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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF SOTALOL CONTROLLED RELEASE MATRIX TABLETS

GOULIKAR SANDHYA*,TUMMALA PRUTHVI RAJ *, VANGOL VARSHITHA*,ARSHIYA KOUSAR*,MIRDODDI SWETHA*

ABSTRACT

The work focuses mainly on controlled the release of Sotalol, formulating them in to matrix tablets by using various matrix materials like Locust Bean gum, Karaya gum and Xanthan gum. Plasma half–life of Sotalol Hcl after oral administration, about 12 hrs and its bioavailability is 90-100 %, So Sotalol is suitable for controlled drug delivery system, which may improve bioavailability. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index. The tablets were subjected to various tests for physical parameters such as thickness, hardness, friability, drug content, and *in vitro* release studies. The prepared tablets were found to have better pharmacopoeial standard values. Among all the formulations F4 formulation showed maximum % drug release i.e., 98.36 % in 12 hours hence it is considered as optimized formulation F4 which contains Locust Bean gum (80mg). The drug release data fit well to the First order release.

KEYWORDS: Sotalol, Locust Bean gum, Karaya gum and Xanthan gum, contolled release tablets

INTRODUCTION

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages

of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. So, controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ . Controlled release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables,utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system.

LITERATURE REVIEW

Othman A Al Hanbali et al.,(2018) Formulation and evaluation of diclofenac controlled release matrix tablets made of HPMC and Poloxamer 188 polymer: An assessment on mechanism of drug release. In this study, hydrophilic hydroxypropyl methylcellulose matrices with various concentrations of Poloxamer 188 were used in the development of oral controlled release tablets containing diclofenac sodium. Four formulations of hydrophilic matrix tablets containing 16.7% w/w HPMC and 0, 6.7, 16.7 and 25.0% w/w Poloxamer 188, respectively, were developed. Tablets were prepared by direct compression and characterized for diameter, hardness, thickness, weight and uniformity of content. The influence of various blends of hydroxypropyl methylcellulose and Poloxamer 188 on the in vitro dissolution profile and mechanism of drug release of was investigated. In the four formulations, the rate of drug release decreased with increasing the concentration of Poloxamer 188 at the initial dissolution stages due to the increase in the apparent viscosity of the gel diffusion layer. However, in the late dissolution stages, the rate of drug release increased with increasing Poloxamer 188 concentration due to the increase in wettability and dissolution of the matrix. The kinetic of drug release from the tablets followed non-Fickian mechanism, as predicted by Korsmeyer-Peppas model, which involves diffusion through the gel layer and erosion of the matrix system.

Kamlesh J. Wadher et al.,(2017) Formulation and Evaluation of Controlled Release Matrix Tablets Using Eudragit RSPO and Gum Copal. In the present investigation an attempt was made

to formulate the oral controlled release metoclopramide hydrochloride matrix tablets by using Eudragit RSPO and natural gums like guar copal as rate controlling polymer and to evaluate drug release parameters as per various release kinetic models. The sustained release matrix tablets of Metoclopramide HCl were prepared by wet granulation process. All tablets were evaluated for their physical parameters for both, precompression and post-compression. FTIR and DSC studies proved that no chemical interaction in drug and polymers. The use of synthetic Eudragit RSPO and gum copal were unable to retard the release of drug more than 10 hrs. The combination of both the polymers found to retard the release of drug for 12 hrs. All the batches showed Mixed Matrix and Peppas best fitted model for release kinetics, which showed that, the release of the drug from the prepared tablets is sustained by swelling, followed by drug diffusion and slow erosion of the polymer. Similarity test was performed between marketed and optimized which shows identical release profile.

AIM AND OBJECTIVES

Aim of the Work

Aim of the study is to formulate and evaluate Sotalol controlled release tablets using different polymers such as Locust Bean gum, Karaya gum and Xanthan gum.
To improve the bioavailability.

PLAN OF WORK

1. Literature Review
2. Selection of drug and polymers
3. Construction of standard graph
4. Drug and Excipient compatibility studies
5. Preparation of powders
6. Evaluation of powders
    - Angle of repose
    - Bulk density
    - Tapped density
    - Powder flow Properties

7. Compression of powder
8. Tablet evaluation Parameters
    - Thickness
    - Hardness
    - Friability
    - Uniformity of weight
    - Drug content

In vitro dissolution

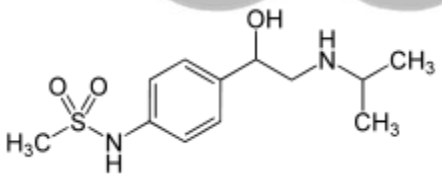
DRUG PROFILE:

Drug : Sotalol

Synonym **:**4'-(1-hydroxy-2-(isopropylamino)ethyl)methane sulfonanilide

Drug category : Hypotensive Agents

Structure :



Chemical name/ Nomenclature / IUPAC Name **:** N-(4-{1-hydroxy-2-[(propan-2-yl)amino]ethyl}phenyl)methanesulfonamide

Molecular Formula : $C_{12}H_{20}N_2O_3S$

Molecular Weight : 272.364 gm/mole.

Official Pharmacopoeia **:** EP, BP

PHYSICOCHEMICAL PROPERTIES:

Description(Physical State): Solid

Solubility: water solubility Soluble (5510 mg/L)

Dosage: Tablet, Injection, Solution

Melting point: 206.5-207 °C

pKa(strongest acidic):10.07

Log P: 0.85

PHARMACOKINETIC PROPERTIES:

Bioavailability : 90 -100 %

Half-life : 12 hrs

Absorption : In healthy subjects, the oral bioavailability of sotalol is 90-100%. Absorption is reduced by approximately 20% compared to fasting when administered with a standard meal.

Protein binding : Sotalol does not bind to plasma proteins. %

Metabolism **:** Sotalol is not metabolized.

Excretion : Kidney Mammary gland (In lactating females)

Adverse effects/Side effects **:** Over 10% of oral sotalol users experience fatigue, dizziness, lightheadedness, headache, weakness, nausea, shortness of breath, bradycardia (slow heart rate), a sensation of the heart beating too hard, fast, or irregularly, or chest pain. Higher doses of sotalol increase the risk for all of these possible side effects.

METHODOLOGY

Analytical method development:

a) Determination of absorption maxima:

100mg of Sotalol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Sotalol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8 and 10 µg/ml of Sotalol per ml of solution. The absorbance of the above dilutions was measured at 227nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Sotalol Total weight of the tablet was considered as 150mg.

Procedure:

1) Sotalol and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

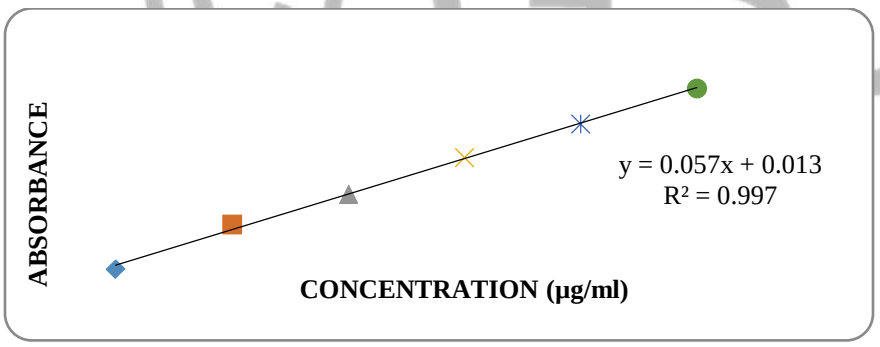
RESULTS AND DISCUSSION

Standard Calibration curve of Sotalol:

Concentration and absorbance obtained for calibration curve of Sotalol in 0.1 N hydrochloric acid buffer (pH 1.2**)**

S. No.	Concentration (µg/ml)	Absorbance* (at 227 nm)
1	0	0
2	2	0.145
3	4	0.244
4	6	0.362
5	8	0.471
6	10	0.586

It was found that the estimation of Sotalol by UV spectrophotometric method at λ_{max} 227.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.



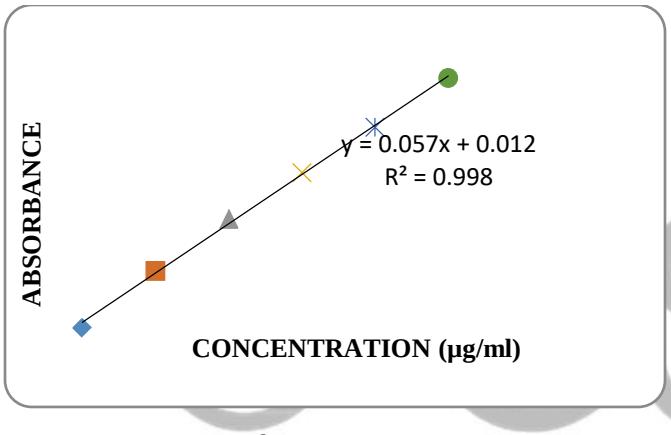
Standard graph of Sotalolin 0.1 N HCl

Concentration and absorbance obtained for calibration curve of Sotalol in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 230 nm)
1	0	0
2	2	0.132

3	4	0.252
4	6	0.359
5	8	0.464
6	10	0.578

It was found that the estimation of Sotalolby UV spectrophotometric method at λ_{max} 230.0 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.



Standard graph of Sotalol in pH 6.8 Phosphate

Formulation composition for tablets

INGREDIENTS	FORMULATION CHART											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Sotalol	40	40	40	40	40	40	40	40	40	40	40	40
Locust Bean gum	20	40	60	80	-	-	-	-	-	-	-	-
Karaya gum	-	-	-	-	20	40	60	80	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	20	40	60	80
Microcrystalline cellulose	81	61	41	21	81	61	41	21	81	61	41	21
Magnesium	4	4	4	4	4	4	4	4	4	4	4	4

stearate												
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150

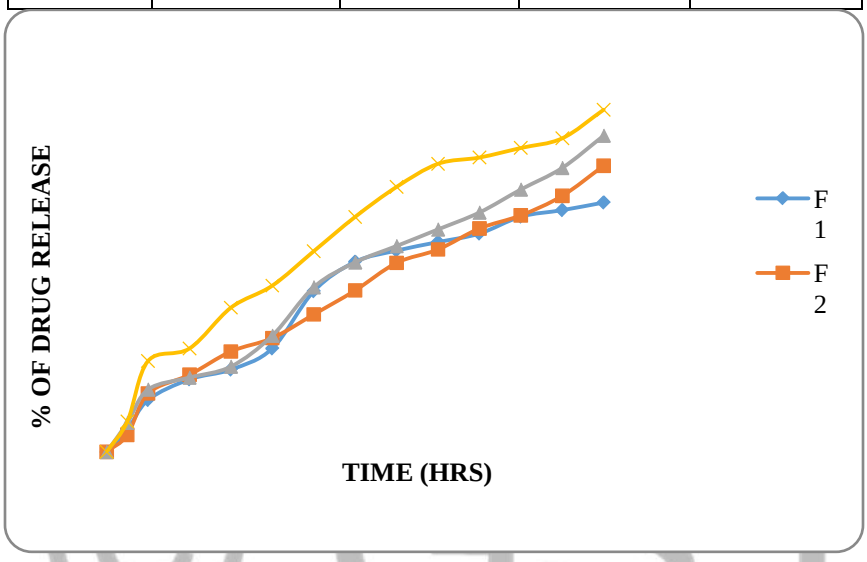
All the quantities were in mg

***In-Vitro* Dissolution studies:** *In-Vitro* dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours.The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7,8,9, 10,11 and 12 hours respectively.

***In vitro* drug release of containing Sotalol F1 to F4 formulations**

TIME (hr)	**CUMULATIVE PERCENT DRUG RELEASED**			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
0.5	6.28	4.86	08.39	8.75
1	14.92	16.79	17.94	26.13
2	20.85	22.15	21.37	29.72
3	23.66	28.86	24.52	41.45
4	29.73	32.70	33.42	47.79
5	46.18	39.50	47.34	57.68
6	54.64	46.40	54.48	67.56
7	57.87	54.33	59.19	76.17

8	60.31	58.17	63.96	82.82
9	62.75	64.21	68.82	84.62
10	67.62	67.98	75.44	87.37
11	69.49	73.59	81.65	90.15
12	71.68	82.25	90.92	98.36

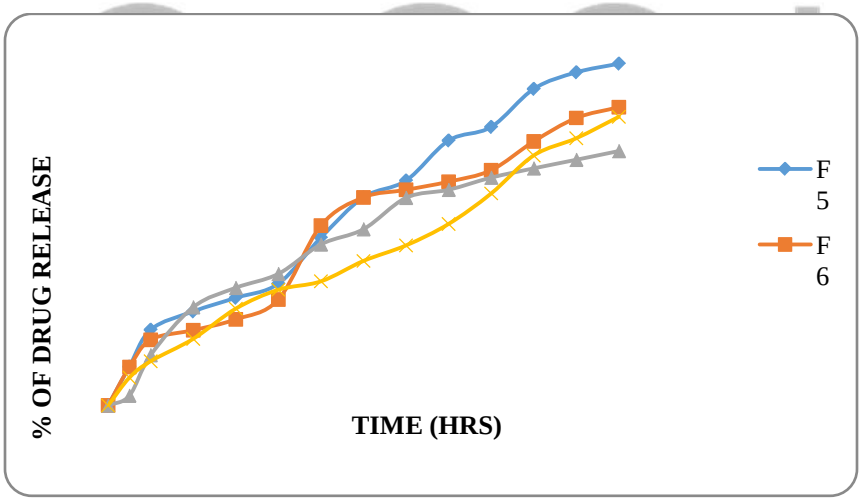


Dissolution profile of formulations prepared with Locust Bean gum polymer

***In vitro* drug release of Sotalol F5 to F8 formulations**

TIME (hr)	**CUMULATIVE PERCENT DRUG RELEASED**			
	F5	**F6**	**F7**	**F8**
0	0	0	0	0
0.5	10.6	10.46	2.68	7.58
1	20.65	17.91	13.72	12.07
2	25.63	20.50	26.77	18.16
3	29.35	23.46	32.05	26.39

4	33.21	28.89	35.85	31.54
5	45.76	49.03	43.87	33.83
6	56.76	56.70	48.02	39.40
7	61.32	58.76	56.57	43.63
8	72.23	60.98	58.76	49.48
9	75.93	64.12	62.07	57.78
10	86.30	71.95	64.59	68.15
11	90.82	78.34	66.93	72.84
12	93.19	81.28	69.31	78.69

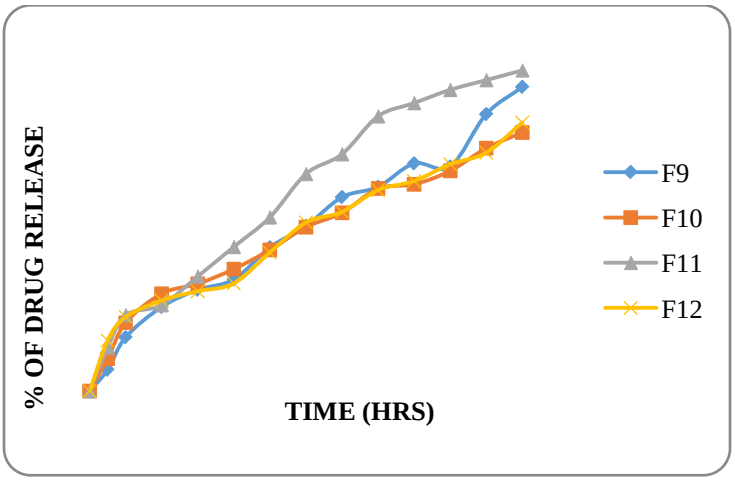


Dissolution profile of formulations prepared with Karaya gum polymer

***In vitro* drug release of Sotalol F9 to F12 formulations**

TIME (hr)	**CUMULATIVE PERCENT DRUG RELEASED**			
	F9	**F10**	**F11**	**F12**
0	0	0	0	0

0.5	5.86	8.85	11.98	13.92
1	14.79	18.81	20.91	20.36
2	23.15	26.80	23.66	24.95
3	27.86	29.52	31.55	27.47
4	30.70	33.58	39.68	29.63
5	39.50	38.85	47.82	38.12
6	45.40	45.12	59.75	46.39
7	53.33	49.05	65.19	49.28
8	56.17	55.73	75.62	55.31
9	62.60	56.92	79.26	57.79
10	61.75	60.60	82.89	62.42
11	76.16	66.84	85.58	65.59
12	83.64	71.18	88.25	73.90



Dissolution profile of formulations prepared with Xanthan gum as polymer

From the tabular column it was evident that the formulations prepared with Locust Bean gum as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. Locust Bean gum in the concentration of 80 mg showed good % drug release i.e., 98.36 in 12 hours.

Where as in case of formulations prepared with Karaya gum as retarding polymer, the formulations with 20 mg concentration of polymer showed complete drug release in 12 hours only, low concentrations the polymer was produce the required retarding action to the tablets. The Formulation Containing Karaya gum in 20 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 93.19 %.

The Formulation Containing Xanthan gum in 60 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e 88.25%.

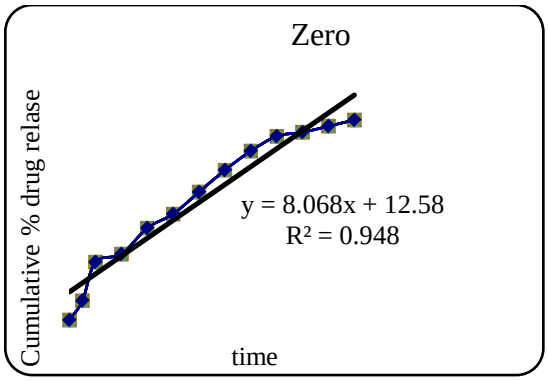
From the above results it was evident that the formulation F4 is best formulation with desired drug release pattern extended up to 12 hours.

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.

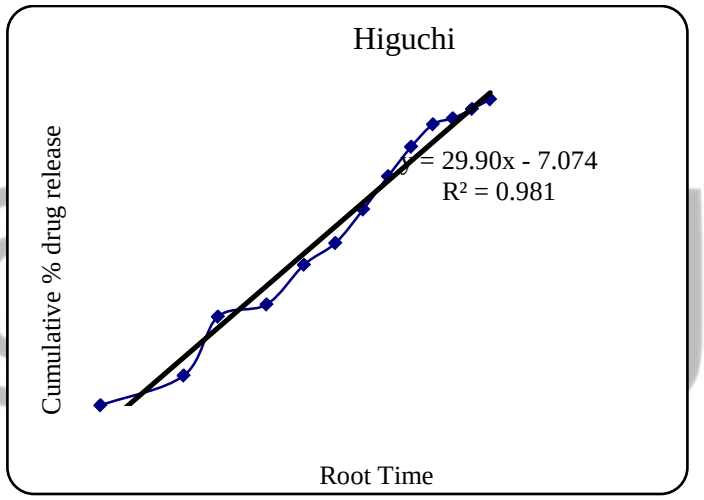
Release kinetics data for optimised formulation

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	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
8.75	**0.5**	0.707	0.942	-0.301	1.960	17.500	0.1143	-1.058	91.25	4.642	4.502	0.140
26.13	**1**	1.000	1.417	0.000	1.868	26.130	0.0383	-0.583	73.87	4.642	4.196	0.446
29.72	**2**	1.414	1.473	0.301	1.847	14.860	0.0336	-0.527	70.28	4.642	4.127	0.515
41.45	**3**	1.732	1.618	0.477	1.768	13.817	0.0241	-0.382	58.55	4.642	3.883	0.759
47.79	**4**	2.000	1.679	0.602	1.718	11.948	0.0209	-0.321	52.21	4.642	3.738	0.904
57.68	**5**	2.236	1.761	0.699	1.627	11.536	0.0173	-0.239	42.32	4.642	3.485	1.157
67.56	**6**	2.449	1.830	0.778	1.511	11.260	0.0148	-0.170	32.44	4.642	3.189	1.452
76.17	**7**	2.646	1.882	0.845	1.377	10.881	0.0131	-0.118	23.83	4.642	2.878	1.764
82.82	**8**	2.828	1.918	0.903	1.235	10.353	0.0121	-0.082	17.18	4.642	2.580	2.061
84.62	**9**	3.000	1.927	0.954	1.187	9.402	0.0118	-0.073	15.38	4.642	2.487	2.155
87.37	**10**	3.162	1.941	1.000	1.101	8.737	0.0114	-0.059	12.63	4.642	2.329	2.313

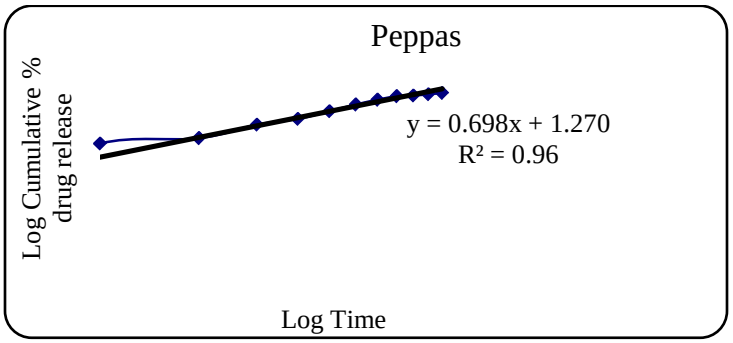
90.15	**11**	3.317	1.955	1.041	0.993	8.195	0.0111	-0.045	9.85	4.642	2.144	2.498
98.36	**12**	3.464	1.993	1.079	0.215	8.197	0.0102	-0.007	1.64	4.642	1.179	3.462



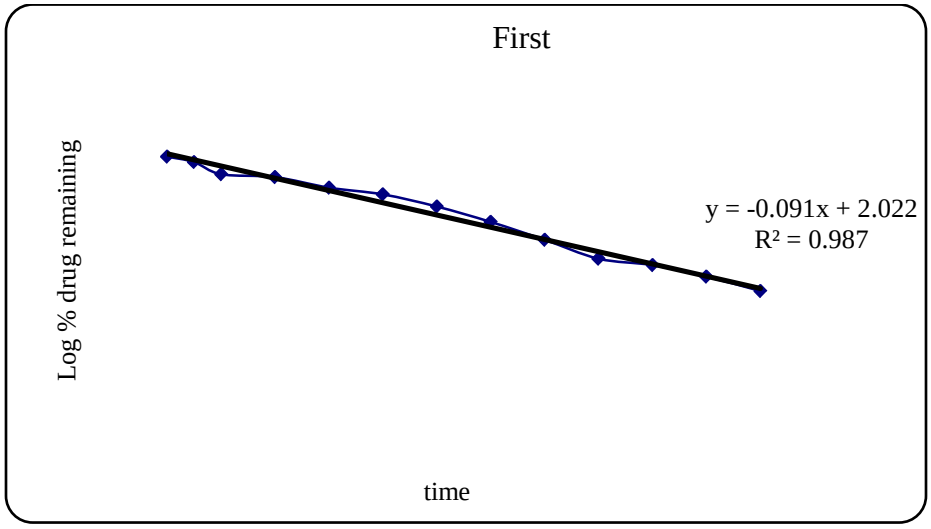
Zero order release kinetics graph



Higuchi release kinetics graph



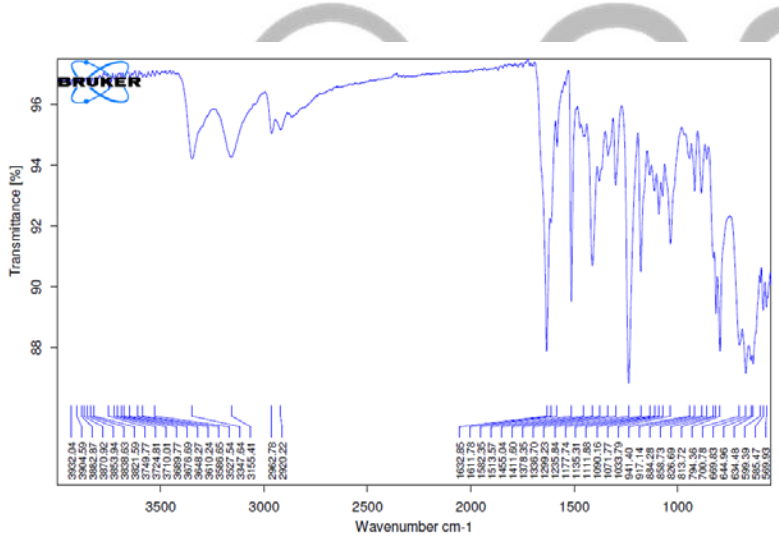
Kars mayer peppas graph



First order release kinetics graph

From the above graphs it was evident that the formulation F4 was followed First order release kinetics mechanism.

FTIR



FT-IR Spectrum of Sotalol pure drug

CONCLUSION

The present study was carried out to evaluate the natural polymers for its matrix forming ability due to formation of thick gel structure, so we concluded that Locust Bean gum, Karaya gum and Xanthan gum formulated tablets were found to be effective in controlled the drug release up to 12 hr. During this study, FT-IR studies resulted that all peaks corresponding to different functional groups of pure drug were present in the drug-exipient mixture no interaction between

the drug and excipients. It can be concluded that stable formulation could be developed by incorporating natural polymer in a definite proportion, so that the controlled released profile is maintained for an extended period. Among all the formulations F4 formulation showed maximum % drug release i.e., 98.36 % in 12 hours hence it is considered as optimized formulation F4 which contains Locust Bean gum (80mg). Release model of sample was found to follow First order release kinetics with high linearity.

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