



FORMULATION AND EVALUATION OF CAPECITABINE SUSTAINED RELEASE TABLETS

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ABSTRACT

The objective of the study was to develop a sustained release tablet of Capecitabine an anti cancer drug. The sustained release tablets were prepared by direct compression Method using different drug and polymer ratios such as C1 to C9. Natural Polymers Like Guar gum , Karaya gum and Xanthan gum were used compatibility of drug with various excipients was studied. The compressed Tablets were evaluated and Showed compliance with pharmacopoeial limits. The optimized formulation C9 on the basis of acceptable tablet properties and in vitro drug release. The resulting formulation were done the pre compression and Post compression parameters are with in the limits. All tablets but one exhibited gradual and near completion sustained release for Capecitabine and 99.36% released at the end of 12hrs. The results of dissolution studies indicated that formulation C9 the most successful best release among all the formulations. The Kinetics study was done for C9 Formulation

Key Words : Capecitabine , Guar gum , Karaya gum and Xanthan gum Sustained release Tablets.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.^{1,2}

SUSTAINED DRUG DELIVERY SYSTEM:

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained release dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Physicians can achieve several desirable therapeutics advantages by prescribing sustained release dosage forms. Since, the frequency of drug administration is reduced, patient's compliance can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing forms of conventional dosage forms is reduced, because a more even blood level is maintained in the design of sustained release dosage forms. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage forms gives increased reliability.

Not all the drugs are suitable candidates for the sustained release dosage form. Ideal characteristics of the drug for the sustained release dosage form are;

- ✓ Drug should have a shorter half-life as drugs with a longer half-life are inherently long acting drugs.
- ✓ Drug should be absorbed from large portions of the gastrointestinal tract, since absorption must occur through the gut.
- ✓ Drug should have a good solubility profile to be a good candidate for sustained release dosage forms.
- ✓ Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage forms.^{3,4,5}

Recent trends in sustained drug delivery system:**Sustained release dosage forms are categorized as:**

- Single unit dosage form.
- Multiple unit dosage form.
- Mucoadhesive system.

Single unit dosage form:

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film.

These systems can be classified as:**Monolithic system:**

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate-limiting step.

These are categorized as:**Hydrophobic/Swellable tablet:**

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from device within the GI tract after oral administration.

Floating tablet or capsule:

Designing of Floating tablet or capsule are called hydro-dynamically balanced drug delivery system is based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

Semisolid matrix system:

In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

Coated tablet and Similar Multilayer system:

Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process. In the simplest form coated tablet comprised a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic).

Multilayered tablet having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water-soluble drugs. In this case, coating which controls the release process covers the core tablet containing the drug only partially.

Osmotic device:

In osmotic device usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

Multiple unit dosage forms:

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are inevitable in a single unit dosage form. The various forms are as:

- Micro granules/Spheroids.
- Beads.
- Pellets.
- Microcapsules.

Mucoadhesive systems:

It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or non-biological origin. If the substance is mucosal membrane the phenomenon is known as mucoadhesion. Conventional controlled release dosage forms described above are restrained localized in selected regions of GIT. Mucoadhesive systems are suitable to increased the contact time of drug with absorbing membrane and localization of delivery of drug at target sites.³

MATERIALS

Capecitabine-Procured From Avik Pharma Pvt. Ltd., Vapi, Gujarat, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Guar gum-Merck Specialities Pvt Ltd, Mumbai, India, Karaya gum-Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum-Merck Specialities Pvt Ltd, Mumbai, India, PVP K 30-Yarrow Chem. Products, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate-Merck Specialities Pvt Ltd, Mumbai, India, MCC-Merck Specialities Pvt Ltd, Mumbai, India

METHODOLOGY**Determination of Wavelength:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

9.2. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

$$h = \text{Height of the cone, } r = \text{Radius of the cone base}$$

Formulation composition for tablets

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9
Capecitabine	150	150	150	150	150	150	150	150	150
Guar gum	25	50	75	-	-	-	-	-	-
Karaya gum	-	-	-	25	50	75	-	-	-
Xanthan gum	-	-	-	-	-	-	25	50	75
PVP K 30	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10
MCC	190	165	140	190	165	140	190	165	145
Total Weight	400	400	400	400	400	400	400	400	400

All the quantities were in mg

RESULTS AND DISCUSSION

The present study was aimed to developing Sustained release tablets of Capecitabine using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Capecitabine were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 240 nm and 240 nm respectively.

Table : Observations for graph of Capecitabine in 0.1N HCl (240nm)

Conc [µg/ml]	Absorbance
0	0
10	0.124
20	0.249
30	0.367
40	0.488
50	0.614

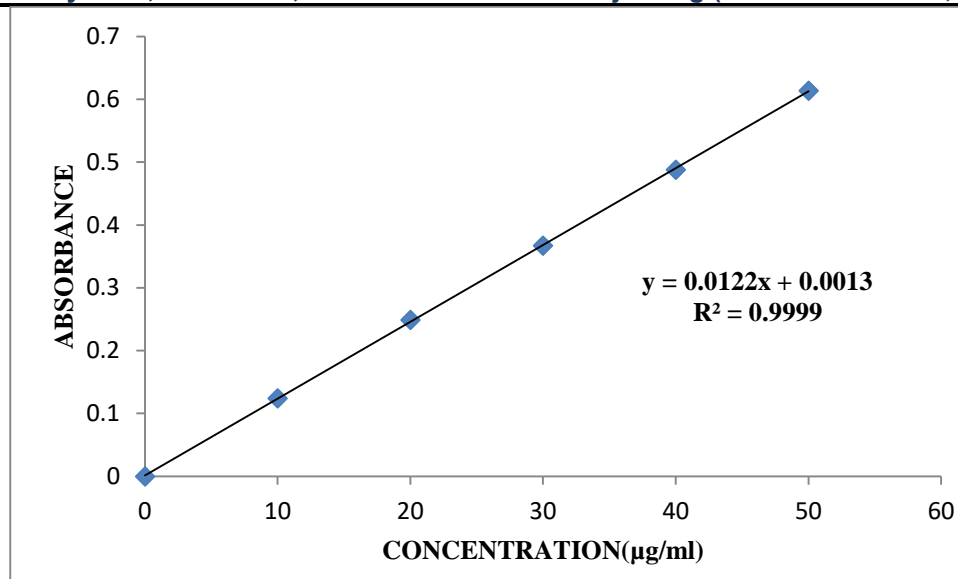


Figure : Standard graph of Capecitabine in 0.1N HCl

Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	27.11	0.389	0.401	10.20	1.077
C2	25.40	0.329	0.348	13.68	1.090
C3	26.19	0.342	0.365	7.92	1.085
C4	25.80	0.322	0.342	14.81	1.176
C5	24.30	0.349	0.371	10.90	1.178
C6	26.88	0.379	0.409	8.88	1.084
C7	26.52	0.383	0.398	16.32	1.181
C8	27.70	0.386	0.406	17.34	1.209
C9	26.86	0.345	0.365	13.68	1.158

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 0.322 to 0.386 (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 0.342 to 0.409 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 25 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.333 indicating the powder has good flow properties.

In Vitro Drug Release Studies

Dissolution data of Floating Tablets

TIME(Hrs)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
1	16.88	15.82	16.96	15.71	14.47	14.23	13.85	18.51	14.32
2	21.74	21.71	19.21	19.32	19.32	23.61	15.55	19.87	23.31
3	29.47	26.98	20.52	23.71	24.85	35.84	26.36	23.32	35.74
4	36.11	33.21	24.54	35.85	36.63	39.54	37.74	35.85	44.89
5	49.69	38.87	35.31	41.13	47.25	40.87	40.25	48.87	58.64
6	53.31	42.92	43.28	47.87	54.85	44.98	45.85	49.27	59.99
7	58.39	57.39	48.27	56.47	59.36	56.74	54.87	51.25	66.41
8	62.74	66.11	50.62	68.52	67.81	63.87	66.85	64.32	74.52
9	74.98	69.84	65.49	74.21	78.99	75.33	74.87	65.95	88.87
10	80.28	72.74	78.68	78.31	83.14	79.25	78.87	75.12	90.74
11	85.57	84.47	86.59	86.84	87.31	83.52	84.19	88.31	91.11
12	95.38	93.89	90.78	93.95	94.14	94.95	92.25	93.74	99.36

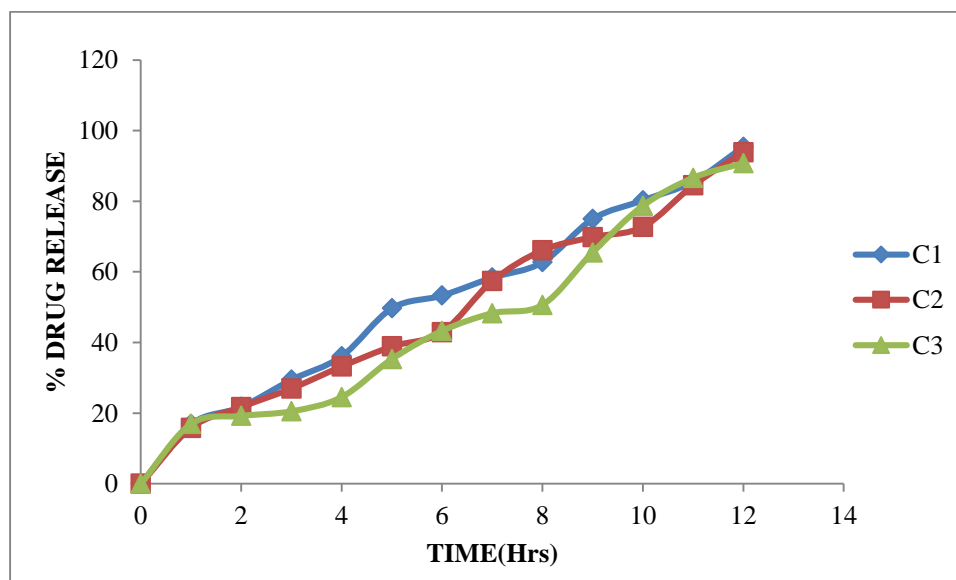


Fig : Dissolution profile of Capecitabine (C1-C3 formulations).

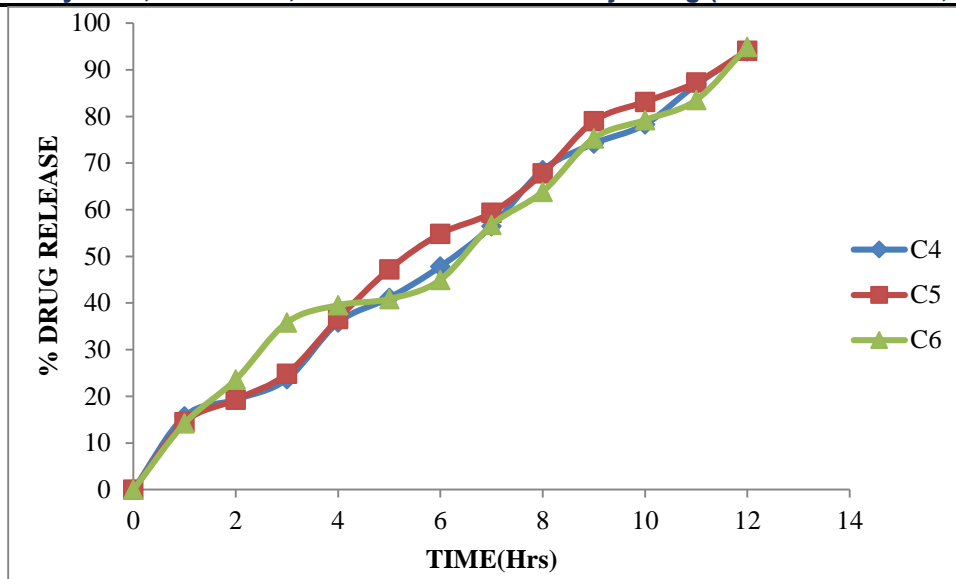


Fig: Dissolution profile of Capecitabine (C4- C6 formulations)

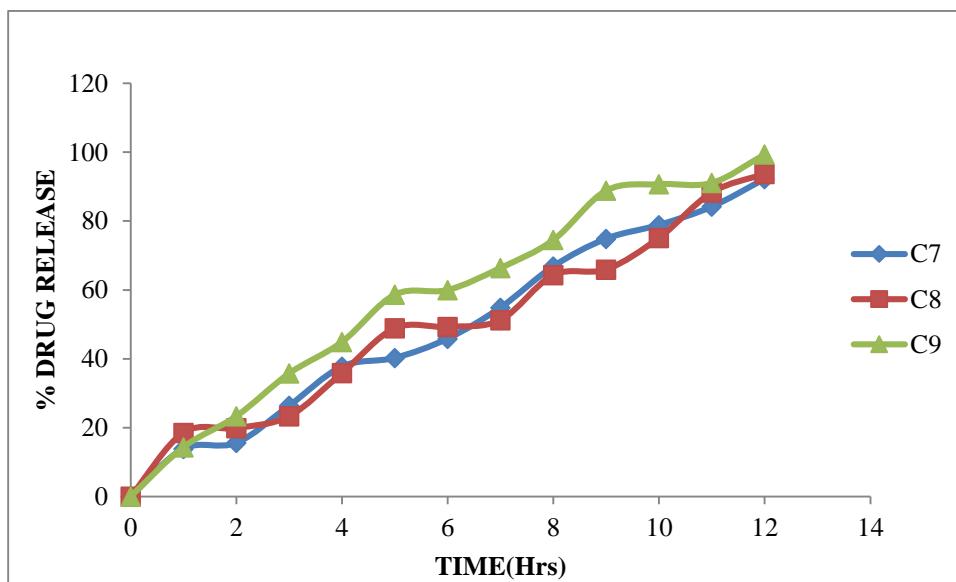


Fig: Dissolution profile of Capecitabine (C7- C9 formulations)

From the dissolution data it was evident that the formulations prepared with Guar gum as polymer were retard the drug release up to desired time period i.e., 12 hours and showed maximum of (C1) 95.38 % in 12 hours with good retardation.

Formulations prepared with Karaya gum retarded the drug release in the concentration of 75 mg (C6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 94.95 % in 12 hours with good retardation but increase the concentration of polymer the release pattern is not uniform.

Formulations prepared with Xanthan gum retarded the drug release in the concentration of 75 mg (C9 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.367% in 12 hours with good retardation but increase the concentration of polymer the release pattern is not uniform.

Among all 9 formulations C9 formulation showed good drug permeation from the patch. Among all *in vitro* evaluation parameters C9 formulation passed all evaluation parameter.

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 : Release Rate Kinetics to Dissolution Data

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
14.32	1	1.000	1.156	0.000	1.933	14.320	0.0698	-0.844	85.68	4.642	4.409	0.233
23.31	2	1.414	1.368	0.301	1.885	11.655	0.0429	-0.632	76.69	4.642	4.249	0.393
35.74	3	1.732	1.553	0.477	1.808	11.913	0.0280	-0.447	64.26	4.642	4.005	0.636
44.89	4	2.000	1.652	0.602	1.741	11.223	0.0223	-0.348	55.11	4.642	3.805	0.836
58.64	5	2.236	1.768	0.699	1.617	11.728	0.0171	-0.232	41.36	4.642	3.458	1.183
59.99	6	2.449	1.778	0.778	1.602	9.998	0.0167	-0.222	40.01	4.642	3.420	1.221
66.41	7	2.646	1.822	0.845	1.526	9.487	0.0151	-0.178	33.59	4.642	3.227	1.415
74.52	8	2.828	1.872	0.903	1.406	9.315	0.0134	-0.128	25.48	4.642	2.943	1.699
88.87	9	3.000	1.949	0.954	1.046	9.874	0.0113	-0.051	11.13	4.642	2.233	2.409
90.74	10	3.162	1.958	1.000	0.967	9.074	0.0110	-0.042	9.26	4.642	2.100	2.542
91.11	11	3.317	1.960	1.041	0.949	8.283	0.0110	-0.040	8.89	4.642	2.072	2.570
99.36	12	3.464	1.997	1.079	-0.194	8.280	0.0101	-0.003	0.64	4.642	0.862	3.780

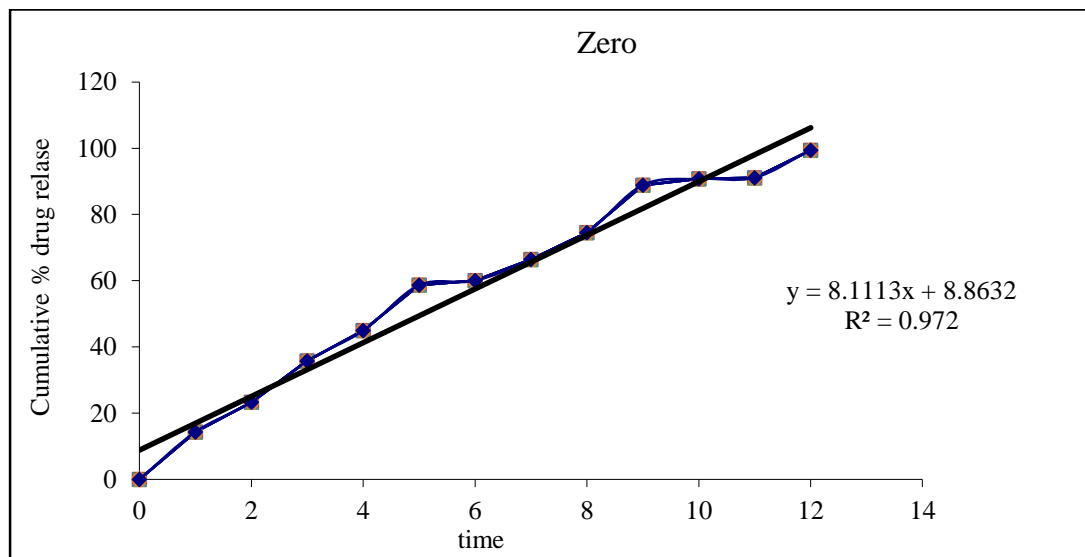


Fig : Zero order release kinetics graph

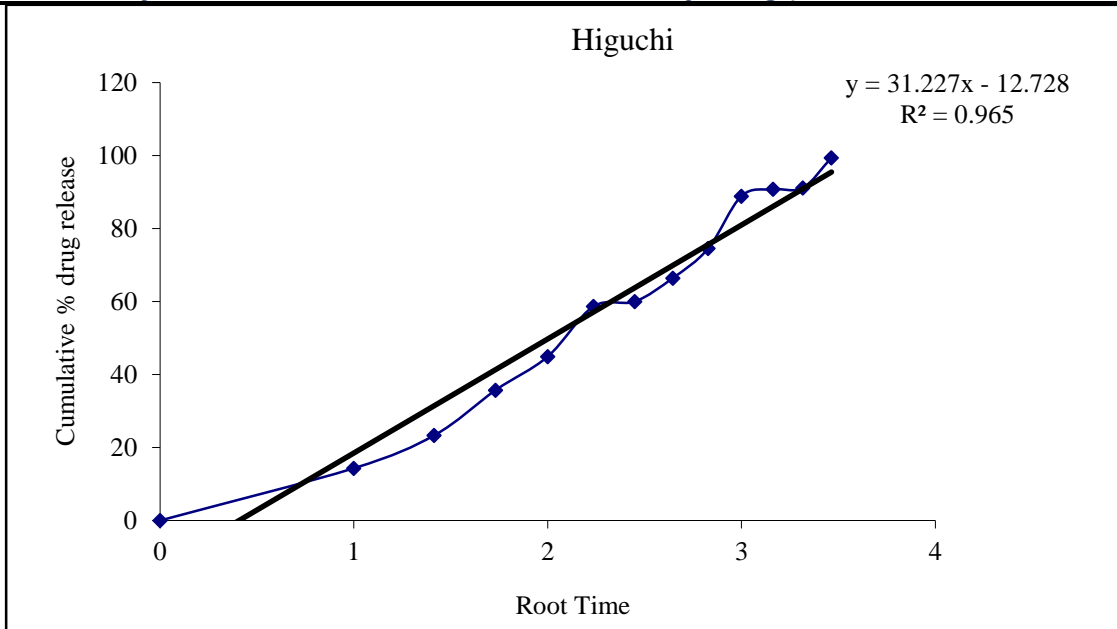


Fig : Higuchi release kinetics graph

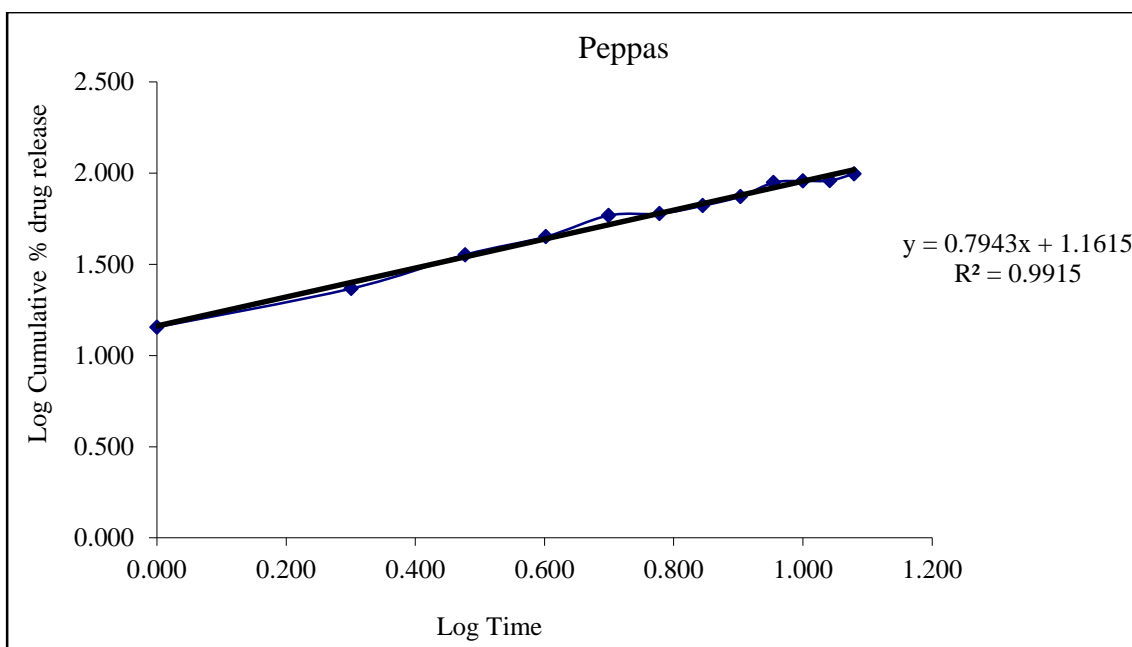


Fig : Kars mayer peppas graph

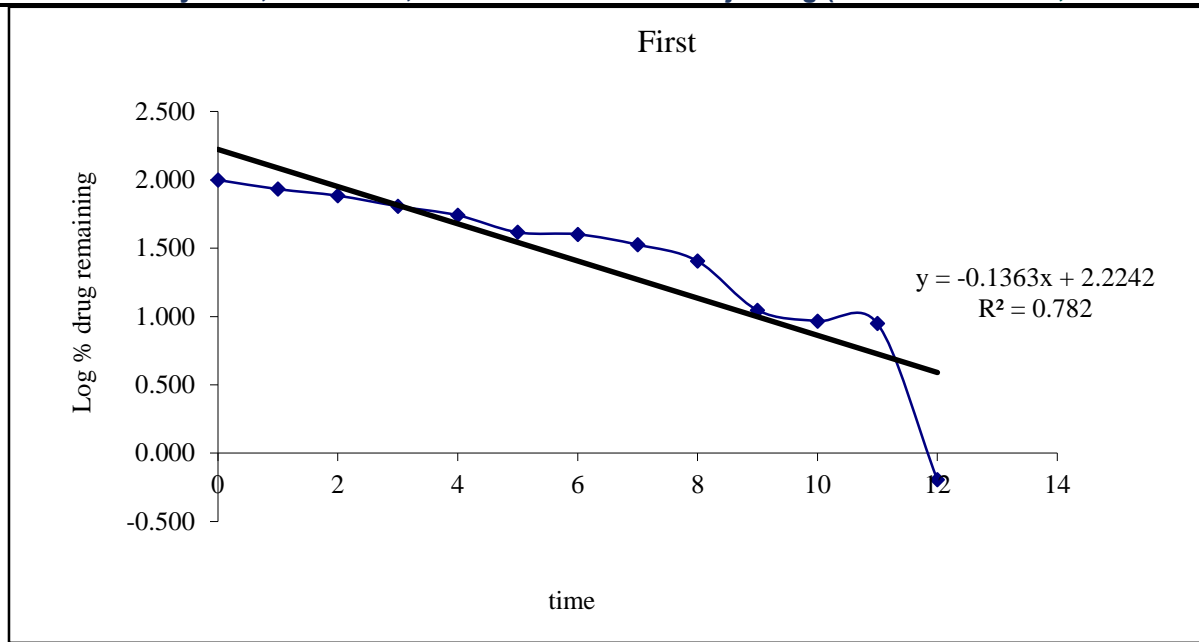


Fig : First order release kinetics graph

From the above graphs it was evident that the formulation F9 was followed Peppas release kinetics.

Drug and excipient compatibility studies

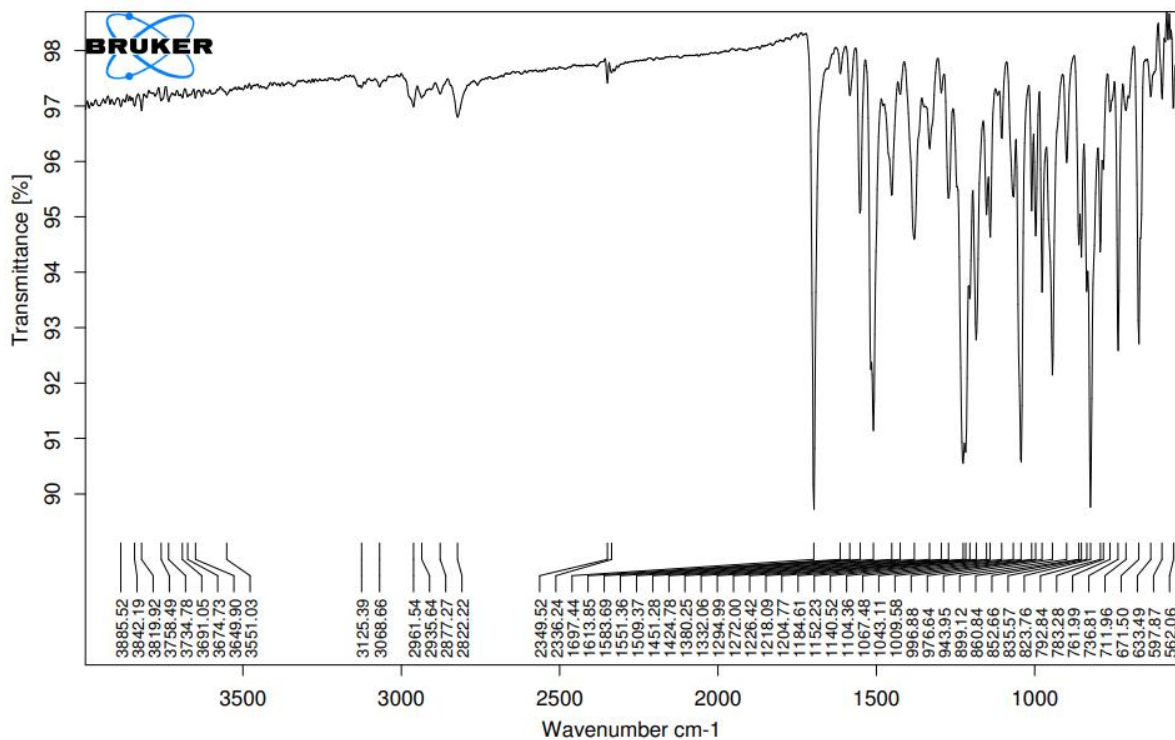


Figure 8.9: FT-TR Spectrum of Capecitabine pure drug.

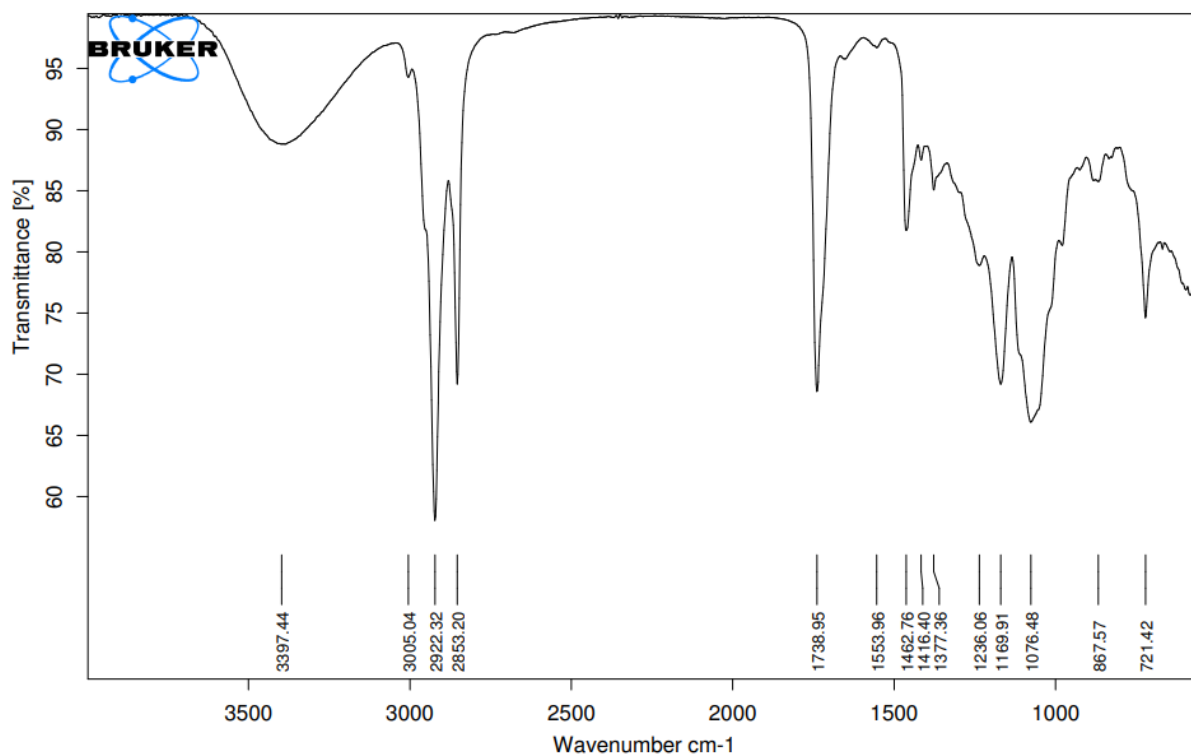


Figure 8.10: FT-IR Spectrum of Optimised Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION:

The aim of the study was to study the effect of various natural polymers on in vitro release rate from sustained release tablets of Capecitabine. Different types of polymers like Guar gum, Karaya gum and Xanthan gum by using Direct Compression Method. The usage of polymer Xanthan gum was successful to achieve the sustained drug release for 12 hours from the Capecitabine sustained release tablets. Formulation C9 showed sustained drug release for 12 hours so it was selected as the best formulation among all the Nine formulations. The Kinetics of drug release was best explained by zero order equation.

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