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Formulation and in Vitro Evaluation of Granisetron and Cabazitaxel Bilayered Tablets

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Abstract: In the present study, the bilayered tablets were effectively formulated using Granisetron as immediate release layer and Cabazitaxel as controlled release layer by using direct compression method. Granisetron, an antagonist of the serotonin 5-HT3 receptor, is used as an antiemetic, while Cabazitaxel, an anticancer drug, is used to treat metastatic prostate cancer. Six Formulations of Granisetron and Cabazitaxel were prepared and evaluated for various physicochemical parameters such as hardness, friability and drug content. The optimized formulation GR-6 in immediate release layer formulation exhibited the average hardness of 4.3 kg/cm^2, friability of 0.40% and drug content 100.8%. The CB-6 as controlled release layer in formulation exhibited an average hardness of 3.4 kg/cm^2, friability of 0.42% and drug content 99.6% was determined. Both Granisetron and Cabazitaxel optimized layers were prepared as bilayered tablets by using polymers such as Ethyl cellulose, Eudragit, Guar gum, Hydroxypropyl cellulose and starch glycolate sodium. Cabazitaxel was released in a controlled manner in the first hour, while the remaining drug was released for up to 12 hours, and the Granisetron formulation showed 100.4% drug release.

Keywords: *Bilayer tablet, Cancer, Immediate release, Control release, Hardness, Friability.*

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I. INTRODUCTION

The development of immediate or controlled drug delivery system has got momentum over the past decade due to immense focus on the marketing of new drug molecules as the combination of these drug molecules has increased to counter multiple diseases that require different dosage regimen. [1-2] Bilayer tablets are innovative drug delivery methods that provide two drugs with different release characteristics, increasing therapeutic outcomes and patient compliance. Designing a bilayer tablet with Granisetron as the immediate layer and Cabazitaxel as the floating layer in controlled release offers multiple benefits. The common side effect of anti-cancer drug is vomiting which can be prevented by giving combination of anticancer and antiemetic drug. The main mechanism of Granisetron is a selective serotonin receptor antagonist that works by blocking 5-HT3 receptors located on vagal nerve terminals and in the chemoreceptor trigger zone in the brain[3]. Whereas Cabazitaxel is effective in targeting cancer cells, even in cases where resistance to other chemotherapies has developed. Within 30 minutes, a high concentration of granisetron is delivered from immediate release layer, which offers a rapid jump to action. Fast absorption rate from the stomach enhances its therapeutic effect, providing prompt relief to patients. By delivering cabazitaxel over a 12-hour period, the controlled release layer lowers the frequency of dosage while preserving constant plasma concentrations. By facilitating greater drug absorption, floating pills prolong their duration in the stomach and increase bioavailability.

II. MATERIALS AND METHODS

GRANISETRON AND CABAZITAXEL WERE SUPPLIED BY CHANDRA LABS, HYDERABAD, GUAR GUM, HPMC, CROSS POVIDONE, SODIUM STARCH GLYCOLATE, CROSS CARBOXYMETHYLCELLULOSE SODIUM WERE SUPPLIED BY MYCHEM, MUMBAI. MAGNESIUM STEARATE, MICROCRYSTALLINE CELLULOSE AND SODIUM BICARBONATE WERE PROCURED FROM S.D FINE CHEMICALS LTD., MUMBAI.

➢ *Formulation Method*

- *Preformulation Studies:*

Preformulation studies helps in studying the drug's physical and chemical properties to produce a stable and effective tablet formulation.

- *FTIR Studies:*

Using Fourier transform infrared (FTIR) spectroscopy, interactions between Cabazitaxel, Granisetron, and excipients were studied.

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- *Flow properties:*

Angle of Repose is the method to determine the flow property of a compound**.**

✓ *Angle of repose:*

Angle of Repose is defined as the maximum angle formed between the free-standing surface of a powder heap and the horizontal.It is calculated The Equation 1",

$$Angle\ of\ repose = \left[\tan \tan? = \frac{h}{r}\right]$$

Where, $[h = height\ of\ a\ pile\ ]$

$$[r = radius\ of\ pile\ base.]$$

✓ *2.Bulk Density:*

Bulk density is the ratio of a particular mass of powder to its total volume. To conduct this test, a known amount of Cabazitaxel and Granisetron is measured in a graduated cylinder and poured into a beaker. "The Equation 2", where,

$$[Bulkdensity(pb) = massofthepowder(M) /bulkvolumeofthepowder(vo)]$$

✓ *Apped Density:*

Tapped density is the volume of reduction in a tapped powder sample. CB and GR powders were tapped until volume stabilized, then calculated by "Equation 3",

$$[Tappeddensity(pt) = massofthrpowder(M) /volumeofthefinaltappingvolumeofthepowder(vt)]$$

✓ *Compressibility Index and Hausner Ratio:*

Using bulk and tapped densities, the Compressibility Index and Hausner Ratio were calculated to evaluate flow and compaction properties, crucial for tablet formation. "The Equation 3",

$$[Hausnerratio = tappeddensity/bulkdensity]$$

➢ *Formulation of Cabazitaxel Layer (Floating Layer);*

A total of 6 formulations CB-1 to CB-6 were prepared using Ethyl cellulose, Eudragit, Microcrystalline cellulose and Guar gum as polymers as specified under table 1.

Cabazitaxel and other ingredients were sieved through a 60-mesh screen, mixed thoroughly in a mortar by triturating for 15 minutes, and then prepared into tablets using direct compression with 12mm round punches, following the specified formulation table1.

➢ *Formulation of Immediate Layer*

A total of 6 formulations of Granisetron were formulated using Hydroxypropyl cellulose, Polyvinylpyrrolidone as polymers specified under table 2.

lactose monohydrate and super disintegrants were weighed and passed through a 40-mesh screen. Granisetron was added and sifted through an 18-mesh. The mixture was triturated for 15 minutes and tablets were prepared with direct compression using 12mm round punches according to the formulation table 2

➢ *Preparation of Bilayer Tablet:*

Bilayer tablets were prepared with one layer of drug for immediate release(granisetron) and second layer(cabazitaxel) designed to release drug in extended-release form.[5-8] After adjusting the batch, both the optimized immediate release layer (GR-6) and the optimized floating layer (CB-5) were formulated as the bilayer floating tablet by direct compression method.

➢ *Evaluation of Tablets:*

Prepared tablets were subjected to undergo physical and chemical evaluation tests. The characteristics include diameter, size, shape, thickness, weight, hardness, friability, and in vitro dissolution studies.

- *Hardness[9]:*

Five tablets were selected, and average hardness was measured. The hardness of the tablet should be 3-6 kg/cm^2.

- *Thickness:*

Tablet thickness should be within ±5%.

- *Friability[10]***:**

The friability test evaluates tablet hardness and its ability to tolerate abrasion during packaging, handling, and shipment.the Roche fibrillator is the instrument used to perform this test.

- *Procedure:*

10 tablets were weighed accurately and measured as weight (W1). Then tablets were rotated in an equipment for 4 minutes (100 revolutions). Repeat the same step for the final weight as (W2). The tablets friability was then evaluated for tablet abrasion. The value is expressed in percentage and should not exceed 1%. The formula for calculating % friability was as follows "The Equation 4",

$$[\%friability = (W1 - W2)/W1X100,]$$

- *Drug Content:*

Ten tablets were taken and crushed in a mortar and weighed. Powder equivalent to 1 tablet was added to 100ml of 0.1N HCL and mixed for two hours. After two hours, UV absorbance was measured at the specific wavelength.

- *Swelling Index:*

A beaker was filled with 100 millilitres of 0.1N HCL. The floating tablet was weighed and placed in the beaker. At regular intervals, the tablet was withdrawn, and excess liquid was removed using tissue paper before being weighed again. The swelling index is calculated using the following "The Equation 5",

$$[Swellingindex = 100(w2 - w1)/w1]$$

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➢ *Dissolution Studies*

- *In Vitro Dissolution Studies for Cabazitaxel (CB) Floating Layer:*

In vitro drug release studies was conducted with a USP class II dissolution apparatus[11]. A 900ml beaker containing 0.1N HCL was filled with cabazitaxel (CB) tablets of different formulations. The dissolved media was kept at 37±1°C for 12 hours at 50 rpm. At regular intervals, 5ml of sample was taken and replaced with an equal amount. The withdrawn sample was filtered through 0.45 µ filter paper, and drug release was measured using UV spectrophotometer at 323nm.

- *In Vitro Dissolution Studies for Granisetron[12] (GR) Immediate Release Layer:*

In vitro drug release was conducted with a USP class II dissolution apparatus. A 900ml beaker containing 0.1N HCL was filled with granisetron (GR) tablets of several formulations. The dissolved media was maintained at 37±1°C for 1 hour at 50 rpm.At regular intervals, 5ml of sample was taken and replaced with an equal amount. The withdrawn sample was filtered through 0.45 µ filter paper, and drug release was measured using UV spectrophotometer at 278nm.

- *Dissolution Study of Granisetron(GR) And Cabazitaxel(CB) from Bilayer Tablet:*

The release kinetics of optimized Granisetron (GR) and Cabazitaxel (CB) from bilayer tablet was studied by conducting dissolution studies. Dissolution tests were performed using USP Type II dissolution apparatus and 900ml of 0.1N HCL at 37± 0.5 0 C at 50rpm for 12hrs. 5ml of sample were withdrawn at the intervals, sampling was carried out and every time replaced with fresh 5ml of buffer. The absorbance of solution was recorded at 323nm and 278nm using 0.1N HCL as blank. The percentage drug release of Granisetron(GR) and Cabazitaxel(CB) was assessed.

III. RESULTS AND DISCUSSION

➢ *FTIR Studies:*

The IR spectra of Cabazitaxel shows O-H/N-H stretching (3554-3363 cm^{-1}), C-H stretching (3184, 2942, 2845 cm^{-1}), and C≡N stretching (2280 cm^{-1}). Peaks at 1589-1427 cm^{-1} indicate aromatic C=C stretching, and 1300-1000 cm^{-1} signifies C-O stretching. Lower wave numbers demonstrate C-H bending, which indicates complex organic functional groups. (Fig 1)

The IR spectra of Granisetron contains peaks for O-H/N-H stretching at 3483-3401 cm^{-1}, C-H stretching at 2965-2553 cm^{-1}, and a carbonyl peak at 1752 cm^{-1}. Peaks at 1591-1439 cm^{-1} indicate aromatic C=C stretching, whereas 1300-1000 cm^{-1} signifies C-O stretching, distinguishing different organic functional groups. (Fig 2)

In bilayered tablet the IR spectra shows O-H/N-H stretching at 3472-3304 cm^{-1}, C-H stretching at 2923-2868 cm^{-1}, and a potential nitrile peak at 2079 cm^{-1}. Peaks at 1601-1410 cm^{-1} exhibit aromatic C=C stretching, while 1200-500 cm^{-1} reflects fingerprint area vibrations in organic molecules by indicating no interaction between drug and excipients used in final formulation. (Fig 3)

The table: 3 provides the physical and chemical properties of six formulations of Cabazitaxel (CB-1 to CB-6). CB-6 has high hardness (3.4 kg/cm^2), thickness(3.7mm), friability (0.42) and drug content (99.6%). Low friability, average thickness and high drug content may enhance sustained release by allowing tablets remain in the stomach for a longer period of time.

➢ *Swelling index:*

The table 4 provides information about the swelling index of different formulations (CB-1 to CB-6) measured at intervals of 4,8 and 12hours. The CB-6 formulation exhibits high swelling index with (60.18) in 4hrs, (92.21) in 8hrs, (150.26) in 12hrs as compared to remaining formulations (CB-1 to CB-5).

Table 1 Composition of Floating Layer

Ingredients	**CB-1**	**CB-2**	**CB-3**	**CB-4**	**CB-5**	**CB-6**
Cabazitaxel	20mg	20mg	20mg	20mg	20mg	20mg
Ethyl Cellulose (%)	15	--	--	10	10	10
Eudragit (%)	--	15	--	15	--	10
Guar gum (%)	--	--	15	--	15	10
Sodium bicarbonate (%)	15	15	15	15	15	15
Microcrystalline Cellulose	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate (%)	2	2	2	2	2	2
Talc (%)	2	2	2	2	2	2
Polyvinylpyrrolidone	5	5	5	5	5	5
Total weight	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**

Table 2 Composition of Immediate Release Layer

Formulation	**GR-1**	**GR-2**	**GR-3**	**GR-4**	**GR-5**	**GR-6**
Granisetron(mg)	2mg	2mg	2mg	2mg	2mg	2mg
Magnesium stearate	10%	10%	10%	10%	10%	10%
Aerosil	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Lactose monohydrate	q.s	q.s	q.s	q.s	q.s	q.s
Hydroxypropyl cellulose	5%	7%	10%	-	-	-
Polyvinylpyrrolidone	5%	5%	5%	5%	5%	5%
Total weight	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**	**150mg**

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Table 3 Evaluation of Cabazitaxel Layer

Formulation Code	Avg. Weight	Hardness(kg/cm 2)	Thickness (mm)	Friability	% Drugcontent
CB-1	200	3.6	3.4	0.48	99.2
CB-2	201	3.3	3.8	0.45	97.4
CB-3	197	3.2	3.9	0.49	99.6
CB-4	199	3.7	3.2	0.52	98.4
CB-5	200	3.2	3.9	0.45	99.1
CB-6	198	3.4	3.7	0.42	99.6

Table 4: Swelling Index of Cabazitaxel

Time in hrs	CB-1 (%)	CB-2 (%)	CB-3 (%)	CB-4 (%)	CB-5 (%)	CB-6 (%)
4hr	15.84	30.18	21.82	20.12	40.56	60.18
8hr	30.18	48.91	40.60	56.21	82.12	92.21
12hr	60.21	85.21	83.24	83.21	135.21	150.26

Table 5: Evaluation of Immediate Release Layer

Formulation code	Avg. weight	Hardness (kg/cm$^{2)}$	Thickness(mm)	Friability	%Drug content
GR-1	150	4.0	2.8	0.43	99.8
GR-2	152	4.8	3.1	0.42	98.4
GR-3	150	4.3	3.3	0.40	98.6
GR-4	149	4.8	3.1	0.39	100.1
GR-5	150	4.5	3.3	0.39	100.3
GR-6	151	4.3	3.5	0.40	100.8

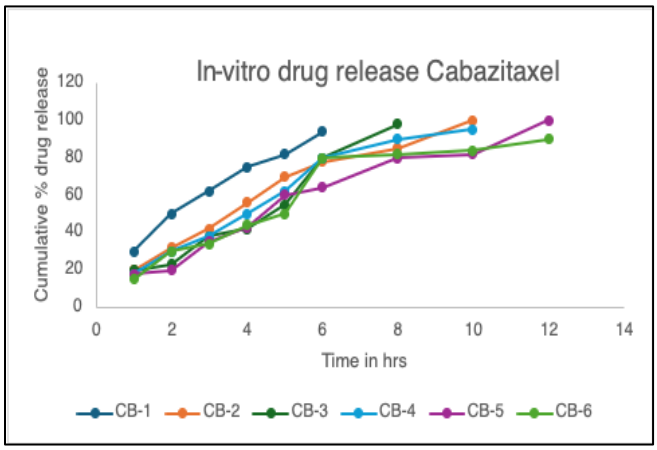

Fig 1 Dissolution Graph for Floating Layer of Cabazitaxel

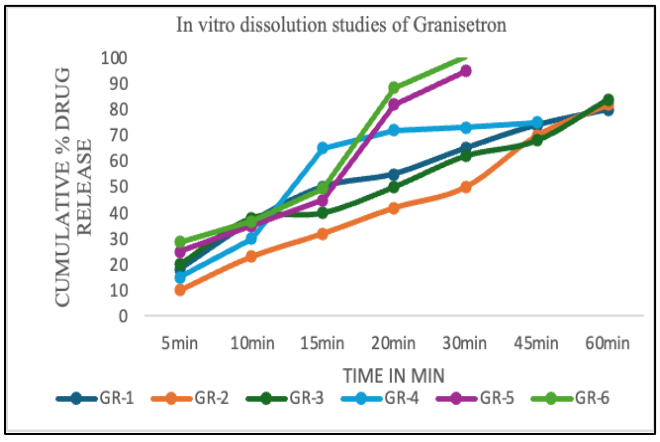

Fig 2 in Vitro Dissolution Studies of Granisetron Layer

The formulations (CB-1 to CB-6) show consistent average weights (197–201 mg) and acceptable hardness (3.2–3.7 kg/cm²). Thickness ranges from 3.2–3.9 mm, friability is within limits (0.42–0.52%), and drug content is high (97.4–99.6%), demonstrating good formulation uniformity and stability for pharmaceutical applications. Granisetron as immediate release for improving patient's compliance.

In vitro drug release study: - CB-6 has more sustained release compared to other formulation, Cabazitaxel formulations (CB-1 to CB-6) mostly failed to maintain 12-hour drug release, with CB-5 as the only effective formulation. Optimized for floating behaviour, CB-5 demonstrated 99.5% cumulative release over 12 hours, indicating superior performance and consistency in prolonged delivery, ideal for continuous therapeutic effects.

In the above data (table4 GR-6 is optimized formulation due to the optimal hardness (4.3 kg/cm$^{2)}$, high thickness(3.5mm), low friability (0.40), and drug content (100.8%).

The immediate-release Granisetron (GR) formulations (GR-1 to GR-6) provided to overcome bioavailability problem,reducing side effects[13] and rapid drug availability, making them suitable for treatments requiring immediate effects. GR-6 achieved 100.4% release within 30 minutes, exhibiting fast release among the GR formulations. GR-4 and GR-5 also showed high release rates of 95.10% and 98.4% at 45 minutes. Other GR formulations (GR-1 to GR-3) had slower release, reaching up to 88.6% by 60 minutes.

➢ *In Vitro Dissolution Studies of Bilayered Tablet:*

The Bilayer Tablet formulation of Cabazitaxel and Granisetron promotes optimal drug release. The Cabazitaxel layer (CB-5) obtained 99.5% release over 12 hours, ensuring for a long time therapeutic benefits, while other formulations failed with a prolonged release. The Granisetron layer (GR-6) obtained 100.4% immediate release within 30 minutes, while GR-4 and GR-5 had similarly high release rates (95.10%

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and 98.4% at 45 minutes, respectively). This bilayer system consists of extended Cabazitaxel activity with immediate Granisetron availability, improving therapy efficacy.

Evaluation of bilayered tablets prepared with granisetron as immediate release layer and cabazitaxel as controlled release met with the official standards, with weight uniformity, hardness, and thickness, ensuring robust, compact tablets. Friability was observed to be 0.5% indicated durability. The bilayered tablets showed immediate release of 97.5% Granisetron within 30min and exhibited controlled release of 99.5% Cabazitaxel for a period of 12hrs.

IV. CONCLUSION

The bilayered tablets were successfully formulated (BLT) layer Granisetron(GR) as immediate release and Cabazitaxel (CB) as controlled release by direct compression.

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