatibility. The optimized formulation dissolution data was subjected to release kinetics, from which it was evident that the formulation followed zero order mechanism of drug release.

KEYWORDS: Captopril, Guar gum, HPMC polymers, Floating tablets.

INTRODUCTION

Captopril is chemically (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid having the molecular formula of $C_9H_{15}NO_3S$ with the molecular weight 217.29 gm/mol. It is an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension and some types of congestive heart failure.[1,2,3,4] It was the first ACE inhibitor that was developed and was considered as a revolutionary development process because of its novel mechanism of action. When it is given orally, 90% of the drug gets absorbed through it and reaches the maximum concentration within 1-2 hrs. As it under goes hepatic metabolism, it has very low bioavailability (10-20%) and short half-life (2.8-7.4) due to which the drug is administered in multiple doses.[5] A literature study reveals that there are several drugs for which floating tablets were prepared.[6,38] A floating tablet with captopril was also prepared using different grades of HPLC and evaluated.[39,40] In this present study, to enhance the bioavailability and to reduce the dosage regimen, Captopril floating tablets using different polymers like Methocel K15M, Methocel K100M, and Guar gum were prepared and evaluated.

MATERIALS AND METHODOLOGY

Materials and instrumentation

Captopril standard drug was obtained as a gift sample by K.P Labs, Hyderabad, India. HPMC, Sodium bicarbonate, Magnesium stearate, Micro crystalline cellulose and talc were purchased from Merck Specialties Pvt Ltd, Mumbai, India.

FT-IR spectrophotometer of Per Kin Elmer, USA was used to study drug excipient compatibility studies. Multi-station tablet compression machine was used to formulate the tablet. Weighing balance, Monsanto hardness tester, Vernier Caliper, Roche friabilator, pH meter were used for post formulation evaluation studies. Double beam UV-Visible spectophotemeter was used to obtain calibration curve at 271nm taking 0.1N HCl as blank and USP apparatus –II (Paddle Method) was used for dissolution studies.

Preparation of floating tablets

Captopril HCl and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 minutes followed by lubricating it with talc followed by which the pre-formulation parameters were performed. Values of the pre-formulated granules are shown in table no 3.

The tablets were then prepared by multi-station tablet compression machine using direct compression method. Concentration of sodium bicarbonate which acts as effervescent gas generating agent, was optimised to 50mg by observing floating lag-time and floating duration. Details of the composition of the tablets are given in the table no 1.

Table 1: Shows the ingredients and quantities of different formulation of tablets.

Formulation no.	Captopril	Methocel K15M	Methocel K 100M	Guar gum	$NaHCO_3$	Magnesium stearate	Talc	MCC
F1	100	60	-----	-----	50	5	5	QS
F2	100	120	-----	-----	50	5	5	QS
F3	100	180	-----	-----	50	5	5	QS
F4	100	-----	60	-----	50	5	5	QS
F5	100	-----	120	-----	50	5	5	QS
F6	100	-----	180	-----	50	5	5	QS
F7	100	-----	-----	60	50	5	5	QS
F8	100	-----	-----	120	50	5	5	QS
F9	100	-----	-----	180	50	5	5	QS

MCC is microcrystalline cellulose

In vitro Buoyancy studies

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

Evaluation of tablets

Hardness test

The hardness of the tablet was found by placing it between two anvils of Monsanto hardness tester and the force was gradually increased until the tablet breaks. The marked scale reading determines the force required to break the tablet.

Friability

It is a measure of mechanical strength of tablets and Roche friabilator was used to determine the friability by taking pre-weighed tablets in it. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = [(W1-W2)/W1] \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Drug content

Ten tablets were finely powdered and quantities of the powder equivalent to one tablet weight of captopril were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV – Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

Weight variation

Twenty tablets were randomly taken and their weight was determined individually for the respective batches on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Preparation of calibration curve

100mg of Captopril pure drug was dissolved in 100ml of 0.1N HCl (stock solution) of which 10ml of solution was taken and make up with100ml of 0.1N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 5,10,15,20 and 25 µg/ml of Captopril per ml of solution. The absorbance of the above dilutions was measured at 271 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Standard curve was plotted (Figure No: 1) from the observations recorded in (Table No: 2).

Table 2: Shows the absorbance values of different concentration.

Concentration[µg/l]	Absorbance
5	0.107
10	0.195
15	0.304
20	0.417
25	0.503

In vitro dissolution studies

In vitro dissolution studies of all the formulations of floating tablets of captopril were carried out by placing 900ml 0f 0.1N HCl in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was

allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and was operated for 12 hours and then at frequent intervals of 1 hr. each, the aliquotes each of 5ml was withdrawn from the vessel and replaced with 5ml of 0.1N HCL. This study was performed for 12 hours at 50rpm. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 271 nm using UV-spectrophotometer. The studies are shown in the figure no's: 4, 5 and 6.

Application of Release Rate Kinetics to Dissolution Data

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. The released data were plotted according to following equations

Zero order: $F = K_o t$
First order: Log (100-F) = kt
Higuchi release model: F = k t1/2
Korsmeyer-Peppas release model: $M_t/ M_\infty = K t^n$

Where, 'F' is the drug release at time 't'. 'K_o' and 'k' are the zero and first order release rate constants respectively. In the Higuchi release model, 'k' is the Higuchi constant and in Korsmeyer-Peppas model, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process.

For non-Fickian release, the value of n falls between 0.5 and 1.0; while for Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1.

RESULTS AND DISCUSSION

Preformulation studies

Table 3: Shows the pre-formulation parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	27.91	0.45	0.55	18.18	1.22
F2	28.23	0.47	0.55	14.54	1.17
F3	29.34	0.50	0.58	13.79	1.16
F4	26.71	0.46	0.55	16.36	1.19
F5	29.34	0.50	0.58	13.79	1.16
F6	28.23	0.47	0.55	14.54	1.17
F7	29.34	0.50	0.58	13.79	1.16
F8	26.78	0.41	0.50	18	1.21
F9	26.78	0.41	0.50	18	1.21

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.50(gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50 to 0.58 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 14 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Preparation of calibration curve

Standard curve was plotted as shown in figure No: 1 from the observations recorded in (Table No: 2) and the correlation coefficient was found to be 0.9977.

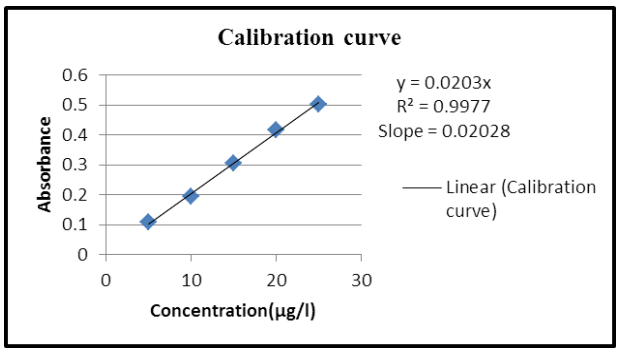

Figure 1: shows the calibration curve of the recorded absorbance values.

FT-IR data analysis

FT-IR spectrum of pure drug and the optimized formulation are shown in the figure no: 2 and 3.

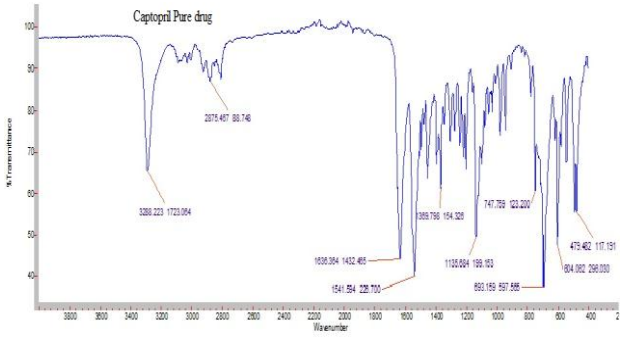

Figure 2: FT-IR spectrum of captopril pure drug.

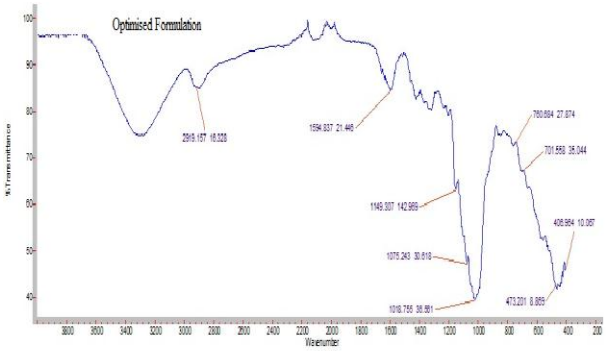

Figure 3: Ft-IR spectrum of Optimised formulation

From figure no: 2 and 3, the FT-IR spectra of drug and polymers revealed that, the major frequencies of functional groups of pure drug remain intact in the mixture containing different polymers. Therefore, no interactions were found between the drug and polymers used in the study.

Table 4: Shows the Values of Post Formulation Studies.

Formulation codes	Weight variation (mg)	Hardness(kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (sec)
F1	602.5	4.5	0.51	4.8	98.76	5.0
F2	600.4	4.5	0.51	4.9	97.45	5.2
F3	599.6	4.4	0.52	4.9	102.34	5.5
F4	611.6	4.5	0.53	4.9	101.87	5.1
F5	607.4	4.4	0.54	4.7	104.14	5.0
F6	600.7	4.3	0.50	4.5	98.56	5.4
F7	601.3	4.3	0.53	4.4	108.42	5.5
F8	600.2	4.3	0.50	4.7	103.65	5.6
F9	594.3	4.4	0.51	4.6	104.12	5.7

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

Table 5: Dissolution data of captopril tablets prepared with methocel k15 m in different concentrations

Time (hr.)	Cumulative Percent Drug Dissolved (n=3+sd)		
	F1	F2	F3
0.5	45.56	24.67	10.45
1	87.45	38.98	16.54
2	97.23	43.44	19.89
3		51.23	27.99
4		64.25	34.19
5		78.90	39.66
6		89.56	41.77
7		97.66	55.23
8			69.89
9			78.22
10			89.90
11			98.66

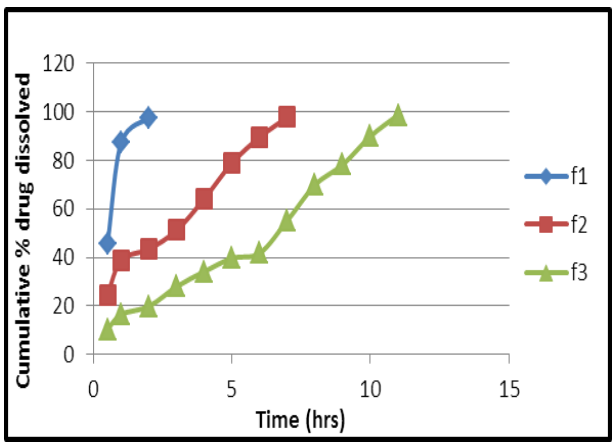

Figure 4: graphical representation of the dissolution data of captopril tablets prepared with methocel k15 m in different concentrations.

Table 6: Dissolution data of captopril tablets prepared with methocel k 100 m in different concentrations.

Time (hr)	Cumulative Percent Drug Dissolved (n=3±SD)		
	F4	F5	F6
0.5	22.77	16.90	9.89
1	30.21	27.55	16.76
2	39.54	39.20	22.53
3	51.20	48.13	27.43
4	69.66	54.76	33.66
5	77.33	69.87	37.11
6	90.10	78.23	44.67
7	95.77	85.40	53.87
8		92.33	61.30
9		97.66	69.10
10			78.20
11			84.22
12			90.33

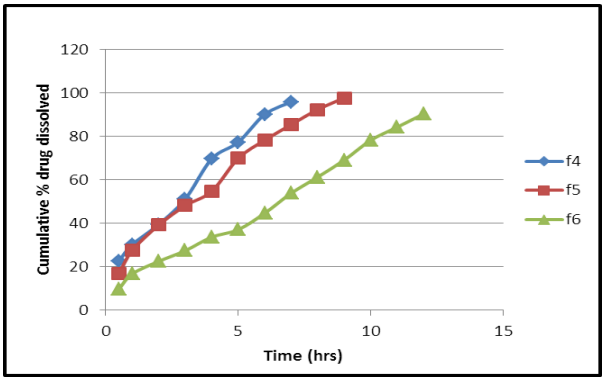

Figure 5: graphical representation of dissolution data of captopril tablets prepared with methocel k 100m in different concentrations.

Table 7: Dissolution data of captopril hydrochloride tablets prepared with guar gum in different concentrations.

Time(hr)	Cumulative Percent drug dissolved (n=3±SD)		
	F7	F8	F9
0.5	43.32	28.04	18.87
1	77.22	53.81	27.19
2	96.90	69.43	43.32
3		83.52	57.13
4		97.33	69.71
5			85.97
6			95.77

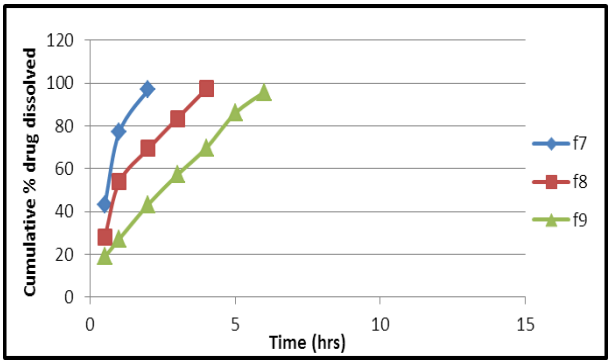

Figure 6: graphical representation of dissolution data of captopril hydrochloride tablets prepared with guar gum in different concentrations.

From the dissolution data it was evident that the formulations prepared with Methocel K15M as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 180 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F3 Formulation, 98.66% Drug release) whereas the formulations prepared with Methocel K100M retarded the drug release in more than 12 hours in higher concentrations. In lower concentrations the polymer was unable to retard the drug release. The formulations prepared with Guar gum showed very less retardation capacity hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 8: Release kinetics data for optimised formulation.

Cumulative % release Q	Time (T)	Root (T)	Log % Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release/T)	1/Cum % Release	Peppas Log Q/100	% Drug Remaining	$Q_0$1/3	Q_T1/3	$Q_0$1/3-Q_T1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.89	0.5	0.707	0.995	-0.301	1.955	19.780	0.1011	-1.005	90.11	4.642	4.843	0.158
16.76	1	1.000	1.224	0.000	1.920	16.760	0.0597	-0.776	83.24	4.642	4.366	0.275
22.53	2	1.414	1.353	0.301	1.889	11.265	0.0444	-0.647	77.47	4.642	4.263	0.379
27.43	3	1.732	1.438	0.477	1.861	9.143	0.0365	-0.562	72.57	4.642	4.171	0.470
33.66	4	2.000	1.527	0.602	1.822	8.415	0.0297	-0.473	66.34	4.642	4.048	0.593
37.11	5	2.236	1.569	0.699	1.799	7.422	0.0269	-0.431	62.89	4.642	3.977	0.665
44.67	6	2.449	1.650	0.778	1.743	7.445	0.0224	-0.350	55.33	4.642	3.811	0.831
53.87	7	2.646	1.731	0.845	1.664	7.696	0.0186	-0.269	46.13	4.642	3.586	1.055
61.3	8	2.828	1.787	0.903	1.588	7.663	0.0163	-0.213	38.7	4.642	3.382	1.259
69.1	9	3.000	1.839	0.954	1.490	7.678	0.0145	-0.161	30.9	4.642	3.138	1.504
78.2	10	3.162	1.839	1.000	1.338	7.820	0.0128	-0.107	21.8	4.642	2.794	1.848
84.22	11	3.317	1.925	1.041	1.198	7.656	0.0119	-0.075	15.78	4.642	2.508	2.133
90.33	12	3.464	1.956	1.079	0.985	7.528	0.0111	-0.044	9.67	4.642	2.130	2.511

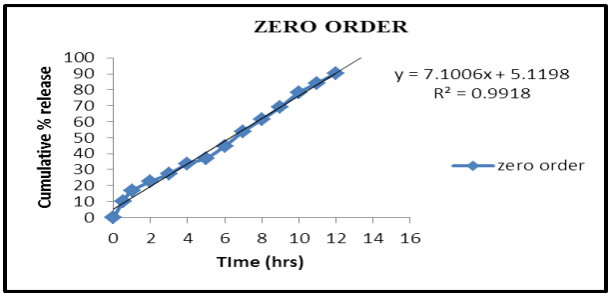

Figure 7: Zero Order Release Kinetics Graph.

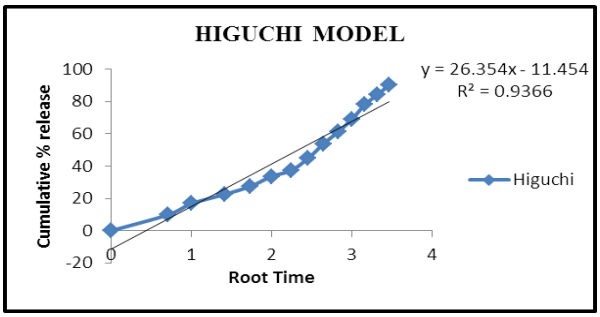

Figure 8: Higuchi Release Kinetics Graph.

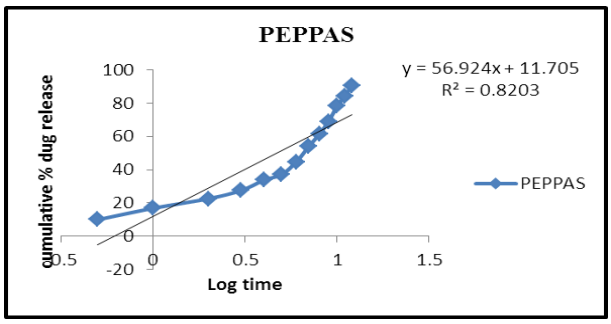

Figure 9: Korsmeyer-Peppas Graph.

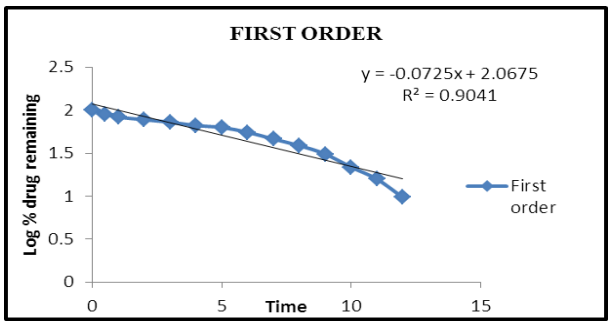

Figure 10: First Order Release Kinetics Graph.

From the figure no's: 7, 8, 9 and 10 it is evident that the formulation F3 followed Zero order release mechanism.

CONCLUSION

In this research work, gastro retentive floating matrix formulation of Captopril by using various hydrophilic polymers was developed. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Methocel and Guar gum as polymeric substances. FTIR studies showed there was no drug-excipient incompatibility. The formulation blend was subjected to various pre-formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations, Methocel K15M as polymer retarded the drug release up to desired time period i.e., 12 hours in the concentration of 180 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F3 Formulation, 98.66% Drug release). The formulations prepared with Methocel K100M were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order mechanism of drug release.

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