DESIGN AND DEVELOPMENT OF CAPECITABINE AND GRANISETRON BILAYER TABLETS

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Abstract:

With the extra advantage of administering multiple pharmaceuticals with distinct release patterns in a single tablet, bilayer tablets have developed into a versatile dosage form in the pharmaceutical industry. In order to increase the therapeutic efficacy for cancer and chemotherapy-induced nausea and vomiting, a bilayer tablet comprising Capecitabine and Granisetron was meticulously created and tested in this study. Capecitabine, which forms the sustained release layer and is created using a combination of HPMC K4M and HPMC K100, provides prolonged drug release, while Granisetron, the immediate release layer, which is made with the super disintegrant agent croscarmellose sodium, ensures rapid medicine availability. Comprehensive pre-compression analyses were conducted separately for the Immediate and Sustained release layers.

The direct compression method was subsequently used to incorporate these evaluations. The rapid release layer (formulation F8) provided a complete release in 30 minutes, while the Sustained release layer (formulation F7) showed a prolonged release over 12 hours. The development of a bilayer tablet including Capecitabine and Granisetron is highlighted by the study's findings, highlighting its potential as a helpful therapeutic substitute for the treatment of cancer and the side effects of chemotherapy.

Keywords: Bilayer tablet, Sustained release, Immediate release, Granisetron, Capecitabine

1. Introduction:

Drug delivery systems that come in solid dose forms include tablets, capsules, sachets, pills, powders, granules, and more. Oral solid dosage forms are the most significant and play a key role in the pharmaceutical industry among the several dosage forms. Oral medicine delivery is widely appropriate and simple to use. In order to achieve systemic effects, almost 80% of medications are designed as solid dosage forms [1]. A potential development in pharmaceutical science, bilayer tablets provide a flexible and efficient drug delivery method for a variety of therapeutic uses. We can anticipate more advancement in bilayer tablet technology that will improve patient outcomes and drug delivery as this field of study develops. The immediate-release component of the medication, which is intended to provide a quick onset of effect, is usually found in the first layer of a bilayer tablet. The medication is released into the bloodstream for instant action when this layer swiftly dissolves in the stomach or intestine. On the other hand, the second layer is made to deliver the drug's steady release over a long duration. A polymer that regulates the drug's release is typically applied to this layer, enabling a consistent and uninterrupted distribution of the active ingredient [2].

When thymidine phosphorylase is present, the oral prodrug Capecitabine, a commonly used chemotherapeutic medication for the treatment of malignancies, transforms into 5-fluorouracil. Once more, fluorouracil underwent metabolism, yielding two active metabolites: 5-flurouridine triphosphate (FUTP) and 5-fluro 2-deoxyuridine monophosphate (FdUMP), the latter of which inhibits RNA and protein synthesis whereas FdUMP inhibits DNA synthesis [3] [4] [5]. Granisetron is a selective 5-HT3 receptor antagonist [6] that is frequently used to stop nausea and vomiting brought on by chemotherapy. 5-HT3 receptors that are located peripherally (abdominal vagal afferents) and centrally (chemoreceptor trigger zone) are antagonistic. The patient requires two dosages during chemotherapy: one for the side effects of the chemotherapy and another for the cancer treatment. But the combination of Capecitabine and Granisetron in a single dosage form could provide a convenient and effective treatment option for cancer patients undergoing chemotherapy with desirable release [7].

2. MATERIALS AND METHODS

2.1. Chemicals:

Capecitabine and Granisetron were purchased from Chandra labs, Hyd. HPMC, PVP, Lactose monohydrate, Crospovidone, Cross Caramellose sodium and Sodium starch glycolate

were purchased from MYL CHEM Mumbai. Magnesium stearate, MCC and talc purchased from S.D Fine chem. LTD Mumbai.

2.2. Preparation of Sustained release layer:

After 20 minutes of dry blending, powdered combinations of Capecitabine, Microcrystalline cellulose, Polymers, and binder were added. Magnesium stearate and talc were then added. Following 10 minutes of blending, 400 mg of the resulting powder blend was manually compressed using a KBr hydraulic press at 1 ton of pressure, utilizing a 12mm punch and die to create the tablet. Table 1 lists the sustained release layer's composition.

Table 1: Formulae for Sustained Release layer of Capecitabine.

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Capacetabine (mg)	150	150	150	150	150	150	150	150	150	150
HPMC K4M (%)	50	60	70	80	--	--	--	--	--	--
HPMC K100 (%)	--	--	--	--	50	60	70	80	--	--
EC (%)	--	--	--	50	60	--	--	--	70	80
PVP K30 (%)	15	15	15	15	15	15	15	15	15	15
Talc (%)	5	5	5	5	5	5	5	5	5	5
Magnesium stearate (%)	5	5	5	5	5	5	5	5	5	5
MCC(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)	325	325	325	325	325	325	325	325	325	325

MCC- Micro crystalline cellulose, EC – Ethyl cellulose, PVP- Poly vinyl pyrrolidine, HPMC – Hydroxy Propyl methyl cellulose.

2.3. Preparation of Immediate release layer:

All the ingredients were passed through sieve 80# and mixed in a motor and pestle for 30min for uniform mixing. The addition of ingredients was done in a geometrical manner.

Then the Granisetron layer was compressed using 8mm round punch. Composition of immediate release layer is given in Table 2.

Table 2: Formulae for Granisetron immediate release layer.

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Granisetron	2	2	2	2	2	2	2	2	2
CMC (%)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
CCS (%)	2.5	5	7.5	10		--	--	--	--
SSG (%)	--	--	--	--	2.5	5	7.5	10	12.5
CP (%)	--	2.5		--	--	2.5	--	--	--
Lactose monohydrate	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate (%)	10	10	10	10	10	10	10	10	10
Talc (%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	150	150	150	150	150	150	150	150	150

CP- crospovidone, CCS: Cross caramellose sodium, SSG: Sodium starch glycolate, CMC- Carboxy methyl cellulose

2.4. Bilayered tablet compression

The bilayer tablet was prepared by direct compression method. After the batch was optimized in both immediate release layer (F7) and sustained release layer (F4). Bilayered tablets were prepared by taking 325 mg of Sustained release granules into die cavity and compress them. Then add 150 mg of immediate release granules into same die cavity and applied final compression using rotatory tablet press.

2.5. Evaluation of Pre- compression blend:

2.5.1. Angle of Repose (Flow Property) [8] :

The flow property of powder was determined by measuring the Angle of Repose. It is the maximum angle possible between heights of a pile to radius of pile base.

Angle of repose= $\tan^{-1}$ (h/r)

Where,

h = height of a pile (2.5 cm)

r = radius of pile base.

2.5.2. Bulk density [9]**:**

Bulk density is a ratio of mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been taken in to graduated cylinder or into volume measuring apparatus in to cup.

Bulk density = M / V_0

Where M= mass of the powder;

V_0=bulk volume of the powder.

2.5.3. Tapped density:

Tap density = M / V_F

Where M = mass of the powder,

V_F = final tapping volume of the powder.

2.5.4. Compressibility index and Hausner ratio:

The compressibility index and hausner ratio are calculated from the values of bulk volume and tapped volume

Compressibility index = $100X(V_O - V_F)/V_O$

Hausner ratio = V_O/V_F

2.6. Evaluation of tablets:

2.6.1. Physical Appearance [10]:

The control of general appearance involves the measurement of size, shape of tablet and visual inspection for detecting any capping, breaking and lamination of tablet.

2.6.2. Thickness [11]**:**

Tablet thickness can be measured by micro-meter or by other vernier caliper. Tablet thickness should be controlled within a ± 5% variation of standard value.

2.6.3. Weight variation test:

As per Indian pharmacopeia take 20 tablets and weighed individually, calculate average weight and compare the individual tablet weight to the average.

2.6.4. Friability [12]:

It is usually measured by the use of the Roche friabilator.

2.6.5. Hardness:

Tablets should possess a certain amount of hardness for resistance to withstand mechanical shocks of handling in packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. Hardness results are expressed in **Kg/cm^2**.

2.7. Dissolution study of Capecitabine and Granisetron from bilayer tablet [13] [14]

- In-vitro drug release of optimized Capecitabine and Granisetron from bilayer tablet was studied by conducting dissolution studies.
- Dissolution tests performed using USP Type II dissolution apparatus. A 900ml of 0.1N HCL at 37± 0.5^0 C at 50rpm for 2hrs.
- 5ml of sample was taken at the intervals of every 60min and replaced with fresh 5ml of buffer.
- After 2hrs, the 0.1N HCL buffer was replaced with 6.8pH phosphate buffer.
- The absorbance of solution was recorded at 304nm and 323nm using buffer as blank.
- The result was calculated as Percentage drug release of Capecitabine and Granisetron.

3. RESULTS

3.1. Pre-Compression Parameters for Capecitabine Sustained Release Blend

The final bilayer tablet's quality and functionality are determined by the pre-compression settings for the sustained release formulations. Ten formulations (F1 to F10) were assessed using the following parameters: Hausner's Ratio, Carr's Index for Compressibility, Tapped Bulk Density (g/ml), Loose Bulk Density (g/ml), and Angle of Repose (θ) are all included. Table 3 presents the completed data for the pre-Compression Parameters of the powdered capecitabine sustained release.

Table. 3: Pre-Compression Parameters for Capecitabine Sustained Release

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner'sratio
F1	25.30 ±0.092	0.34± 0.03	0.41 ± 0.05	21.93 ± 0.10	1.36 ± 0.07

F2	24.50 ± 0.13	0.39 ± 0.06	0.47 ± 0.04	15.21 ± 0.11	1.27 ± 0.01
F3	26.2±0.21	0.52±0.03	0.60±0.04	11.47±0.7	1.12±0.08
F4	25.9±0.13	0.60±0.04	0.67±0.04	11.12±0.06	1.16±0.06
F5	23.96 ± 0.13	0.40 ± 0.02	0.48 ± 0.02	17.32 ± 0.08	1.19 ± 0.01
F6	23.36 ± 0.13	0.39 ± 0.03	0.46 ± 0.06	16.77 ± 0.12	1.11 ± 0.07
F7	25.58±0.14	0.41±0.05	0.48 ± 0.03	13.24±0.5	1.12±0.05
F8	26.44±0.12	0.48±0.04	0.56 ± 0.2	11.72±0.5	1.13±0.03
F9	24.36±0.12	0.42±0.046	0.52 ± 0.03	16.64±0.9	1.11±0.09
F10	25.35±0.13	0.42±0.045	0.51± 0.02	13.09±0.2	1.14±0.07

The results from Table 3 indicate the following:

Angle of Repose: The majority of formulations have good flow characteristics, with an angle of repose below 30°. This assures that throughout the tablet compression process, the powder mix will pass through the hopper and die cavity without obstruction.

Loose and Tapped Bulk Density: The measurements demonstrate the powder mixes' compactibility and uniformity. Achieving consistency in tablet weight and content requires doing this.

Compressibility: Values ranging from 11.47% to 20.93% demonstrate good to exceptional compressibility in the formulations. Lower compressibility index values (less than 20%) suggest that there won't be any major volume reduction problems when compressing the powder mixes into tablets.

Hausner's Ratio: All formulas have ratios that are less than 1.26, which further attests to the powder mixes' superior flow characteristics. Powders with a Hausner's ratio of less than 1.25 are generally considered free-flowing, which is necessary for the reliable production of tablets.

The superior flow characteristics of the powdered blends of the sustained release formulations are evident from the pre-compression measurements mentioned above. These characteristics are essential to guaranteeing the final bilayer pills' consistency, quality, and uniformity. The high-quality bilayer tablets with consistent drug release profiles are produced using manufacturing techniques that are made more efficient by the powder blends' superior flowability and compressibility.

3.2. Pre-compression parameters of Granisetron Immediate Release Blend

Granisetron Immediate Release formulation with acceptable flow characteristics and appropriateness for direct compression are indicated by the pre-compression parameters. The range of 22.1° to 29.4° for the angle of repose indicates that the flow parameters of all the formulations are satisfactory. The fine particles are light and fluffy but compress well under pressure; loose bulk density values vary from 0.3 to 0.57 g/ml and tapped bulk density values from 0.35 to 0.68 g/ml. The powders are compressible but not unduly so, as indicated by the compressibility values (%), which vary from 12.24% to 17.78%. Formulation F6 has a little higher value of 17.78%. Good flow qualities for all formulations are further confirmed by Hausner's ratio values, which range from 1.14 to 1.22 and a complied data of pre-compression parameters of Granisetron is given in Table 4. All things considered, these metrics show that the medication and excipients may be successfully combined to form tablets without experiencing any serious manufacturing problems.

Table 4: Pre-compression parameters of Granisetron

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner'sratio
F1	24.9^0	0.35	0.33	14.29	1.17
F2	23.5^0	0.33	0.44	15.56	1.18
F3	25.2^0	0.45	0.61	14.52	1.17
F4	25.7^0	0.57	0.67	16.18	1.19
F5	24.8^0	0.42	0.45	12.24	1.14
F6	23.2^0	0.38	0.45	17.78	1.22
F7	28.4^0	0.45	0.51	14.00	1.16
F8	23.10^0	0.44	0.5	13.73	1.16
F9	25.4^0	0.41	0.48	14.89	1.18

3.3. Post Compression Parameters for Capecitabine Sustained Release Tablet

Important details on the uniformity and quality of the tablets may be found in the post-compression parameters of the Capecitabine Sustained Release formulations. For the post compression parameters for capecitabine sustained release, please refer to Table 5.

Table 5: Post Compression Parameters for Sustained Release Tablet

Formulations	Weight variation	*Hardness*	Thickness (mm)	Friability (%)
F1	325	7.3	2.5	0.55
F2	324	7.5	2.3	0.45
F3	324	7.5	2.6	0.52
F4	324	6.6	2.4	0.55
F5	326	6.5	2.1	0.45
F6	326	7.3	2.3	0.50
F7	324	7.5	2.4	0.51
F8	325	7.5	2.2	0.53
F9	325	7.4	2.7	0.45
F10	326	7.8	2.7	0.57

The weight variance across all formulations is about 400 mg, suggesting strong tablet weight consistency. The range of tablet hardness, which impacts the mechanical integrity and disintegration time, is 6.5 to 7.9 kg/cm^. This suggests that the tablets are hard enough for prolonged release. The thickness ranges from 2.0 to 2.8 mm, which is suitable to guarantee consistency. All formulations had friability, a measurement of the tablet's resistance to shattering or crumbling, below 1%, with values ranging from 0.40% to 0.52%. This suggests that the tablets are robust and can tolerate handling without suffering appreciable deterioration. All things considered, these measurements show that the Capecitabine Sustained Release pills are regularly made with the proper weight, hardness, thickness, and durability.

3.4. Post compression parameters for Granisetron Immediate Release tablets

Granisetron Immediate Release tablet post-compression metrics reveal that every batch satisfies the specified standards for weight homogeneity, hardness, thickness, and friability. The pills' average weight, which falls between 147 and 152 mg, shows good consistency. The range of tablet hardness, which guarantees that the tablets are appropriately hard, is 3.1 to 3.6 kg/cm². The thickness falls between 2.1 and 2.5 mm, which is within uniformity-acceptable bounds. Less than 0.5% friability scores which range from 0.25% to 0.52%. A complied data of post compression parameters for Granisetron immediate release tablets is given in Table 6.

These findings demonstrate that every physical characteristic of the manufactured tablets is fully under control, guaranteeing a constant level of quality throughout several batches.

Table 6: Post compression parameters for Granisetron immediate release tablets

Formulations	Average weight (mg)	*Hardness* Kg/cm^2	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
F7	148	3.1	2.5	0.44
F8	149	3.4	2.4	0.43
F9	150	3.3	2.3	0.42

3.5. In-Vitro Drug Release Studies for SR layer

The outcomes of in-vitro drug release studies on Capecitabine sustained release (SR) tablets are shown in the table. The effectiveness of each formulation in maintaining drug release over a 12-hour period is clarified by these studies. The cumulative percentage drug release at different time intervals indicates how well each formulation sustains the medication's release over-time. As seen in Table 7, formulations F1, F2, F3, F4, F5, F6, and F8 did not sustain the drug for 12 hours due to either an early or inconsistent release of the drug. Figure 1 displays the dissolution graph for formulations F1–F10 of Capecitabine.

Some of these formulations, including F1, F4, F5, and F8, showed substantial release percentages before they reached the 12 hour mark, while F3 had almost completely released by the second hour and F2 by the fourth. With medication release lasting up to 12 hours, formulation F7 which was made by combining HPMC K4M and K100 showed the best effects. The medication release was gradually and meticulously controlled, reaching a total release of 96.5% after 12 hours. This implies that HPMC K100 and HPMC K4M cooperate effectively to sustain Capecitabine release, making formulation F7 the least successful one that was examined.

Table 7: Cumulative percentage drug release of Sustained Release of Capecitabine Layer

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Dissolution medium 0.1N HCL										
1	39.4	43.8	90.4	35.5	26.5	17.9	23.5	33.4	38.4	27.3
2	44.6	70.3	95.6	47.6	40.1	25.3	38.2	43.2	40.3	34.3
6.8pH phosphate buffer										
3	54.6	81.6	--	68.6	43.6	32.6	47.6	55.1	50.2	42.8
4	71.5	92.5	--	75.7	58.8	46.4	54.6	61.5	56.4	49.3
5	85.7	--	--	86.4	88.2	58.3	69.3	73.6	63.5	57.4
6	92.5	--	--	96.8	92.2	82.3	76.3	82.1	72.9	65.9
8	--	--	--	--	--	95.3	82.2	86.9	77.3	73.8
12	--	--	--	--	--	--	97.3	89.3	84.5	82.5

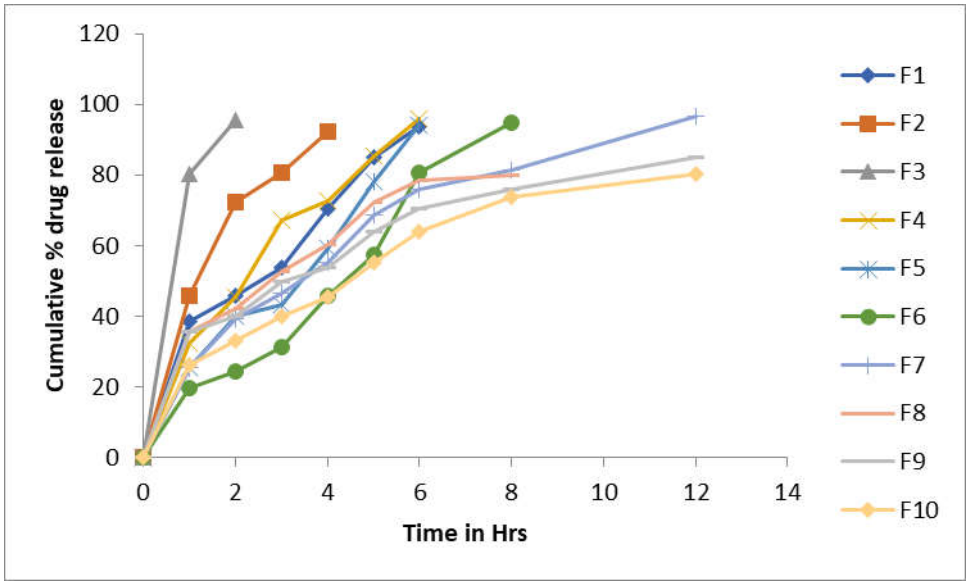

Figure 1: Dissolution of Capecitabine formulations F1-F10.

Overall, F7 was the only formulation that fulfilled the sustained release criteria over a 12-hour period, making it the optimal choice for achieving a prolonged therapeutic effect.

3.6. In-Vitro Drug Release Studies for IR layer

The Granisetron quick release tablet dissolution study indicates that F8 and F9 have the most rapid and comprehensive drug release, dissolving almost entirely in 30 minutes. Other formulations, such as F7 and F6, also exhibit substantial release rates, albeit at a slightly slower pace. When taken right away, F3, F4, and F1 lose some of their efficacy due to their delayed drug releases. F8 is the best formulation for rapid therapeutic action out of all of them. Table 8 provides comprehensive combined data for In-Vitro Drug Release Studies for the IR layer, whereas Figure 2 displays the dissolution graph.

Table 8: Dissolution for Immediate Release Layer of Granisetron

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	26	23	15	20	35	32	41	64	47
10	38	37	27	44	58	57	68	71	64
15	44	50	41	57	66	66	78	80	81
30	52	57	55	64	71	73	85	99	94
45	58	73	62	77	89	85	94	--	--
60	62	82	77	89	92	93	--	--	--

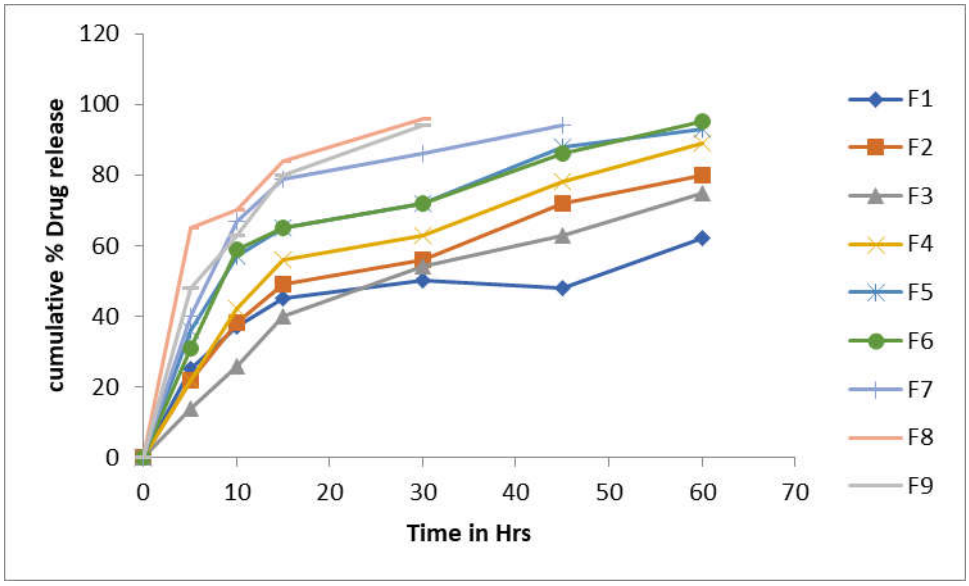

Figure 2: Dissolution graph for Granisetron formulations F1-F9

3.7. Dissolution Profile of Bilayered Tablet

The disintegration curve of the bilayered tablet illustrates the rates of release of Capecitabine and Granisetron over time. Granisetron releases 80.7% of its total weight in 15 minutes and 99.8% in 30 minutes, and it dissolves almost completely in 30 minutes. It's meant to be released quickly. This is best demonstrated by capecitabine, which is designed for sustained release and has a slow, regulated release over an extended period of time; it begins at 4.2% release in 15 minutes and reaches 97.3% release by 12 hours. Granisetron's efficient rapid release and capcitabine's delayed release in the bilayered tablet are both confirmed by this profile. Refer to Table 9 for compiled statistical data.

Table 9: Comparison in dissolution profile of Bilayered tablet

S.NO	Sampling time	Percentage drug released (%)	
		GRANISETRON	CAPECITABINE
1	15mins	80.7	4.2
2	30 mins	99.8	6.6
5	1hr	--	20.6
6	2hr	--	37.7
7	3hr	--	45.4
8	4hr	--	53.8
9	5hr	--	69.7
10	6hr	--	77.9
11	8hr	--	89.0
12	12hr	--	97.3

SUMMARY AND CONCLUSION

The bilayered tablets containing Granisetron IR and Capecitabine SR were successfully produced using the direct compression method. Numerous formulations presenting Capecitabine as a sustained release and Granisetron as an instant release were developed and evaluated in an attempt to improve patient compliance. The granules in each trial's physiochemical analysis satisfied the required values for angle of repose and compressibility index. The blends developed for the SR and IR layers showed the proper physiochemical properties, including thickness, hardness, weight fluctuation, and friability.

The enhanced IR formulation F8 was measured to have an average thickness of 2.3 mm, a hardness of 3.3 kg/cm2, a weight of 149 mg, and a friability of 0.39%. The enhanced SR formulation F7 had an average thickness of 2.42 mm, a hardness of 7.29 kg/cm2, and a friability of 0.5%. F7 released 23.5% of the entire amount of Capecitabine in the first hour, with the remaining medication being released over a period of up to 12 hours. Granisetron IR F8 showed 99% drug release after 30 minutes.

The F7 formulation showed the best linearity in the plot of Higuchi's Equation, according to kinetic analysis, suggesting that non-Fickian diffusion is the mechanism underlying drug release from the matrix tablet. The optimized bilayer tablet's dissolving research was connected to the medication release properties of the various layers. To sum up, continuous release layers and direct compression tablets for instant release are practical formulations for reducing side effects in cancer treatment.

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