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FORMULATION AND EVALUATION OF BILAYERED FLOATING TABLETS OF ONDANSETRON AND CAPECITABINE

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Abstract

In the present study an attempt is made to prepare bilayer floating tablets of an immediate release layer of Ondansetron and a sustained release layer of Capecitabine were prepared by Direct Compression method, which remains in stomach for prolonged period of time in a view to maximize bioavailability of drug. By using various concentrations of polymers. Different formulations of ondansetron immediate release and capecitabine sustained release having polymers at different concentration levels were prepared. Ondansetron immediate release is prepared by using Croscarmellose sodium as super disintegrant, which showed excellent drug release. So the composition of immediate release layer is kept constant in all formulations. F5 showed the best formulation for Capecitabine sustained release so which is optimised. F6 of immediate release and F5 of sustained release show the promising results and were optimised for preparing of bilayered floating tablets of immediate release and sustained release. Dissolution profile of optimised ondansetron immediate release formulation (F6) shows 99.8 % drug release in 30 mins.And an optimised capecitabine sustained release formulation (F5) shows 97.3 % drug release at 12 hrs.The release of capecitabine in sustained release is found to follow Higuchi Release model. Accelerated stabilty studies were carried out on the prepared tablets in accordance with ICH Guidelines Q1. And the stability studies data indicates promising an acceptable and stable formulation.

Key words: Bilayer, Super disintegrant, Ondansetron, Capecitabine, , K100M, HPMC K4M, NaHCO3,Direct compression.

Introduction [1,2] :

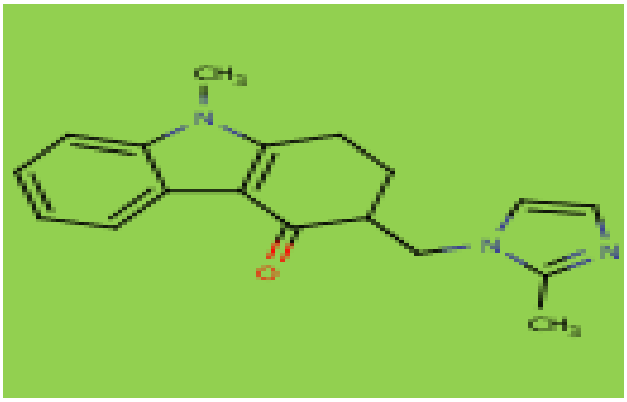
Nowadays various developed & developing countries move towards combination therapy for treatment of various

diseases & disorders requiring long term therapy. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects minimized, a low-dose combination of two different agent reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other. Using low dosage of two different agents minimizes the clinical & metabolic effects that occur with maximal dosage of individual component of the combined tablet & thus dosage of the single component can be reduced.

Bilayered Tablets [1,2]:

Bilayer tablets contain two layers one with immediate release layer and other with extended release layer or sustained or both layers with immediate release.Two drugs can be combined in different layers of tablets and these tablets incompatible substances are also separated which helps in reducing chemical incompatibilities. Due to this reason bilayer tablets offer advantage over conventional single layered tablets. In bilayer tablets delivery rate of either single or two active pharmaceutical ingredients can be controlled. It is also beneficial to active gastric retention by forming floating bilayer tablets with different active pharmaceutical ingredient in a fixed dose combination and also to increase the life cycle of drug product. Various forms of bilayer tablets are bilayer modified release tablets, bilayer floating tablets, bilayer bucoadhesive tablets, bilayer mucoadhesive tablet. The term bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablets are preferred when the release profiles of the drugs are different from one another.

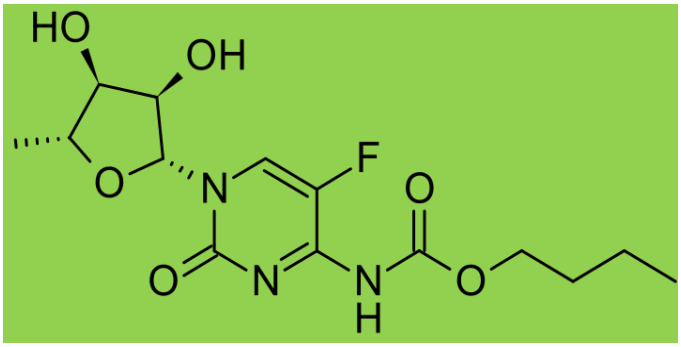
Drug Profile :



ONDANSETRON

Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist, not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serontonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery, and centrally in the chemoreceptor trigger zone of the area postrema. The temporal relationship between the emetogenic action of emetogenic drugs and the release of serotonin, as well as the efficacy of antiemetic agents suggest that chemotherapeutic agents release serotonin from the enterochromaffin cells of the small intestine by causing degenerative changes in the GI tract. The serotonin then stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT_3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT_3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT_3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone[5,6].



CAPECITABINE

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity indicated for the treatment of metastatic breast cancer and colon cancer. It is an orally administered systemic prodrug that has little pharmacologic activity until it is converted to fluorouracil by enzymes that are expressed in higher concentrations in many tumors. Fluorouracil it then metabolized both normal and tumor cells to 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP).

Capecitabine is a prodrug that is selectively tumour-activated to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase, an enzyme found in higher concentrations in many tumors compared to normal tissues or plasma. Fluorouracil is further metabolized to two active metabolites, 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP)

and 5-fluorouridine triphosphate (FUTP), within normal and tumour cells. These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deaxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, therefore a deficiency of this compound can inhibit cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis through the production of fraudulent RNA[7,8].

Materials And Methods [3,4]:

Materials:

ondansetron and capecitabine is a sample from Chandra labs, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K100M, HPMC K4M non-ionicpolymers),HPC, Sodium Lauryl Sulphate, Sodium Starch Glycolate, crospovidone, Croscarmellose Sodium, Ethyl Celluloe, Carbpol,Microcrystalline Cellulose,Magnesium Stearate,PVP K30,Talc, NaHCO3,Lactose Monohydrate was donated by SD Fine chemicals, Mumbai, India. All other chemicals and reagents used from SD Fine chemicals, Mumbai, India. Chemicals.

Formulation of Bi-Layer Tablets:

The bilayer tablets of ondansetron and capecitabine were prepared by the Direct Compression method. The drug and polymers for both IR and SR layer were passed through a # 40 sieve before their use in the formulation.In the present study bilayer tablet was prepared manually using multiple station punching machine. Accurately weighed amount of SR powder mix was fed manually into die cavity. SR layer was compressed at mild compression force. After that accurately weighed IR powder mix was manually fed into the die on SR layer and compressed using 12-mm flat punches. Formulations are shown in detail in table 1 and 2.

Table No.1: Formulation Development Of Ondansetron IR Layer

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Ondansetron()	8	8	8	8	8	8
HPC(%)	5	5	5	5	5	5
Sodium starch glycolate(%)	5	-	-	-	-	-

Croscarmellose sodium(%)	-	5	-	7.5	10	12.5
Crospovidone(%)	-	-	5	-	-	-
Lactose monohydrate(%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate(%)	2.5	2.5	2.5	2.5	2.5	2.5
Talc(%)	2.5	2.5	2.5	2.5	2.5	2.5

• Total weight of immediate layer is 150 mg.

Table no.2: Formulation development of Sildenafil citrate SR layer.

Ingredients	F1	F2	F3	F4	F5	F6
Capecitabine(mg)	150	150	150	150	150	150
HPMCK4M(%)	10	20	30	-	-	-
NaHCO3(%)	15	15	15	15	15	15
HPMCK100M(%)	-	-	-	10	20	30
EC(%)	5	5	5	5	5	5
PVPK30(%)	5	5	5	5	5	5
Talc(%)	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate(%)	2.5	2.5	2.5	2.5	2.5	2.5
Micro crystalline cellulose(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

• Total weight of sustained layer is 400 mg.

Table no.3: Formulation development of ondansetron and capecitabine bilayer (Optimised).

Ingredients	Optimised I.R layer	Optimised S.R layer	Optimised Bilayer
Ondansetron(mg)	8	-	8
HPC (%)	5	-	5
CCS(%)	12.5	-	12.5
Lactose monohydrate	Q.S	-	Q.S
Magnesium stearate(%)	2.5	2.5	5
Talc (%)	2.5	2.5	5
Capacetabine (mg)	-	150	150

NaHco3	-	15	15
HPMC K100M	-	20	20
EC(%)	-	5	5
PVP K30 (%)	-	5	5
MCC(mg)	-	Q.S	Q.S

• Total weight of bilayer layer is 550 mg.

Evaluation of Bilayer Tablets [12,13] :

Determination of physicochemical parameters of tablets:

1. Weight Variation: Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets were calculated. Then each batch passes the weight variation test if not more than two of the individual tablet deviate from the average weight by more than the percentage.

2. Thickness: Ten tablets were selected randomly from each batch and thickness was measured by using vernier calipers.

3. Hardness: Hardness was measured by usingMonsanto Hardness Tester. For each batch five tablets were tested. The force is measured in kilograms.

4. Friability: It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

5. % Swelling Index: Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2 .The microspheres were removed periodically from the solution, blotted to remove

excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight.

Table no.3: Swelling index values for sustained release formulations.

Time(hrs)	F1	F2	F3	F4	F5	F6
1	10	11	20	20	25	22
2	19	19	25	26	30	28
3	28	25	29	35	34	35
4	37	34	32	45	39	40
5	40	38	38	49	42	48
6	43	44	49	53	46	54
7	46	49	57	58	51	64
8	49	54	64	60	56	72
9	52	58	68	63	60	75
10	57	62	71	67	64	79
11	60	67	75	69	71	81
12	64	69	78	71	78	85

6. In –vitro Dissolution studies (I.R):

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium.5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 245 nm.

In –vitro Dissolution studies (S.R):

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 8 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium for first 2 hours and 6.8 pH phosphate buffer for next 12hours. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 242 nm.

7. Drug release kinetics and mechanism:

To analyze the mechanism of drug releasefrom the formulation, the dissolution profile of all thebatches were fitted to zero order, first order, Higuchiand Peppasmodels to ascertain the kinetic modelling of drug release.

• **Zero Order:** $Q = K0\ t$

Where, Q is the amount of drug release at time, t and Kois the release rate constant.

• **First order:** $\text{Log } Qt = \text{Log } Qo + K1t / 2.303$

Where Qt is the amount of drug released in time t, Qois intial amount of drug in the solution and K1 is the first order release rate constant. In this way a graphical relationship between log percent drug remaining versus time to get the first order constant from the slope.

• **Peppas model:** $Mt/M\infty = ktn$

Where, $Mt/M\infty$ is fraction of drug released at time‘t’, k represents a constant, and n is the diffusionalexponent, which characterizes the type of release mechanism during the dissolution process. For nonfickianrelease, the value of n falls between 0.5 and1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and forsuper case II transport, n >1.

• **Higuichi model:** $Q = K2\ t1/2$

Where, Q is the percentage of drug release at time t and K2 is the diffusion rate constant.

8. Fourier Transform infrared (FTIR) Spectroscopic studies: Fourier Transform Infrared spectrophotometer (FTIR) was used for infrared analysis of samples to intercept the interactions of drug with polymers and other ingredients. The powder sample along with KBr was used for FTIR studies. The samples were analyzed between the wave numbers 4000 and 400 cm2.

Results and Discussion:

Discussion:

The Pre formulation studies were performed and the results were shown in table no.3(For I.R). Bulk density was found in the range of 0.37 g/cm3 and the tapped density between 0.45 g/cm3. Using these two density data compressibility index was calculated. The compressibility index was found between 14.14 and the compressibility flowability correlation data indicated a fairly good flowability of the blend. Angle of repose was found to be in the range of 33.2 indicating excellent flowability, hausner's ratio in range of 1.16 indicating good flow ability.And for S.R Bulk density in the range of 0.41 g/cm3, Tapped density is 0.49 g/cm3, Compressibility % 13.32, Hausner's ratio 1.15, Angle of repose 24.36.And it indicates good flowability.

The tablets of different formulations were subjected to various evaluation tests such as weight variation, hardness, thickness, friability and drug content. For I.R Tablet(ondansetron) weight variation 150mg,Hardness 3.2kg/cm2, Thickness 2.2 mm,Friability 0.49% The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablets. For S.R Tablet(Capecitabine) weight variation 401 mg,Hardness 7.5 kg/cm2, Thickness 2.1 mm,Friability 0.40%,Lag time 2 mins, Floating time 12 hrs. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablets.. The detail of Physico-chemical parameters of all the formulations is shown in table no. 5(I.R) and 6(S.R) Respectively.

Evaluation of pre-compression parameters of Tablets:

Results for Flow properties: (I.R)

Table no.4: Flow properties : (I.R)

Formulations	Angle of repose(*)	Bulk Density(g/cm3)	Tapped Density(g/cm3)	%Compressibility	Hausner's Ratio
F1	23.9^0	0.3	0.35	14.29	1.17
F2	24.2^0	0.38	0.45	15.56	1.18
F3	27.2^0	0.53	0.62	14.52	1.17
F4	25.5^0	0.57	0.68	16.18	1.19
F5	23.8^0	0.43	0.49	12.24	1.14
F6	33.2^0	0.37	0.45	14.14	1.16

Results for Flow properties: (S.R)

Table no.5: Flow properties: (S.R)

Formulations	Angle of repose(*)	Bulk Density(g/cm3)	Tapped Density(g/cm3)	%Compressibility	Hausner's Ratio
F1	25.40^0	0.34	0.43	20.93	1.26
F2	23.50^0	0.39	0.46	15.21	1.17
F3	27.2^0	0.54	0.61	11.47	1.12
F4	24.9^0	0.58	0.66	12.12	1.13
F5	32.96^0	0.41	0.49	13.32	1.15
F6	24.36^0	0.37	0.45	17.77	1.21

Characterization of physicochemical parameters of Tablets: (I.R)

Table no.6: physicochemical parameters of Tablets: (I.R)

Formulations	Average weight(mg)	Hardness(kg/cm2)	Thickness(mm)	Friability(%)
F1	149	3.4	2.1	0.29
F2	147	3.5	2.3	0.25
F3	150	3.1	2.5	0.30
F4	152	3.3	2.2	0.41
F5	150	3.6	2.4	0.52
F6	150	3.2	2.2	0.49

Characterization of physicochemical parameters of Tablets: (S.R)

Table no.7: physicochemical parameters of Tablets: (S.R)

Formulations	**Weight variation(mg)**	***Lag time(mins)***	***Floating time(hrs)***	***Hardness*** **kg/cm^2**	**Thickness (mm)**	**Friability (%)**
F1	401	5 mins	8hrs	7.5	2.3	0.45
F2	400	3 mins	12hrs	7.3	2.5	0.48
F3	398	2 mins	12hrs	6.5	2.7	0.50

F4	400	2 mins	12hrs	7.6	2.3	0.52
F5	401	2mins	12hrs	7.5	2.1	0.40
F6	399	3 mins	12hrs	7.5	2.4	0.49

In–vitro Dissolution studies (I.R): In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium.5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 245 nm.

Table no.:8Cumulative % drug release for immediate release.

Time(mins)	F1	F2	F3	F4	F5	F6
5	25	22	14	22	36	65
10	37	38	26	42	57	70
15	45	49	40	56	65	84
30	50	56	54	63	72	96
45	48	72	63	78	88	--
60	62	80	75	89	93	--

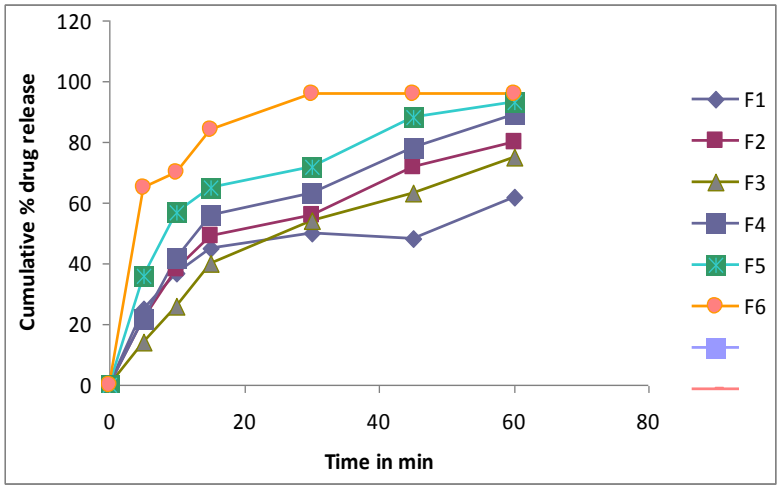


Fig.No-1. Dissolution graph for formulations f1-f6(Immediate Release).

In–vitro Dissolution studies(S.R): In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 8 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium for first 2 hours and 6.8 pH phosphate buffer for next 12hours. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The

samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 242 nm.

Table no.9: Cumulative % drug release for sustained release.

Time(hrs)	F1	F2	F3	F4	F5	F6
1	32.4	25.5	19.6	34.5	25.5	35.6
2	45.5	39.9	24.3	42.1	39.2	40
3	67.4	43.4	31.4	52.7	46.5	49.7
4	72.6	59.4	45.9	60.3	55.2	53.9
5	85.4	78.2	57.3	72.4	68.5	63.8
6	95.8	94.2	80.7	78.3	75.9	70.4
8	--	--	94.9	98.1	81.3	75.8
12	--	--	--	--	96.5	84.9

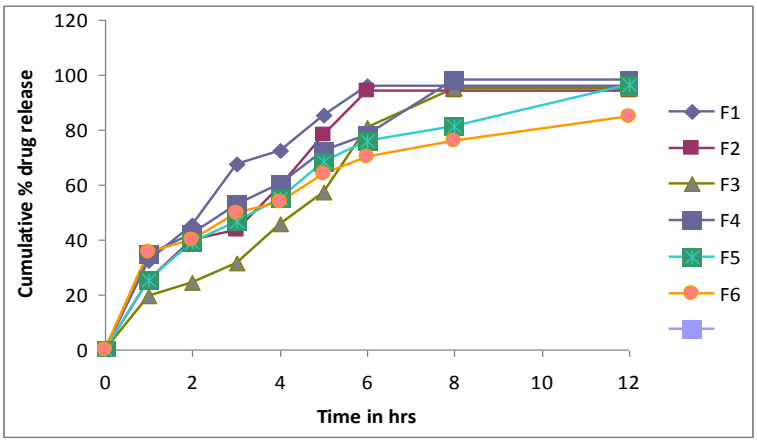


Fig.No-2. Dissolution graph for formulations f1-f6 (Sustained Release).

Dissolution Profile of Bilayered Tablet:

(Optimized Formulation)

Table no.10: Optimised Formulation.

S.No	Sampling Time	% drug release (ondansetron)	% drug release (capecitabine)
1	15mins	80.7	4.2
2	30mins	99.8	6.6
3	1hr	--	20.6
4	2hr	--	37.7
5	3hr	--	45.4
6	4hr	--	53.8
7	5hr	--	69.7
8	6hr	--	77.9
9	8hr	--	89.0
10	12hr	--	97.3

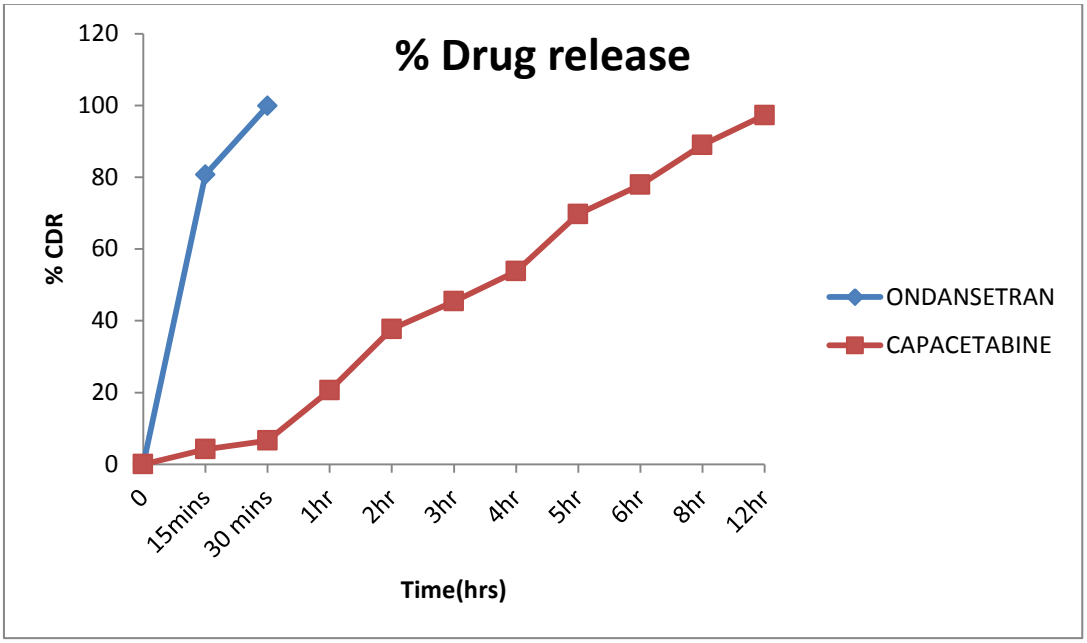


Fig.No-3. Dissolution graph for formulation f5-f6 (Optimised Formulation).

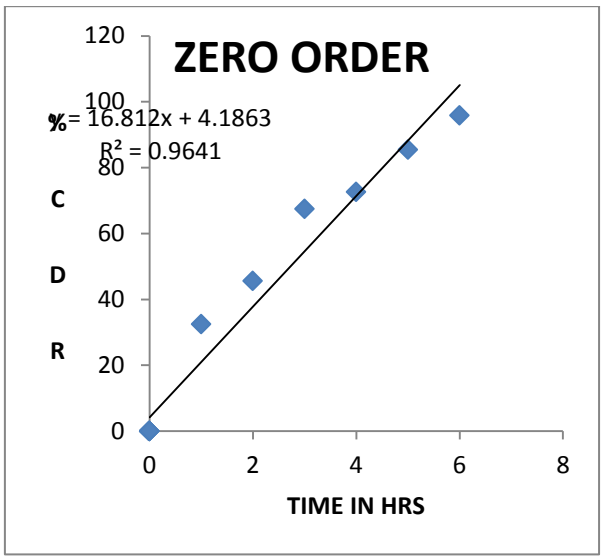
Table No: 11. Drug Release Kinetics Of Optimise Bilayered Tablet.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.875127877	-0.145144174	32.88551269	1.473677434
Intercept	5.486598465	2.237319463	-16.27573336	0.61652778
Correlation	0.980490698	-0.931226742	0.972678789	0.910592137
R 2	0.961362008	0.867183244	0.946104027	0.82917804

Discussion:

From the above dissolution graph for optimised formulations we can say that the optimised formulations were prepared after showing the good results by the selection of the drug and excipients ,polymers in good concentration and the bilayered tablet was prepared.Then the dissolution profile was carried for the optimised formulation by maintaining all the dissolution parameters and the percentage drug release was noted a different time intervals the immediate release layer (Ondansetron) shows the drug release (99.8%) with in 30 min .And even for the sustained release layer (Capecitabine) the percentage drug release was noted at different intervals it showed the drug release (97.3%) in 12 hrs.So we can say that the optimised formulation which was prepared was good which has shown the targeted results .

Kinetic Release Model: Drug Release Kinetics of Optimized Bilayered Tablet.



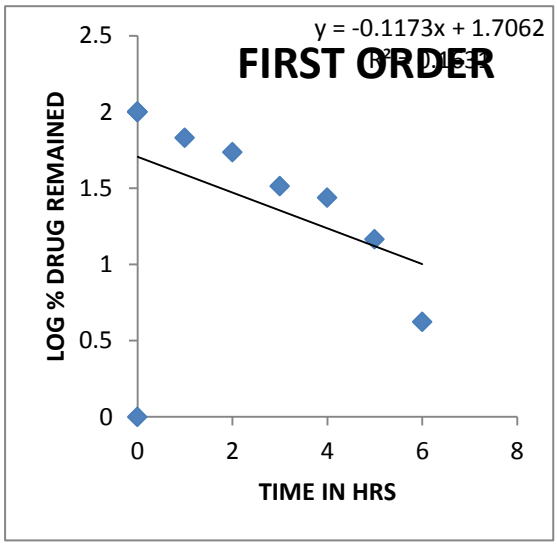
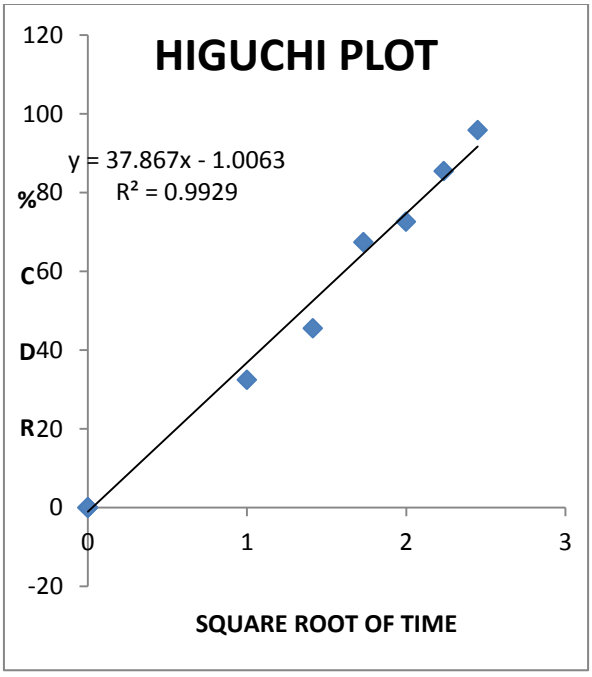


Fig.no - 4. Zero order release graph for Sustained Release F5 Formulaton (Optimised)

Fig.no - 5. First order release graph for Sustained Release F5 Formulation (Optimised)



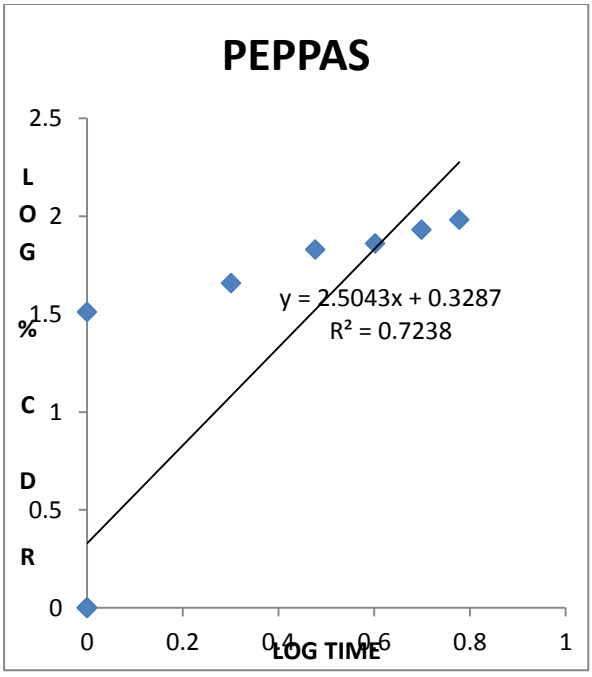


Fig.no-6. Higuchi model graph for sustained release f5 formulation (optimised)

Fig.no-7. Peppas model graph for sustained release f5 formulation (optimised)

Discussion:

The Dissolution data were fitted into different kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) of optimized Bilayered floating tablet of ondansetron and capecitabine indicate that the drug release was following Zero order release kinetics and fickian mechanis

Fourier Transform Infrared (FTIR) spectroscopic studies:

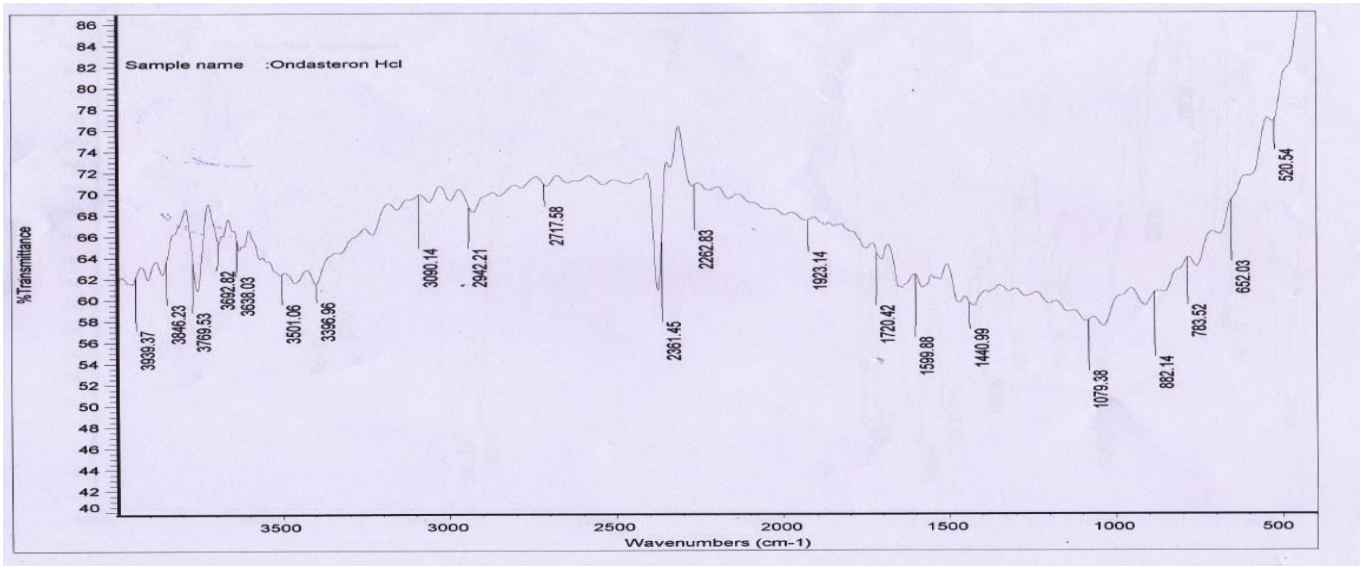


Fig.No-8. FTIR spectra of ondansetron pure drug.

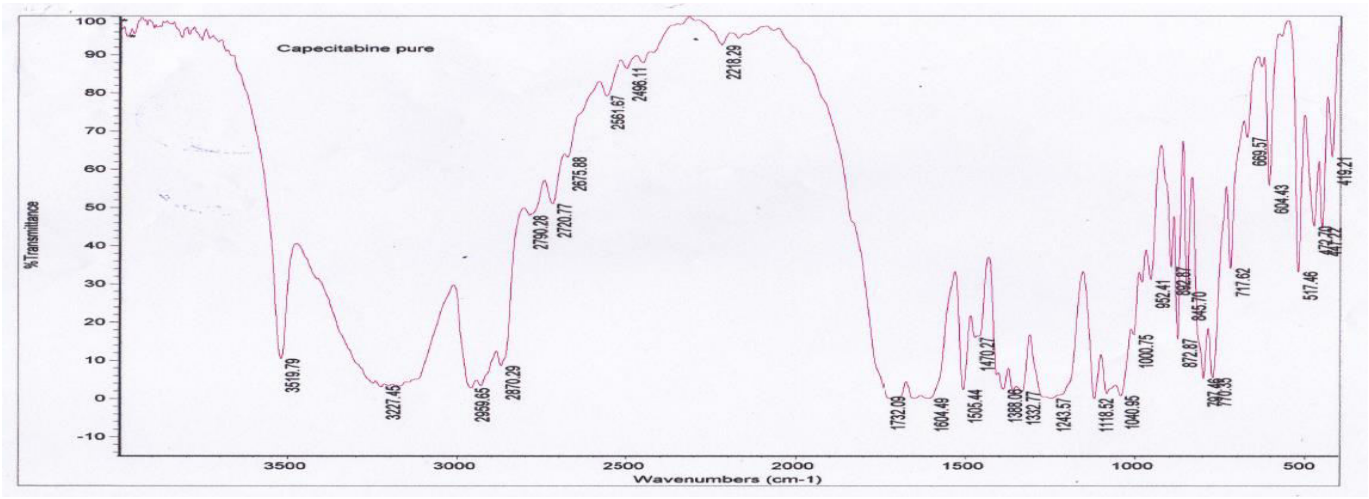


Fig.No -9. FTIR Spectra of Capecitabine Pure Drug.

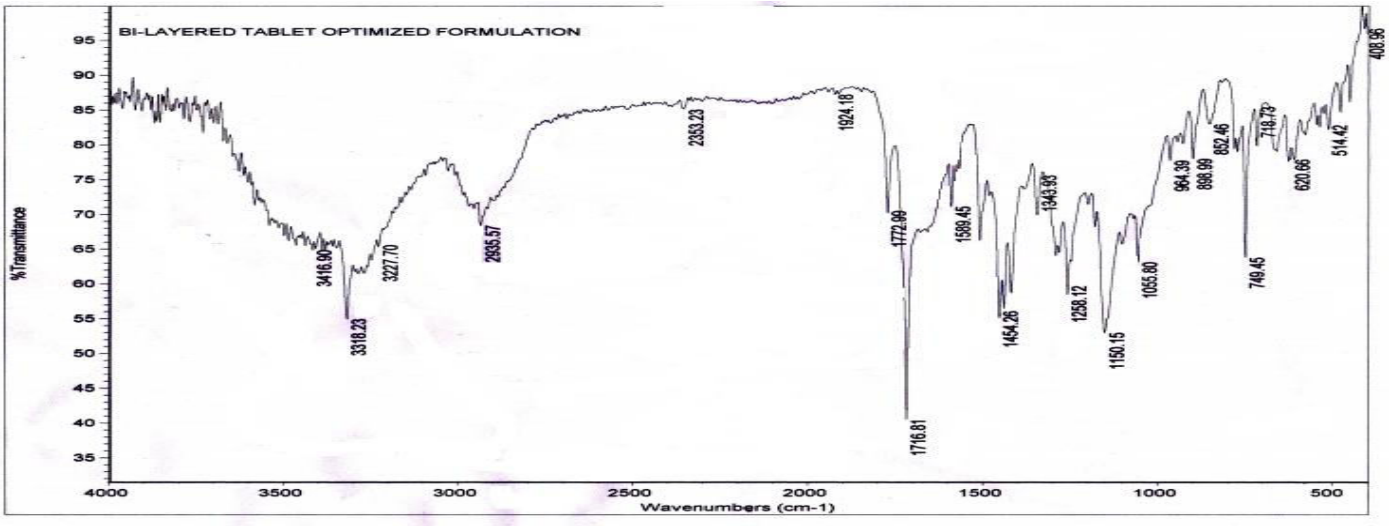


Fig.No -10. FTIR Spectra of Bilayered Tablet.

Table No-12: Interpretation data -IR spectra of ondansetron and capecitabine.

Bond		IR Absorption bands		
	Characteristic peak(frequency, cm–1)	Observed peak in pure form (Ondansetron)	Observed peak in pure form (Capecitabine)	Observed peak in combined final form
O-H Stretch, H-Bond	3500-3200	_	3227.45	3227.70
C-H Stretch	3000-2850	_	2959.65	2935.57
C≡O Stretch	1740-1720	_	1732.09	1716.81
N-H Stretch	3400-3250	3396.98	_	3416.90
C≡ N Stretch	2850-2350	2361.45	_	2353.23

Stability Studies: Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of six months at various accelerated temperature and humidity conditions of 25°C/65%RH, 40°C/75%RH.The accelerated stability study of the best formulations was carried out as per the ICH guidelines.

Table No-13: Stability Studies of Bilayeredtablet at Room Temperature.

Time	**Colour**	**Assay**		**Cumulative % drug release at 30minutes**		**Cumulative % drug release at 12 hrs**	
		25±2^{0}c and 65±5%RH	**40±2^{0}c and 75±5%RH**	**25±2^{0}c and 65±5%RH**	**40±2^{0}c and 75±5%RH**	**25±2^{0}c and 65±5%RH**	**40±2^{0}c and 75±5%RH**
First day	White	99	99	96	100.74	99	97.5
30 days	White	99.18	100.10	99.24	99.64	99.8	98.45
60 days	White	98.15	99.88	98.56	99.35	99.94	100.60
90 days	White	100.12	96.56	99.95	99.88	99.90	98.22

Conclusion:

Bilayered matrix system is one of the important method of providing sustained drug delivery in a predetermined manner. Among all the formulations, the formulation F6 prepared with Croscarmellose Sodium showed the best result (99.8%) in 30 mins in Immediate release formulations and F5 prepared with HPMC K100M, Ethyl cellulose , NaHco3 showed the best result (97.3%) in 12 hrs. This dosage form can be considered suitable for further in vivo studies which can be studied on small animal models.

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