ISSN: 2306-6091

International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.13 | Issue 4 | Oct - Dec -2025

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v13.iss4.2025.607 -620

Review

Formulation and Evaluation of Paclitaxel Controlled Release Tablets

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Published on: 24 Oct 2025

Published by:
Futuristic Publications

Abstract

The aim of the present study was to develop Paclitaxel controlled release tablets to maintain constant therapeutic levels of the drug for over 12 hrs. Carbopol974P, Xanthan Gum and HPMC K 15M were used as polymers. All the formulations were passed various physicochemical evaluation parameters such as Bulk Density, Tapped Density, Carrs Index, Hausners Ratio, Angle of Repose, Weight Variation, Hardness, Thickness, Friability and Drug Content. From the dissolution studies it was evident that the formulation F5 showed better and desired drug release pattern i.e., 99.16 % in 12 hours. It contains the Xanthan Gum as polymer. It followed peppas order release kinetics.

Keywords: Paclitaxel, Carbopol974P, Xanthan Gum and HPMC K 15M, Controlled release tablets.

1. INTRODUCTION[1-9]:

Controlled release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first Controlled release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Controlled release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing Controlled or Controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- If the active compound has a long half-life, it is Controlled on its own,
- If the pharmacological activity of the active is not directly related to its blood levels,
- If the absorption of the drug involves an active transport and
- If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as Controlled release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of Controlled release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of Controlled release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the Controlled release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.3.1. Diffusion Controlled System:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx.

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane. The drug release rate dm/ dt is given by

dm/ dt= ADKΔ C/L

Where;

A = Area.

K = Partition coefficient of drug between the membrane and drug core.

L= Diffusion path length (i.e. thickness of coat).

Δc= Concentration difference across the membrane.

i) Reservoir Type:

In the system, a water insoluble polymeric material encases a core of drug (Figure 4). Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

CHARACTERIZATION:

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages: Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails

ii) Matrix Type:

A solid drug is dispersed in an insoluble matrix (Figure 5.) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system:

$Q = D\varepsilon / T [2A - \varepsilon C_s] C_s t^{1/2}$

Where;

Q = Weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix.
Cs = Solubility of drug in release medium.
T= Tortuosity of the matrix.
A = Concentration of drug in the tablet, as gm/ ml.

CHARACTERIZATION:

Description: Homogenous dispersion of solid drug in a polymer mixture.
Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.
Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat.

The release rate can be given by following equation.

Release rate = AD / L = [C1- C2]
Where;
A = Area.
D = Diffusion coefficient.
C1 = Drug concentration in the core.
C2 = Drug concentration in the surrounding medium.
L = Diffusional path length.

Thus diffusion Controlled products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

METHODOLOGY

7.1. Analytical method development:
Determination of absorption maxima:

100mg of Paclitaxel 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 – 400nm.

a) Preparation calibration curve:

100mg of Paclitaxel 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 5,10,15,20 and 25 µg/ml of Paclitaxel per ml of solution. The absorbance of the above dilutions was measured at 225 nm 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.

7.3. Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Paclitaxel. Total weight of the tablet was considered as 300mg.

Procedure:

1. Paclitaxel 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.

Table 7.3: Formulation composition for tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paclitaxel	100	100	100	100	100	100	100	100	100	100	100	100
Carbopol974P	20	40	60	80	-	-	-	-	-	-	-	-
Xanthan Gum	-	-	-	-	20	40	60	80	-	-	-	-
HPMC K 15M	-	-	-	-	-	-	-	-	20	40	60	80
MCC	171	151	131	111	171	151	131	111	171	151	131	111
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight(mg)	300	300	300	300	300	300	300	300	300	300	300	300

All the quantities were in mg
Total Tablet Weight = 300 mg

RESULTS AND DISCUSSION

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

8.1. Analytical Method

Graphs of Paclitaxel was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 225 nm and 227 nm respectively.

Table 8.1:Observations for graph of Paclitaxel in 0.1N HCl (225)

Concentration [µg/mL]	Absorbance
0	0
5	0.132
10	0.241
15	0.369
20	0.478
25	0.582

It was found that the estimation of Paclitaxel by UV spectrophotometric method at λ_{max} 225.0 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, 5-25µg/ml. The regression equation generated was y = 0.023x+0.009

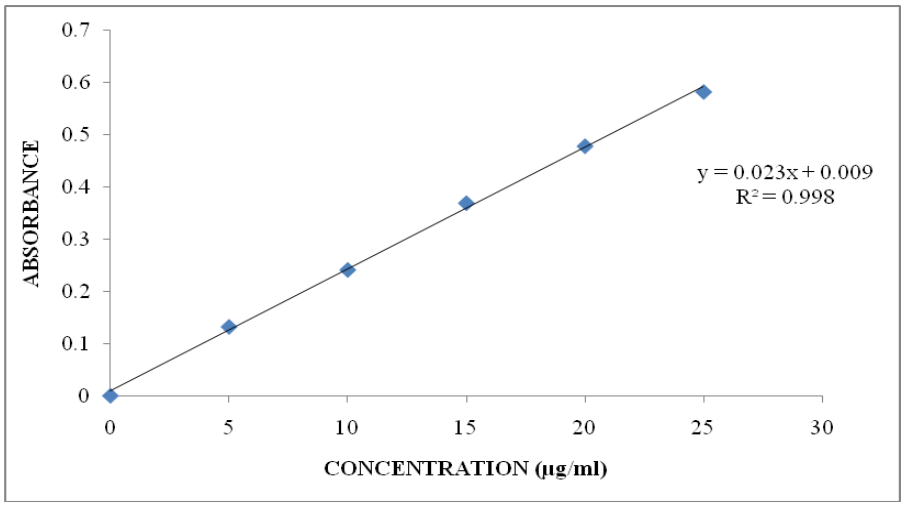

Figure 8.1: Standard graph of Paclitaxel in 0.1N HCl

Table 8.2: Observations for graph of Paclitaxel in p H 6.8 phosphate buffer (227nm)

Conc [µg/ml]	Abs
0	0
5	0.117
10	0.248
15	0.359
20	0.471
25	0.594

It was found that the estimation of Paclitaxel by UV spectrophotometric method at λ_{max} 227 nm in pH 6.8 Phosphate buffer. 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, 5-25µg/ml. The regression equation generated was y = 0.023x + 0.002.

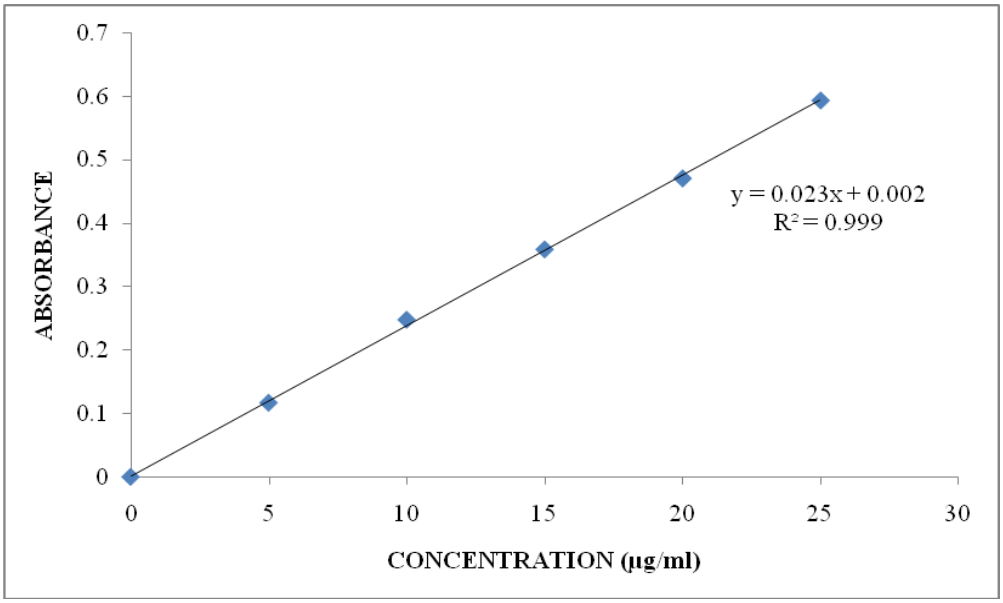

Figure 8.2: Standard graph of Paclitaxel pH 6.8 phosphate buffer (227nm)

8.2. Preformulation parameters of powder blend

Table 8.3: 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
F1	24.2	0.419	0.486	13.95	1.162
F2	24.5	0.409	0.485	15.68	1.186
F3	25.2	0.409	0.480	14.77	1.173
F4	27.8	0.429	0.488	12.14	1.138
F5	27.2	0.450	0.501	10.25	1.114
F6	26.4	0.462	0.522	11.54	1.130
F7	30.2	0.450	0.507	11.25	1.127
F8	29.3	0.439	0.504	12.93	1.148
F9	28.5	0.462	0.526	12.31	1.140
F10	28.0	0.450	0.500	10.00	1.111
F11	27.5	0.439	0.496	11.46	1.129
F12	28.3	0.429	0.493	13.10	1.151

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 0.409 to 0.450 (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 0.480 to 0.526 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 12.14 to 15.68 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.111 to 1.173 indicating the powder has good flow properties.

8.3. Quality Control Parameters for tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 8.4: *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	298.15	5.1	0.25	4.31	98.68
F2	299.65	5.3	0.41	4.68	97.35
F3	295.79	5.0	0.63	4.39	99.25
F4	300.02	5.9	0.58	4.82	96.90
F5	297.32	5.6	0.49	4.93	97.58
F6	298.54	5.7	0.11	4.52	99.12
F7	299.78	5.8	0.57	4.33	98.45
F8	300.0	5.1	0.62	4.27	97.65
F9	297.28	5.9	0.75	4.12	99.10
F10	299.82	5.4	0.61	4.96	100.0
F11	299.10	5.6	0.38	4.86	97.52
F12	300.1	5.9	0.27	4.33	99.44

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

8.4. *In Vitro* Drug Release Studies

Table 8.5: Dissolution Data of Paclitaxel Tablets Prepared With Carbopol974P Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F1	F2	F3	F4
0	**0**	**0**	**0**	**0**
0.5	16.4	13.2	9.6	9.28
1	23.7	15.8	12.3	13.40
2	31.6	17.2	14.8	19.75
3	40.4	22.8	18.9	26.05
4	53.4	33.3	22.3	30.58
5	59.4	39.2	33.9	40.04
6	65.4	47.8	38.7	47.96
7	71.5	56.4	44.8	52.45
8	87.3	59.9	53.6	56.11
9	97.45	62.2	66.6	63.74
10	99.2	72.8	72.8	68.91
11		83.8	79.5	70.04
12		89.2	81.2	78.74

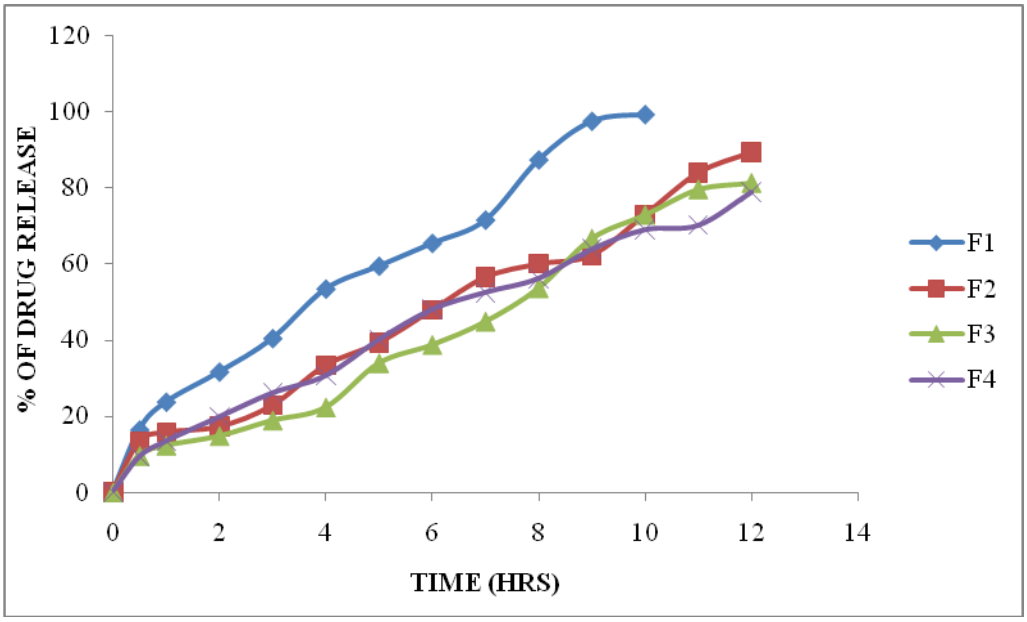

Figure 8.3: Dissolution profile of Paclitaxel (F1, F2, F3 and F4 formulations).

Table 8.6: Dissolution Data of Paclitaxel Tablets Prepared With Xanthan Gum in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F5	F6	F7	F8
0	0	0	0	0
0.5	09.61	8.59	9.28	10.22
1	18.06	17.56	13.40	17.97
2	24.35	25.70	19.75	28.22
3	34.59	39.05	26.05	37.35
4	41.78	44.9	30.58	41.10
5	48.35	58.54	40.04	45.34
6	56.50	63.54	47.96	52.23
7	64.52	65.47	58.45	58.76
8	70.90	70.17	66.11	63.38
9	75.53	74.36	72.74	69.45
10	81.27	79.67	78..91	74.56
11	89.19	85.75	80.04	76.12
12	99.16	90.48	84.74	79.27

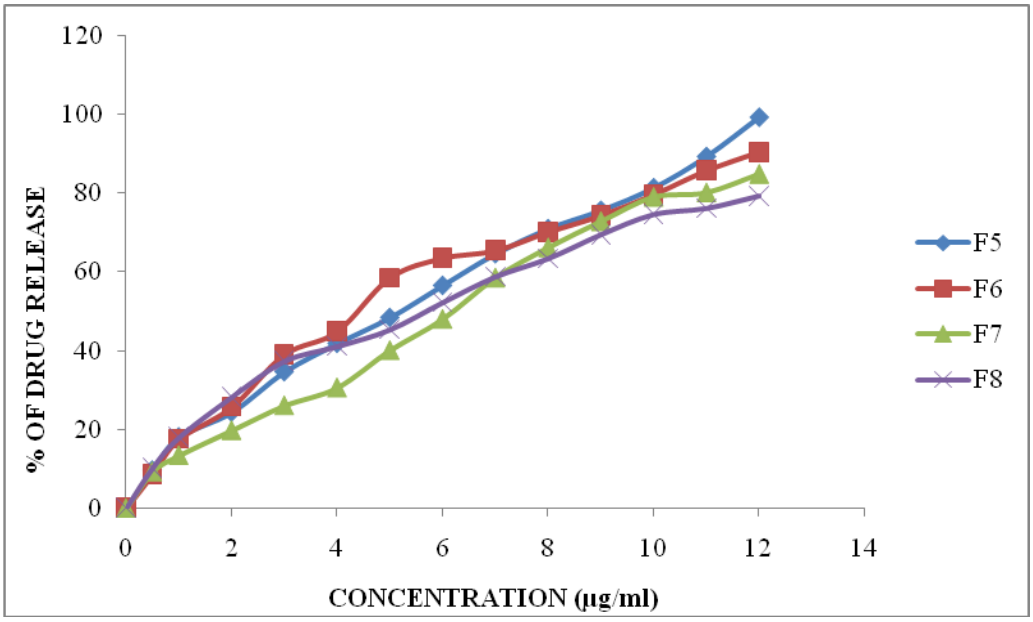

Figure 8.4: Dissolution profile of Paclitaxel (F5, F6, F7 and F8 formulations)

Table 8.7: Dissolution Data of Paclitaxel Tablets Prepared With HPMCK15 in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F9	F10	F11	F12
0	0	0	0	0
0.5	12.63	9.14	7.23	13.28
1	24.87	26.05	13.24	15.87
2	33.41	33.52	29.06	17.29
3	40.54	48.45	37.25	22.85
4	46.00	56.74	49.98	33.32
5	54.10	64.86	54.57	39.21
6	66.06	69.52	69.67	47.86
7	75.28	73.29	72.50	56.47
8	88.95	77.19	81.60	59.93
9	95.72	81.87	87.34	62.24
10		90.78	90.17	72.88
11		98.31	93.23	83.42
12			98.64	89.12

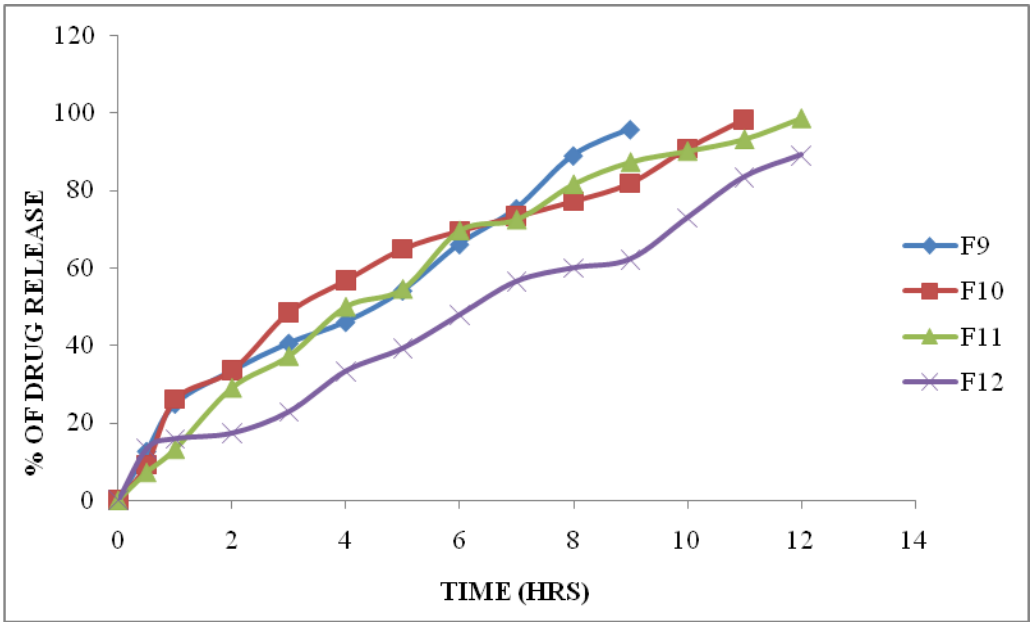

Figure 8.5: Dissolution profile of Paclitaxel (F9, F10, F11 and F12 formulations)

From the dissolution data it was evident that the formulations prepared with Carbopol974P as polymer were able to retard the drug release up to desired time period i.e., 12 hours.

The formulations prepared with Xanthan Gum were able retarded the drug release. they were shown total drug release.

Whereas the formulations prepared with HPMC K 15M were retarded the drug release in the concentration of 60 mg (F11 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.64 % in 12 hours with good retardation.

From the above results it was evident that the formulation F5 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.

Table 8.8: 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	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.61	0.5	0.707	0.983	-0.301	1.956	19.220	0.1041	-1.017	90.39	4.642	4.488	0.154
18.06	1	1.000	1.257	0.000	1.913	18.060	0.0554	-0.743	81.94	4.642	4.343	0.298
24.35	2	1.414	1.386	0.301	1.879	12.175	0.0411	-0.614	75.65	4.642	4.229	0.412
34.59	3	1.732	1.539	0.477	1.816	11.530	0.0289	-0.461	65.41	4.642	4.029	0.612
41.78	4	2.000	1.621	0.602	1.765	10.445	0.0239	-0.379	58.22	4.642	3.876	0.766
48.35	5	2.236	1.684	0.699	1.713	9.670	0.0207	-0.316	51.65	4.642	3.724	0.917
56.5	6	2.449	1.752	0.778	1.638	9.417	0.0177	-0.248	43.5	4.642	3.517	1.125
64.52	7	2.646	1.810	0.845	1.550	9.217	0.0155	-0.190	35.48	4.642	3.286	1.356

70.9	8	2.828	1.851	0.903	1.464	8.863	0.0141	-0.149	29.1	4.642	3.076	1.566
75.53	9	3.000	1.878	0.954	1.389	8.392	0.0132	-0.122	24.47	4.642	2.903	1.738
81.27	10	3.162	1.910	1.000	1.273	8.127	0.0123	-0.090	18.73	4.642	2.656	1.986
89.19	11	3.317	1.950	1.041	1.034	8.108	0.0112	-0.050	10.81	4.642	2.211	2.430
99.16	12	3.464	1.996	1.079	-0.076	8.263	0.0101	-0.004	0.84	4.642	0.944	3.698

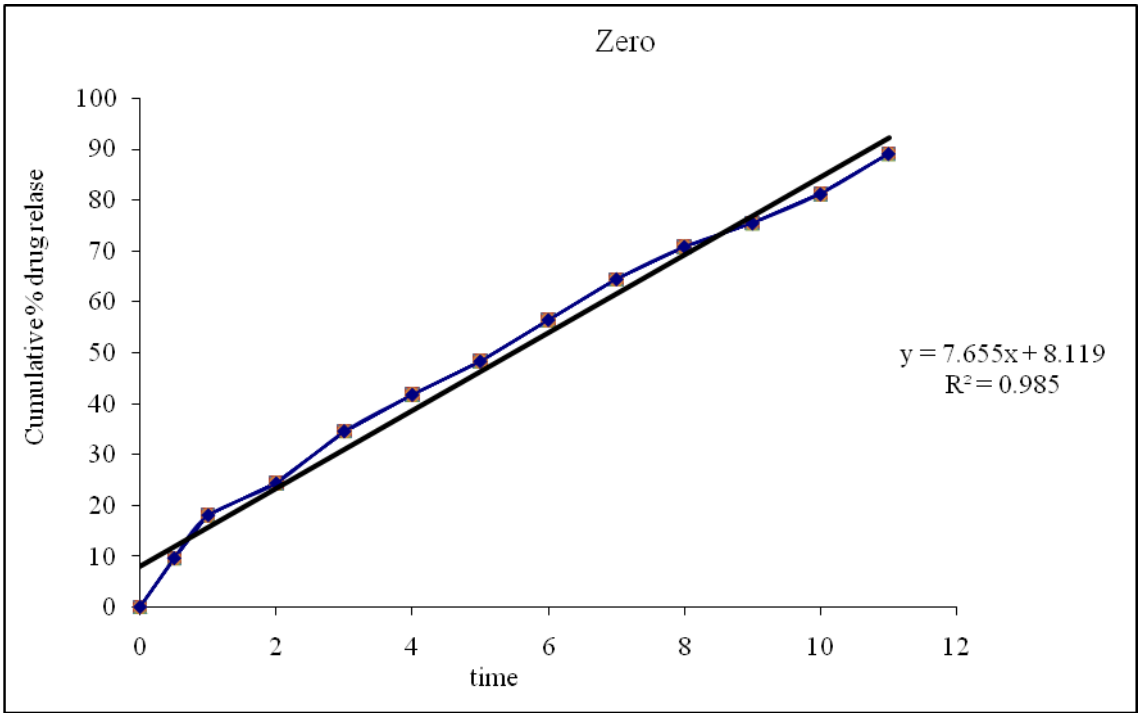

Figure 8.6: Zero order release kinetics graph

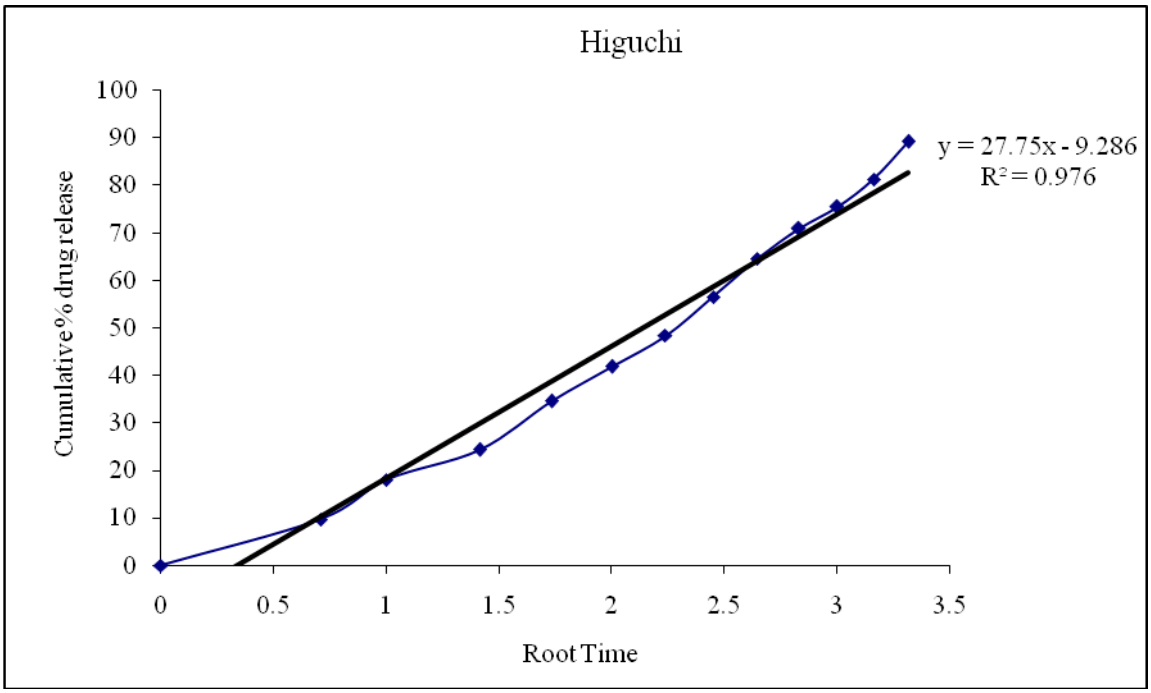

Figure 8.7 : Higuchi release kinetics graph

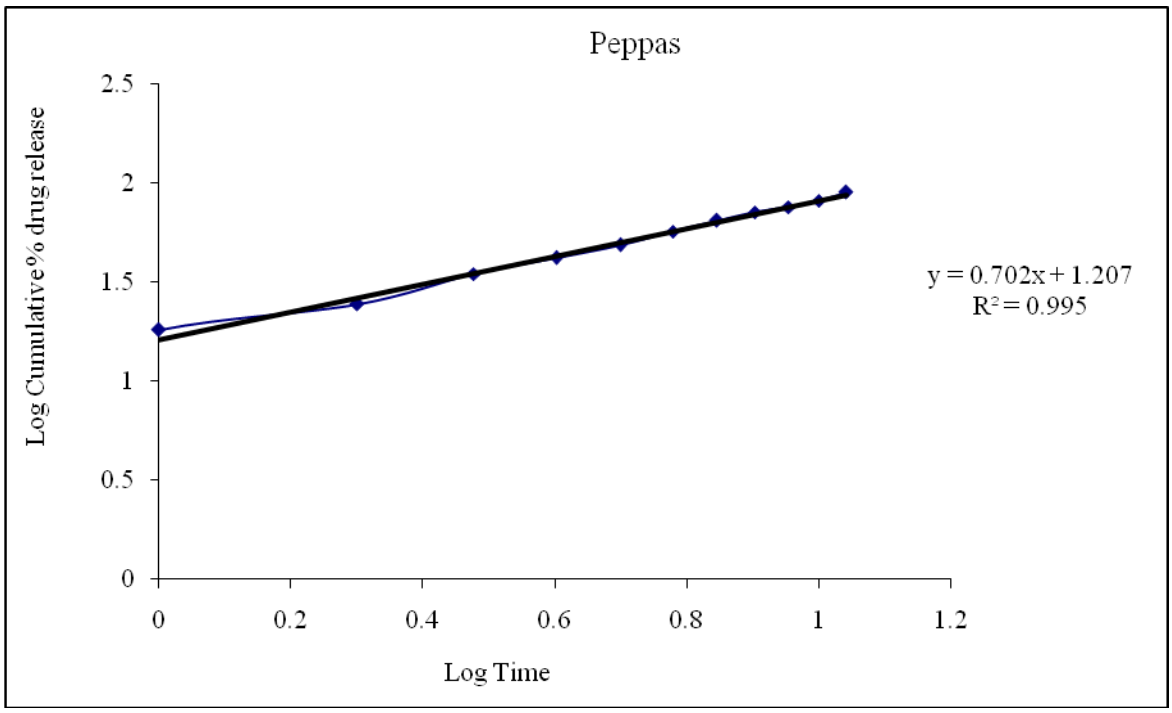

Figure 8.8: Kars mayer peppas graph

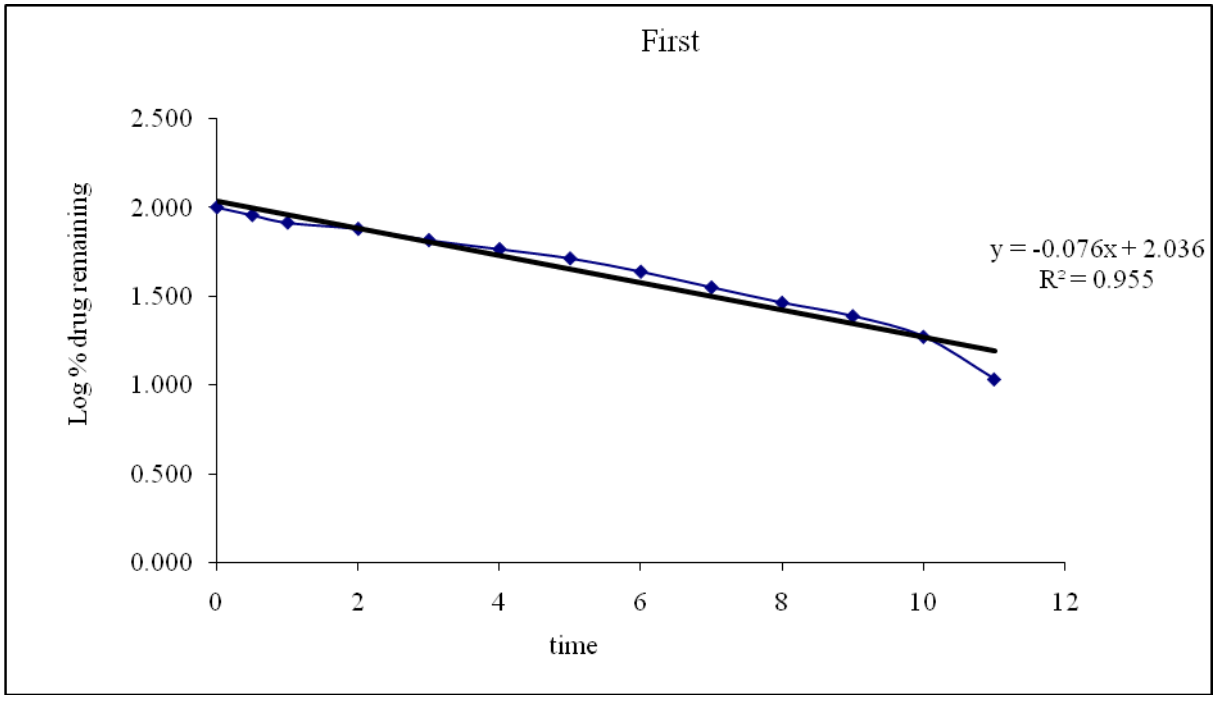

Figure 8.9: First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed peppas order release kinetics.

8.5. Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

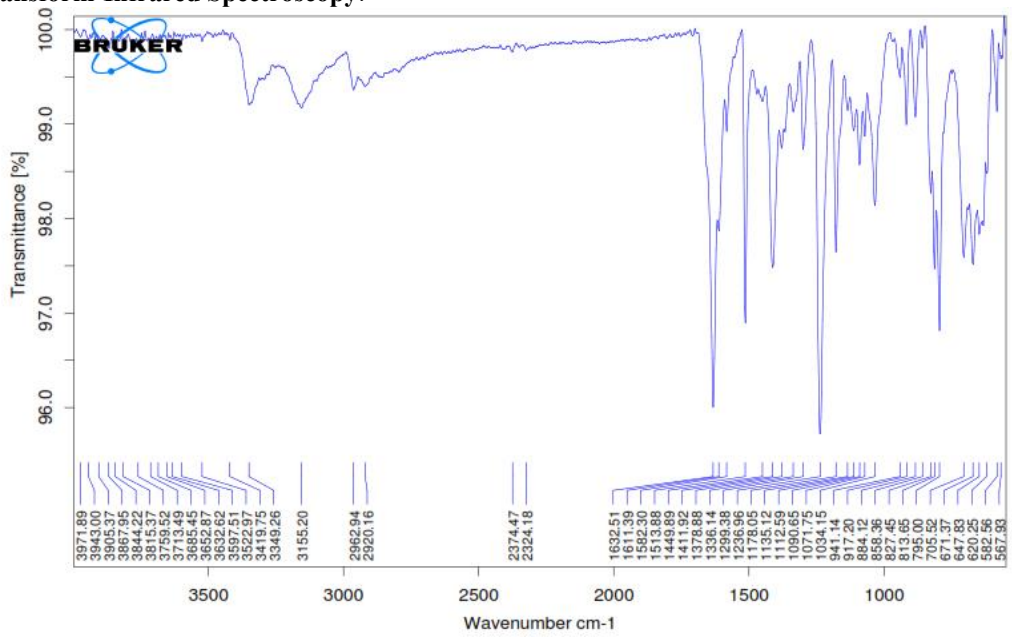

Figure 8.10: FT-IR Spectrum of Paclitaxel pure drug

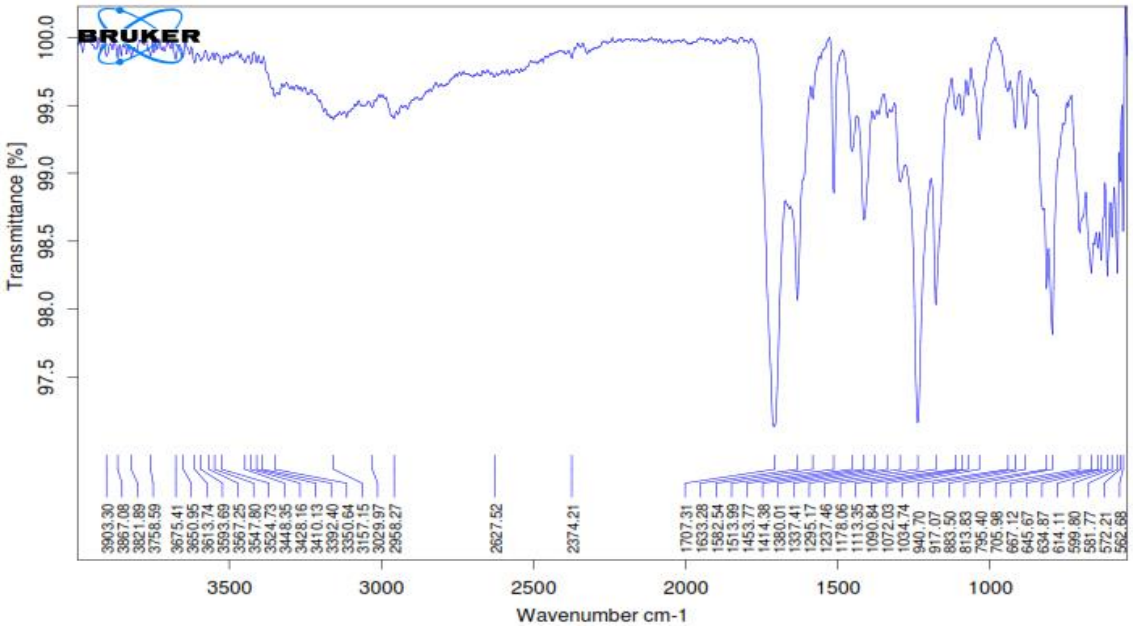

Figure 8.11: FT-IR Spectrum of Optimised Formulation

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

9. CONCLUSION

In the present work, an attempt has been made to develop Controlled release tablets of Paclitaxel by selecting different Types of polymers Carbopol974P, Xanthan Gum and HPMC K 15M as retarding. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow

properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 99.16 % in 12 hours hence it is considered as optimized formulation F5 which contains Xanthan Gum (20mg) . Whereas the formulations with HPMC K 15M showed high retarding with increasing concentration of polymer. The formulations with Carbopol974P were did not produce the desired drug release pattern.

ACKNOWLEDGEMENT

The Authors are thankful to the Management and Principal, Princeton College of Pharmacy, Narapally, Ghatkesar, Telangana, for extending support to carry out the research work. Finally, the authors express their gratitude to the Sura Pharma Labs, Dilsukhnagar, Hyderabad, for providing research equipment and facilities.

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