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Formulation Development and *in vitro* evaluation of Capecitabine (SR) and Ketorolac (IR) bilayer tablet

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ABSTRACT: Background: Capecitabine is a type of chemotherapy called an anti-metabolite which stops cells making and repairing DNA. **Ketorolac** is used for the short-term treatment of moderate to severe pain in adults. **Aim:** The study was aimed to formulate and evaluate the Ketorolac (Sustained release: SR) and Capecitabine (Immediate release: IR) containing Bilayered tablets. **Method:** The tablets were manufactured by direct compression technique. The granules were evaluated for flow properties. The equipped blend for immediate release (IR) release also preserved the physicochemical properties of tablets that are hardness, thickness, friability, weight variation. **Result:** The tablet blends exhibited good flow properties. Almost all tablet formulations possessed good physicochemical properties. The better Tablet formulation K9 having the average thickness of 2.1±0.01 mm, hardness of 3.4±0.04 Kg/cm^2, weight of 150±0.4 mg and friability of 0.29±0.02 %. The optimized tablet formulation C9 having the average thickness of 2.3±0.04 mm, hardness of 4.5±0.07 Kg/cm^2, friability of 0.44±0.005 %. The Capecitabine C9 formulation sustained the drug releases upto 12 h and Ketorolac IR K9 formulation showed 99 % drug release within 60 min. The Bilayered Tablet (IR+SR) showed 97.52 % Cumulative Drug release within 12 h. **Conclusion:** The formulated optimized Ketorolac and Capecitabine containing Bilayered tablets could be successfully used for therapeutic management of pain as well as cancer.

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INTRODUCTION:

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market [1]. The principle objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation. Multilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer [2,3]. An attempt was made to develop bi-layer tablet suitable for

delivering different drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose. To reduce the dose, dosage frequency, dose related side effects and number of tablets per day by formulating Capecitabine and Ketorolac as Bilayer tablets [4,5].

The aim of the present study was to design and evaluate bilayer Floating tablets of Capecitabine and Ketorolac.

MATERIAL AND METHODS:

The drugs Capecitabine and Ketorolac were procured as a gift sample from Indian Pharmaceutical Industry in view of promotion for Institutional Research. The xanthum gum, carbopol and HPMC were purchased from HiMedia Laboratory LLC, Mumbai. The sodium bicarbonate, Hydroxypropyl cellulose, Microcrystalline cellulose, Magnesium stearate, Talc and ethyl cellulose were purchased from Merck, India. All other chemicals and reagents used in this study were of analytical grade and procured from authorized dealers.

Pre-Formulation Studies:

Pre-formulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients [6]. It was the first step in the rational development of dosage forms. The pre-formulation studies of drugs were investigated by determining the color, odor, melting point and solubility.

Scanning and standard curve preparation for Capecitabine and Ketorolac:

About 8.5 ml of HCl was taken in 1000 ml of volumetric flask and the volume was made up to 1000 ml with distilled water. About 10 mg of Capecitabine and Ketorolac was dissolved separately in 100 ml 0.1N HCl to give a solution of strength 100 µg/ml. The stock solution was scanned by using the UV-Visible Spectrophotometer (UV-1900i: SHIMADZU, Japan). The absorption maximum was found to be 243 and 313 nm for Capecitabine and Ketorolac respectively.

For the calibration curve preparation, accurately amount of 100 mg of drug was weighed and transferred into a 100 ml volumetric flask and dissolved with few ml of methanol then volume was made up to 100 ml with 0.1 N HCl to give a solution of concentration of 1000 µg/ml. from above stock solution, about 10 ml of the solution was diluted to 100 ml with 0.1N HCl buffer respectively to get 100 µg/ml stock solution. From this stock solution, aliquots of 2, 4, 6, 8, 10 ml were pipetted out and made up to 100 ml in order to get concentration ranging from 2, 4, 6, 8 and 10 µg/ml. The absorbance of the solution was measured at 243 nm for Capecitabine by UV-Visible spectrophotometry. The same procedure was adopted for the Ketorolac using λ_{max} of 313 nm.

Formulation design and Preparation of Bilayered Tablet:

The pharmaceutical development studies have to be carried out with the purpose of selecting the right dosage form and a stable formulation [7].

Formulation of bilayer matrix tablet (Immediate and sustained release layer):

The Floating tablets were prepared by direct compression method, as shown in Table 1. Each ingredient was individually passed through the sieve no 60 to ensure uniform particle size. The powder mixtures of Capecitabine, microcrystalline cellulose, polymers and sodium bicarbonate were dry blended (Bikon Double cone blender, Mumbai) for 20 min followed by addition of Magnesium Stearate and Talc. The mixtures were then further blended for 10 min. About 350 mg of resultant powder blend was manually compressed using Tablet Compression machine (IYAD CIB3 D-27Automati Compression Machine, Mumbai) hydraulic press at a pressure of 1 ton, with a 9 mm punch and die to obtain the tablet [8,9].

The same method was adopted for preparation of sustained release layer of a tablet containing Capecitabine by using the formulation design as mentioned in Table 2.

Pre-compression study of granules:

The granules containing Ketorolac and Capecitabine, which were used for immediate and sustained drug release, were evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose to determine the flow properties of granules [10,11].

Post-compression evaluations:

The compressed tablets containing Capecitabine for sustained release and Ketorolac for immediate drug release were evaluated for physicochemical parameters of tablets that are weight variation test (By using electronic digital balance), hardness test (By using Pfizer tester), friability test (By using Roche Friabilator), thickness (By using Slide calliper) and drug content. All tablet evaluations were done as per the standard procedure mentioned in Indian Pharmacopoeia [12,13].

Table 1. The formulation design of table for immediate release layer containing Ketorolac.

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F7	F8	F9
Ketorolac	10	10	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4	4	4
SSG	7.5	11.25	15	-	-	-	-	-	-
CP	-	-	-	7.5	11.25	15	-	-	-
HPC	-	-	-	-	-	-	7.5	11.25	15
PVP K30	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Mag. stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	150	150	150	150	150	150	150	150	150

MCC - Micro crystalline cellulose, SSG - Sodium starch glycolate, PVP - Poly vinyl Pyrrolidine, CP – Cross povidone, HPC- Hydroxy Propyl Cellulose.

Table 2. Formulation design for sustained release layer of tablet containing Capecitabine.

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Capecitabine	150	150	150	150	150	150	150	150	150
$NaHCO_3$	30	30	30	30	30	30	30	30	30
Xanthun gum	52.5	70	87.5	-	-	-	-	-	-
Carbopal 934	-	-	-	52.5	70	87.5	-	-	-
HPMC K100				-	-	-	52.5	70	87.5
EC	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Talc	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
PVPK30	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
Mag. stearate	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	350	350	350	350	350	350	350	350	350

HPMC – Hydroxy propyl methyl cellulose, EC – Ethyl cellulose, PVP – Polyvinyl pyrrolidine, MCC – Microcrystaline cellulose and QS – Quantity sufficient.

Table 3. Formulation design for Bilayerd Tablet Formulation.

Sustained Release Formula (F9)	Bilayered formulation (F10)
Capecitabine	150
PVP K30	17.25
EC	17.5
MCC	QS
Magnesium stearate	5.25
Sodium bicarbonate	35
Talc	5.25
Total weight	350 mg
Immediate Release Formula (F9)	
Ketorolac	10
MCC	QS
PVP K 30	3.75
Talc	3
HPC	15
Magnesium stearate	3.75
Total weight	150 mg
Total Weight of The Bilayered Tablet: 500 mg	

HPC – Hydroxy propyl cellulose, EC – Ethyl cellulose, PVP – Polyvinyl pyrrolidine, MCC – Microcrystaline cellulose and QS – Quantity sufficient.

***In vitro* dissolution studies for immediate release layer of Ketorolac:**

The *in vitro* drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900 ml of dissolution medium maintained at 37±1 °C for 1 h, at 50 rpm, 0.1 N HCl was used as a dissolution medium. About 5 ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45 µ membrane filter, and drug release in each sample was analysed after suitable dilution by UV/Vis Spectrophotometer at λ_{max} of 313 nm [14].

The same method was adopted to determine the drug release profile of (sustained release) floating layer of Capecitabine.

Formulation design and Bilayered Tablet Preparation:

After the batch was optimized in both immediate releases layer (F9) and sustained release layer (F9). The optimized batch in both was compressed by using the same ingredients as mentioned in Table 3 [15].

Dissolution study of Capecitabine and Ketorolac from bilayer tablet:

The release kinetic of optimized Capecitabine and Ketorolac from bilayer tablet was studied by conducting dissolution studies. The dissolution tests were performed using USP Type II dissolution apparatus and 900 ml of 0.1N HCl at 37± 0.5 ˚C at 50 rpm. About 5 ml of sample were withdrawn at the intervals of every time interval, sampling was carried out and every time replaced with fresh 5 ml of buffer. The absorbance of solution was recorded at 243 and 313 nm (For Capecitabine and Ketorolac) using buffer as blank. The result was calculated as Percentage drug release of Capecitabine and Ketorolac [16,17].

Drug release kinetic study:

In order to determine the manner of drug release from the dosage form and the mechanism followed by the drug to be release from the dosage form, the *in vitro* drug release data of the optimized tablet formulation for the for Floating layer SR, were fitted with zero order, first order kinetics, Higuchi and Korse-Mayer Peppas equation [18-20].

Statistical analysis:

All parameters were evaluated in triplicate and data are verified statistically by calculating the mean and standard deviation.

RESULTS AND DISCUSSION:

The direct compression method was found to be successful method for bilayer tablet preparation. The absorption maximum was found to be 243 and 313 nm for Capecitabine and Ketorolac respectively. From the standard curve data of both the drugs, it was evident that linear plot was obtained with coefficient of regression close to 1. The pre-formulation study data is given in Table 4. The color of both the drug was white. The drugs Capecitabine and Ketorolac were freely soluble in methanol. The melting point of both the drugs was found within the specified value as mentioned in the literature.

The flow property data of granules for Floating Layer of Capecitabine is given in Table 5. From the data it was evident that almost all formulation exhibited good flow properties with few exception of formulation C2 and C6.

The post compression evaluation data for floating layer of capecitabine is given in Table 6. All the tablet formulations possessed same tablet weight that is more or less close to 350 mg. All tablets exhibited uniform thickness. The hardness and Friability test was passed as per the specified values mentioned in Indian Pharmacopoeia.

The hardness value of all tablet formulations was within the ranges of 4.3 to 5.1 Kg/cm^2, whereas percentage loss found in Friability test was less than 0.1 %. All tablet formulations exhibited excellent drug content in the ranges of 97.1 to 99.28 %.

The percentage drug release from the tablet that is Capecitabine Floating layer (SR) is presented in Table 7. Almost all tablet formulations were able to release the drug in sustained manner but formulation C9 and C6 released the drug in more sustained manner in comparison to other tablet formulation. The tablet formulation C1 and C4 released drug in faster manner, as evident from Fig 1.

From the data, it was confirmed that the tablet formulation C1, C2, C3, C4, C6, C7, and C8 of floating layer does not fulfil the sustained release theory up to 12 h. And also from the table, it was also confirmed that the formulation made with combination of HPMC K100 (mg) and EC (C9) showed maximum drug release up to 12 h.

The flow property data of granules for Ketorolac immediate release tablets is given in Table 8. The cars Index was in the ranges of 11.42 to 17.07 %, which reflected that almost all formulation exhibited good flow properties.

Table 4. Pre-formulation study data Capecitabine and Ketorolac (API).

Sl. No.	Test		Capecitabine	Ketorolac
1	Colour		Off white	White
2	Odour		Odourless	Odourless
3	Solubility	Water	Slightly Soluble	Slightly Soluble
		Methanol	Freely Soluble	Freely Soluble
		Alcohol	Freely Soluble	Slightly Soluble
		Acetonitrile	Soluble	Practically Soluble
4	Melting point		118 °C	166 °C

Table 5. Evaluation of Pre Compression Parameters for Floating Layer of Capecitabine.

Formul-ations	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio
C1	29.32±0.33	0.34±0.04	0.41±0.04	14.62±0.15	1.16±0.04
C2	32.31±0.32	0.32±0.04	0.40±0.03	17.50±0.13	1.19±0.05
C3	25.22±0.33	0.31±0.03	0.36±0.04	13.88±0.14	1.17±0.02
C4	27.06±0.31	0.33±0.04	0.39±0.05	12.81±0.14	1.18±0.03
C5	26.34±0.33	0.35±0.05	0.42±0.04	14.30±0.13	1.17±0.04
C6	29.50±0.32	0.31±0.04	0.37±0.03	18.92±0.11	1.24±0.01
C7	27.42±0.33	0.34±0.03	0.42±0.05	16.68±0.13	1.20±0.04
C8	28.45±0.32	0.35±0.02	0.4±0.04	15.12±0.15	1.18±0.01
C9	27.19±0.31	0.35±0.04	0.40±0.02	12.51±0.12	1.15±0.02

All data are expressed as Mean ± Standard Deviation (n-3).

Tablet 6. Post Compression Parameters for floating layer of capecitabine.

Formul-ations	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
C1	350±0.4	4.6±0.08	2.3±0.04	0.44±0.004	98.4±0.3
C2	351±0.5	4.3±0.07	2.4±0.04	0.47±0.005	98.58±0.2
C3	349±0.4	5.1±0.08	2.5±0.03	0.50±0.004	97.10±0.1
C4	351±0.7	4.5±0.06	2.3±0.04	0.51±0.003	98.6±0.1
C5	350±0.5	4.7±0.08	2.1±0.05	0.40±0.004	99.16±0.2
C6	349±0.6	4.5±0.07	2.4±0.03	0.48±0.005	98.34±0.1
C7	350±0.4	4.3±0.06	2.3±0.04	0.41±0.004	99.28±0.1
C8	350±0.5	4.3±0.08	2.2±0.03	0.43±0.006	98.13±0.2
C9	350±0.4	4.5±0.07	2.3±0.04	0.44±0.005	99.52±0.4

All data are expressed as Mean ± Standard Deviation (n-3).

Table 7. Cumulative percentage drug release of Capecitabine Floating layer (SR).

Time (h)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0.5	58±0.1	36±0.1	25±0.8	91.4±0.3	40.2±0.5	25.8±0.6	39.5±0.2	18.1±0.3	11±0.1
1	66.8±0.2	51.6±0.3	37.7±0.6	100.2±0.2	64.5±0.6	37.2±0.4	55.9±0.4	28.6±0.2	22.6±0.3
2	85.1±0.4	63.6±0.2	52.8±0.5	101.6±0.1	82.1±0.3	44.2±0.1	77.3±0.3	38.6±0.5	36.2±0.4
3	98.7±0.3	72.9±0.4	66.3±0.1	--	98.6±0.4	55.8±0.3	86.4±0.2	55.2±0.8	43.7±0.4
4	--	86.4±0.1	75.8±0.2	--	100.2±0.2	63.7±0.2	91.5±0.4	70.3±0.6	53.6±0.1
6	--	99.6±0.2	83.9±0.4	--	--	74.9±0.1	100.3±0.1	89.7±0.5	67.2±0.2
8	--	--	97.1±0.1	--	--	89.5±0.1	--	99.1±0.2	76.5±0.3
10	--	--	--	--	--	100.3±0.1	--	--	88.2±0.4
12	--	--	--	--	--	--	--	--	97.5±0.4

All data are expressed as % in the form of Mean ± Standard Deviation (n-3).

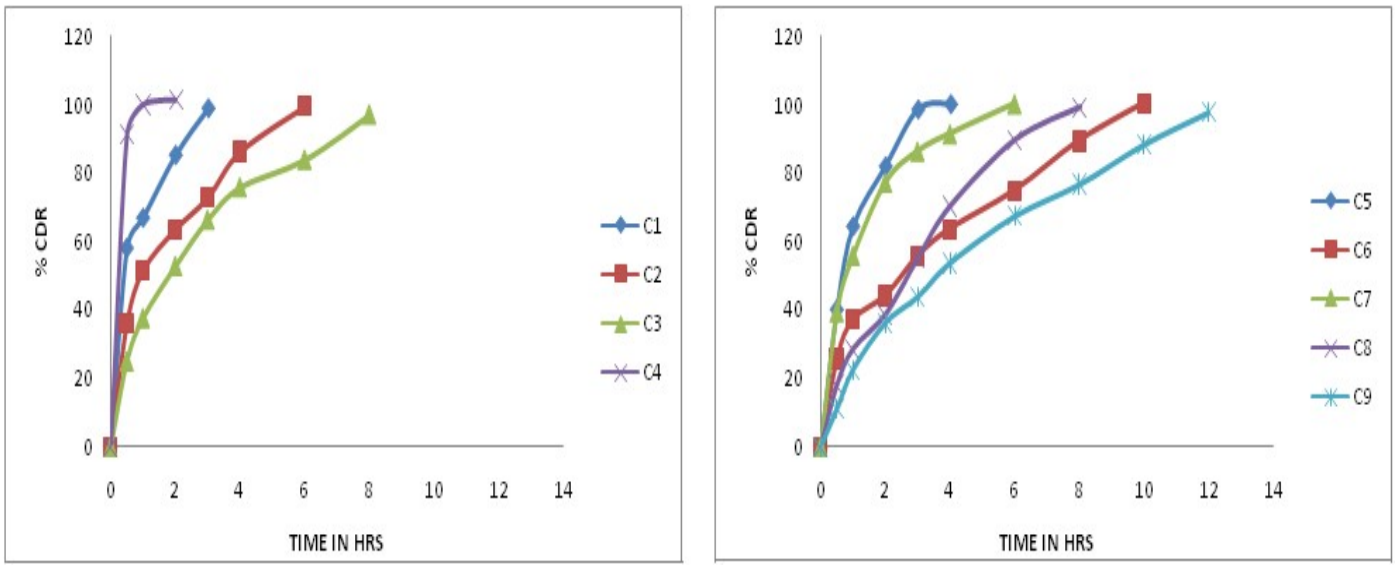

Fig 1. Cumulative percentage drug release of Capecitabine Floating layer (SR).

Table 8. Pre compression parameters of Ketorolac immediate release tablets.

Formul-ations	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's ratio
K1	28.2±0.21	0.32±0.02	0.37±0.02	13.51±0.06	1.15±0.06
K2	27.11±0.20	0.34±0.03	0.41±0.02	17.07±0.05	1.20±0.06
K3	26.32±0.23	0.31±0.02	0.36±0.04	13.88±0.06	1.16±0.04
K4	27.05±0.19	0.31±0.03	0.37±0.03	16.21±0.05	1.19±0.07
K5	28.41±0.15	0.32±0.02	0.37±0.01	13.51±0.04	1.15±0.05
K6	25.61±0.2	0.35±0.01	0.40±0.02	12.5±0.07	1.14±0.04
K7	25.40±0.17	0.31±0.02	0.36±0.03	13.88±0.06	1.16±0.02
K8	26.36±0.19	0.35±0.01	0.41±0.02	14.63±0.02	1.20±0.01
K9	27.8±0.21	0.31±0.04	0.35±003	11.42±0.02	1.12±0.08

All data are expressed as Mean ± Standard Deviation (n-3).

The post compression evaluation data for Ketorolac immediate release tablets is given in Table 9. All the tablet formulations possessed same tablet weight that is more or less close to 150 mg. All tablets exhibited uniform thickness in ranges of 2.1 to 2.5 mm. The hardness and Friability test was passed as per the specified values mentioned in Indian Pharmacopoeia. The hardness value of all tablet formulations was within the ranges of 3.1 to 3.6 Kg/cm^2, whereas percentage loss found in Friability test was less than 0.1 %. All tablet formulations exhibited comparative good drug content in the ranges of 72.21 (K3) to 99.46 (K9) %.

The percentage drug release from the tablet that is immediate release tablet of Ketorolac is presented in Table 10. Almost all tablet formulations were able to release the drug in immediate manner. The tablet formulation K6 and K9 released drug (100 %) in faster manner in 60 min. The best drug release pattern in concern to immediate release was observed in Tablet formulation K9 which took 1 h to release 99.46 % of drug as evident from the Fig 2.

From the drug release kinetic data of optimized tablet formulation C9 containing Capecitabine Floating layer (SR), it was evident that the drug released in zero order manner (Table 11 & Fig 3) which reflected that the drug release rate is independent of concentration of the drug. The drug release mechanism follows Higuchi kinetics, which showed drug released in diffusion control manner. After the batch was optimized in both Ketorolac immediate release layer (K9) and Capecitabine Floating layer (C9). The optimized batch in both was compressed by using same ingredients.

The weight, thickness and hardness of bilayer tablet was 500 ± 0.5 mg, 4.2 ± 0.021 mm and 5.2±0.03 kg/cm^2. The dissolution data of bilayer tablet is given in Table 12. The outer layer of tablet released Ketorolac in 30 min, the inner floating layer released Capecitabine in sustained manner up to 12 h.

Table 9. Post compression parameters for Ketorolac immediate release tablets.

Formul-ations	Average weight (mg)	Hardness Kg/cm^2	Thickness (mm)	Friability (%)	Drug content (%)
K1	148±0.5	3.2±0.01	2.2±0.01	0.49±0.03	87.13±0.2
K2	149±0.2	3.5±0.02	2.3±0.02	0.25±0.01	76.42±0.2
K3	151±0.1	3.1±0.01	2.5±0.01	0.30±0.05	72.21±0.1
K4	150±0.5	3.3±0.05	2.2±0.03	0.41±0.04	80.16±0.4
K5	150±0.6	3.1±0.01	2.1±0.02	0.25±0.03	72.48±0.4
K6	149±0.4	3.2±0.02	2.3±0.01	0.36±0.02	94.18±0.5
K7	152±0.2	3.6±0.01	2.4±0.02	0.52±0.01	68.15±0.2
K8	150±0.1	3.5±0.03	2.1±0.04	0.42±0.02	76.42±0.1
K9	150±0.4	3.4±0.04	2.1±0.01	0.29±0.02	99.46±0.2

All data are expressed as Mean ± Standard Deviation (n-3).

Table 10. Dissolution data for immediate release tablet of Ketorolac.

Time	K1	K2	K3	K4	K5	K6	K7	K8	K9
5	20.6±0.1	21.8±0.6	17.6±0.6	16.2±0.2	11±0.3	25.9±0.2	12.4±0.3	14.7±0.3	32.7±0.6
10	32.9±0.3	36.1±0.4	24.4±0.5	28.6±0.2	21±0.2	38.7±0.4	24.7±0.4	28.4±0.1	49.2±0.4
15	50.5±0.4	48.6±0.2	37.8±0.4	32.8±0.2	32.3±0.1	49.8±0.2	33.7±0.2	42.4±0.2	60.8±0.8
30	67.8±0.1	59.4±0.4	52.7±0.2	49.8±0.4	49.3±0.2	69.8±0.1	46.2±0.1	52.4±0.2	87.3±0.2
45	76.4±0.2	70.1±0.3	64.9±0.1	72.1±0.4	61.9±0.1	80.1±0.2	60.1±0.2	68.5±0.6	94.3±0.5
60	89.1±0.2	76.8±0.1	72.3±0.1	81.7±0.4	73.4±0.4	96.3±0.6	66.7±0.2	72.1±0.4	99.3±0.4

All data are expressed as % in the form of Mean ± Standard Deviation (n-3). Time in minute.

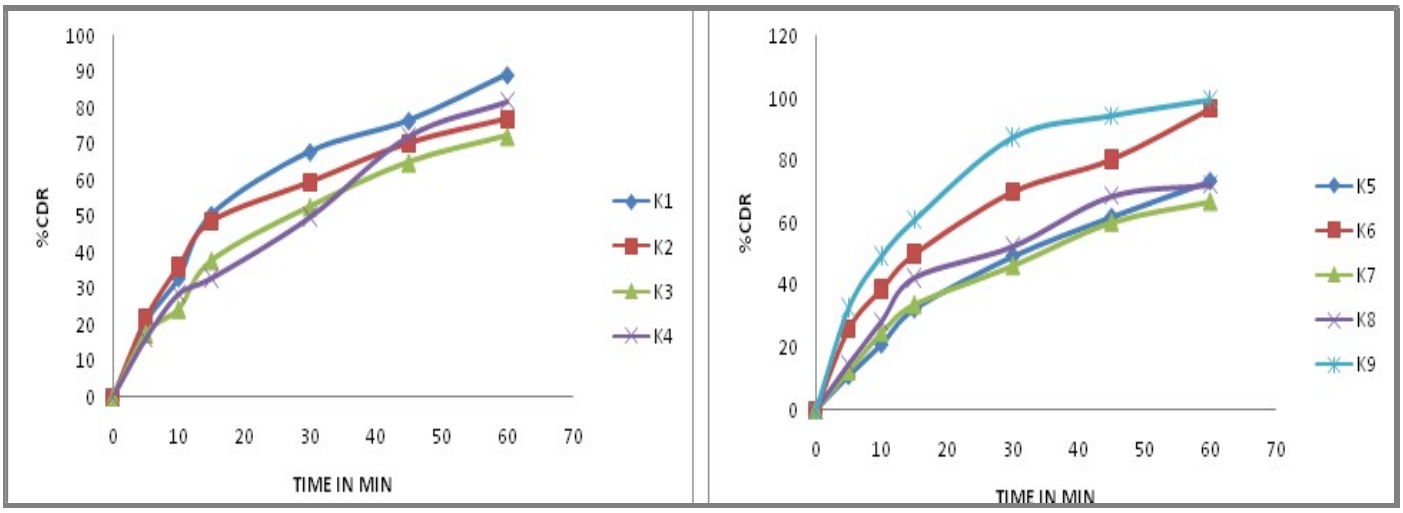

Fig 2. Dissolution profile for immediate release tablet of Ketorolac.

Table 11. The drug release kinetics for C9 formulation for Floating layer SR.

Parameter	Zero	First	Higuchi	Peppas
Slope	7.62343632	-0.14628534	34.08261421	-1.101791717
Intercept	14.42186711	2.199834844	-16.1312068	2.153780181
Correlation	0.988676295	-0.93585635	0.979283304	0.758374413
R^2	0.94380817	0.805827116	0.92299579	0.62213175

Table 12. Dissolution data for bilayered tablet.

Time	Bilayered tablet (IR)	SR	Time	Bilayered tablet (IR)	SR
15 min	42.74±3.45	--	4 h	--	59.62±4.32
30 min	99.3±4.14	--	6 h	--	68.29±4.24
1 h	--	20.57±3.69	8 h	--	79.31±3.41
2 h	--	37.26±3.66	10 h	--	89.47±4.19
3 h	--	47.36±3.46	12 h	--	97.52±3.21

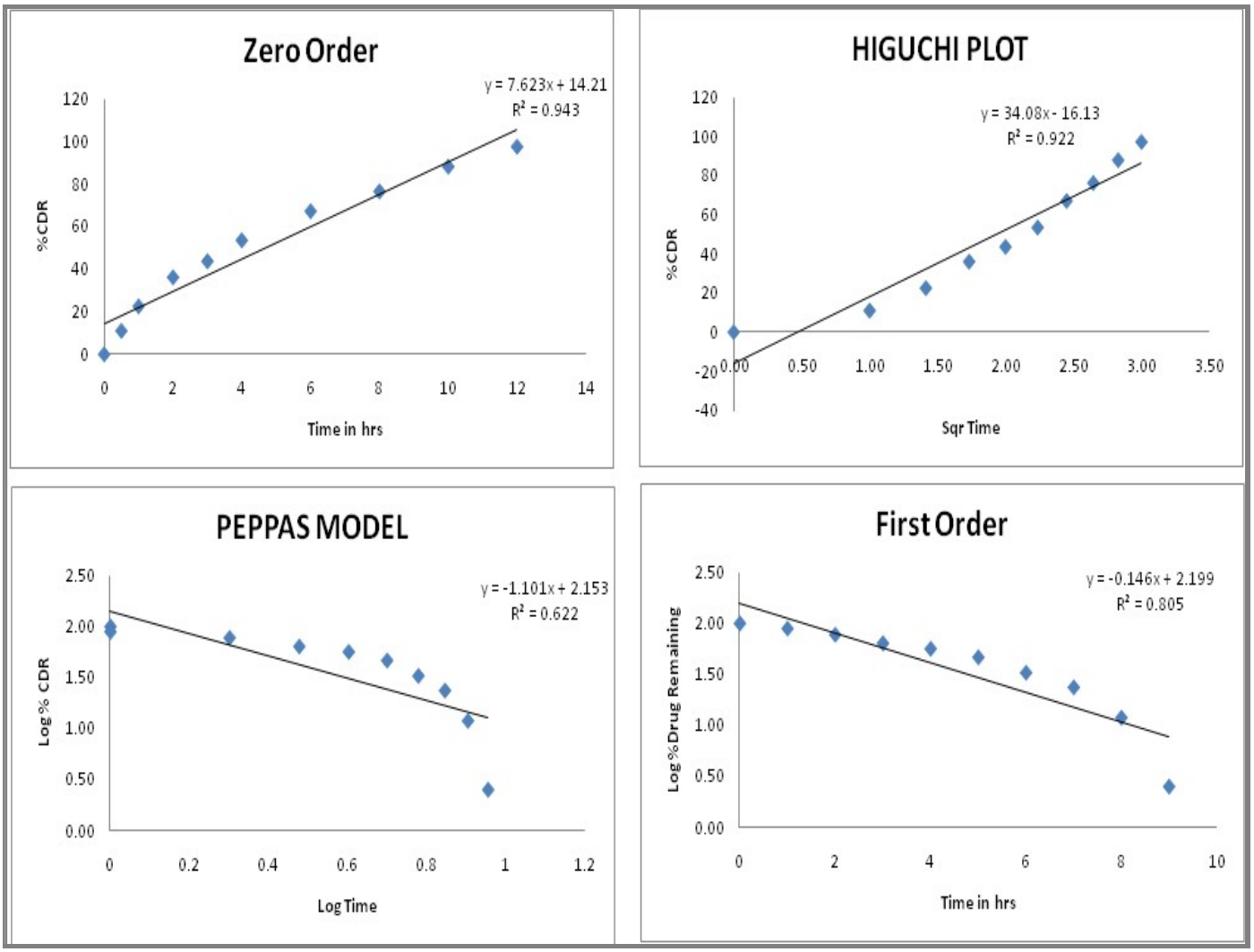

Fig 3. The drug release kinetics data for C9 formulation for Floating layer SR.

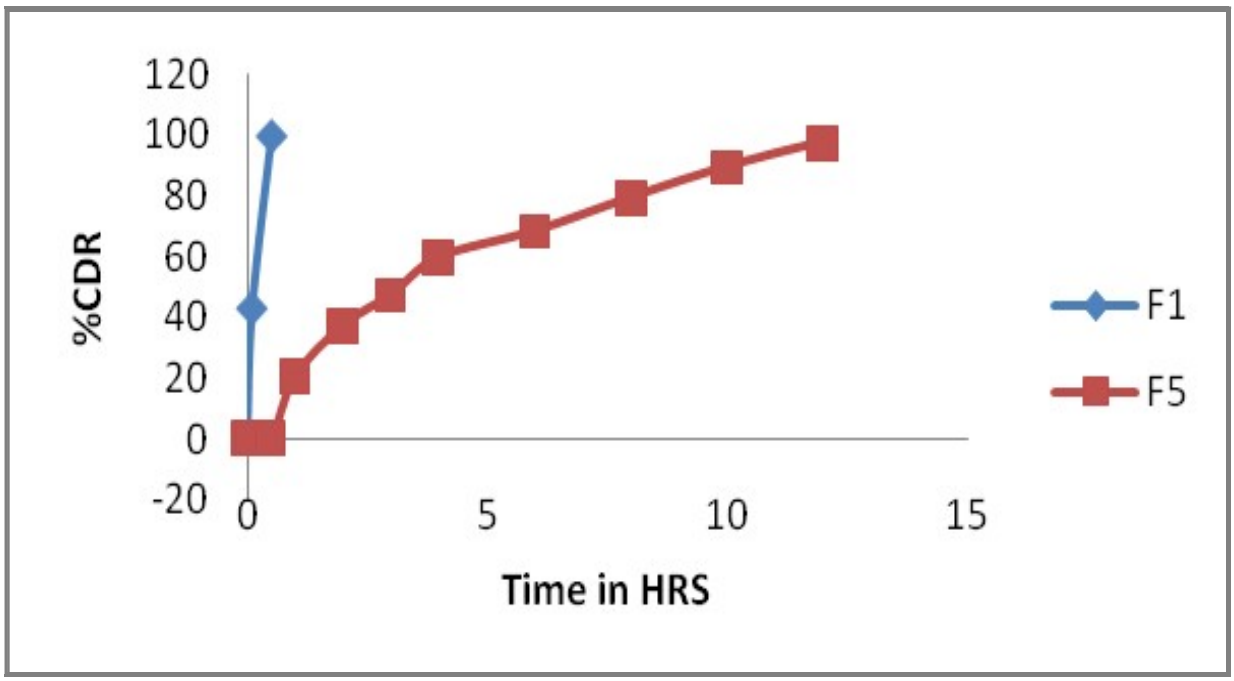

Fig 4. Dissolution profile for Ketorolac and Capecitabine Bilayerd Tablets formulation F10. CDR – Cumulative drug release.

CONCLUSION:

Ketorolac and Capecitabine containing Bilayered tablets were successfully organized by direct compression technique. The equipped blend for IR release were also preserved the physiochemical properties of tablets like, hardness, thickness, friability, weight variation. The better formulation K9 having the average of thickness of 2.1±0.01 mm, hardness of 3.4±0.04 kg/cm^2, weight of 150±0.4 mg, friability of 0.29±0.02 %. The optimized formulation C9 having the average thickness of 2.3±0.04, hardness of 4.5±0.07, friability of 0.44±0.005. Up to 12 h the Capecitabine C9 formulation was sustained the releases manner and Ketorolac IR K9 formulation showed 99 % drug release within 60 min. The Bilayered Tablet (IR+SR) showed 97.52 % Cumulative Drug release within 12 h.

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