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Formulation and in vitro evaluation of bilayer tablets of bicalutamide and koenimbine

Dr. (Mrs.) Shilpa P. Chaudhari
Research Guide, Professor and HOD, Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi - 411 044, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India
Email: shilpachaudhari@dyppharmaakurdi.ac.in

Dhanaji S. Suryavanshi
Research Scholar, Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi - 411 044, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India
Corresponding author email: dhanajipharma@gmail.com

***Abstract*---**This work is about developing, optimizing, and testing *In vitro* a bilayer tablet with Koenimbine (KNB) in the immediate release layer and bicalutamide (BCT) in the sustained release layer. Sodium starch glycolate is used as a super disintegrant in the immediate release layer, and the hydrophilic matrix HPMC-K100 is used in the sustained release layer. Bilayer tablet showed initial burst effect to provide dose of immediate release layer Koenimbine to control the acid secretion level and the sustained release of bicalutamide for 24 hours. The prepared bilayer tablet was tested for its precompression parameters, physical properties like hardness, friability, uniformity of weight, uniformity of drug content, swelling index, and *In-vitro* drug release. In 45 minutes, 100.37 ± 0.35 percent of the Koenimbine in the immediate release layer was found to be released. In 24 hours, 98.32% of the bicalutamide in the layer with slow release was found to have been released. Koenimbine makes bicalutamide work better. So, bilayer tablets of koenimbine and bicalutamide were used to get more patients to take their medicine so that prostate cancer could be treated better.

***Keywords*---**prostate cancer, koenimbine, bicalutamide, bilayer tablets.

Introduction

Prostate cancer is the most prevalent form of the disease that affects men all over the world. There is a significant disparity in the risk of developing prostate cancer and passing away from the disease among the various population subsets around the globe (Van et al., 2016). Cancer of the prostate is the second most frequent form of the disease overall, and it is the fifth biggest cause of death among men all over the world. The number of deaths per year increased from 150,000 to 250,000 during the years 1990 and 2010. In 2018, it was reported that there were 1,276,106 new cases, with a total of 358,989 fatalities (Kaler et al., 2020). The manner in which the illness is transmitted differs from nation to nation. It is especially prevalent in the male population of certain countries in Europe, Australia, the United States of America, and Africa. On the other hand, the incidence of prostate cancer is much lower in Asia. There are a number of risk factors for developing prostate cancer, including having a history of the disease in your family, being overweight, being older, and being of a certain race (Mattiuzzi et al., 2019; Rawla et al., 2019 and Yang et al., 2005). It is recognised that the prostate gland is the origin of the cancerous cells that make up prostate cancer. Within the male population of the United States, it is the second leading cause of mortality overall. The average age of a man diagnosed with prostate cancer is 66 years or older. Nevertheless, if specific risk factors are present, it is possible for it to occur as early as the late 40s (Jenster et al., 1999).

Murraya koenigii creates a natural food component called koenimbin. Koenimbin is a naturally occurring substance that can be found in Murraya koenigii. It is responsible for inhibiting the growth of human prostate cancer (PC-3) cells and focusing on PC-3-derived prostate cancer stem cells. People are under the impression that the bioactive compounds discovered in medicinal plants might be used to cure cancer. 6 In this sense, Murraya koenigii (L.) Spreng is a plant that belongs to the family Rutaceae. It is also known as Surabhinimba in Sanskrit and as the curry leaf in South Asia. 7 The leaves of M. koenigii are utilised in the process of imparting flavour to dishes. 7 M. koenigii is utilised in its entirety or in part for the treatment of a variety of conditions, including persistent fever, diarrhoea, dysentery, dyspepsia, nausea, dropsy, dementia, diabetes, and mental impairment. 7–9 M. koenigii has been utilised to extract several carbazole alkaloids, each of which possesses significant biological activities and characteristics (Duvoix et al., 2005; Goel et al., 2008 and Hatcher et al., 2008).

Bicalutamide is a nonsteroidal pure antiandrogen that is used in the treatment of early prostate cancer that has not progressed to other regions of the body. The treatment consists of a single dosage of 150 mg of bicalutamide once day and is administered as monotherapy. Bicalutamide is a racemate, however the (R)-enantiomer is where virtually all of the antiandrogenic action may be found. The activity of the (S)-enantiomer is either very low or nonexistent. The rate of absorption of (R)-bicalutamide is modest but unaffected by the presence of food in the stomach. It takes approximately a week for half of the plasma to get rid of it, and when it is given daily, it builds up about ten times as much as it would otherwise have. Bicalutamide, which is sold under the brand name Casodex, is a nonsteroidal antiandrogen that prevents the activity of androgens by binding to the androgen receptor. The levels of both testosterone and estradiol are raised as

a result of taking bicalutamide (Goa et al., 1998; Denis et al., 1996 and Furr et al., 1996).

The levels of estradiol are very near to the low normal levels that a woman has before she enters menopause.In recent years, there has been a rise in the popularity of the bilayer tableting technique since, in many respects, bilayer tablets are superior to ordinary tablets. The majority of the time, standard dose forms result in significant alterations in the quantity of medicine that is present in the blood and tissues. These alterations are not only potentially hazardous but also render the drug less effective. Because of issues such as administering the same amount again and being unsure of how well the medication would be absorbed, controlled drug delivery devices have been developed. Using the concept of a two-layer tablet, manufacturers have been able to produce medicines that function in two distinct ways for a significant amount of time. This kind of bilayer tablet has a layer for immediate release and another layer for sustained release. Because the medication is released so rapidly from the first layer of the drug delivery system, a high serum concentration may be achieved in a very short amount of time. This type of dosage is referred to as a "loading dose."(Vishal et al., 2012; Panda et al., 2015 and Abu-Huwaij et al., 2011).

In order to maintain a concentration of the medicine that is within the "therapeutic index," the "sustained release" layer of the bilayer tablet gradually and gradually releases the drug over an extended period of time.Combination therapy, which involves the administration of two or more therapeutic drugs at the same time, is one of the most essential components of cancer treatment. Because it targets important pathways in a manner that is either synergistic or additive, the combination of anti-cancer medications is more effective than monotherapy when compared to its potential anti-cancer effects. This strategy has the potential to treat cancer while simultaneously lowering the risk of developing drug resistance. It does this by inhibiting the growth of tumours and their ability to spread, preventing cells from dividing, lowering the number of cancer stem cells, and ultimately leading to their death (Freudenreich et al., 2002; Smolen et al., 2005 and Felson et al., 1994).

The purpose of this study was to develop a method for producing bilayer tablets consisting of koenimbin and bicalutamide by including an oral dosage form that is able to provide immediate release of koenimbin while maintaining bicalutamide levels in the body for a period of twenty-four hours. This was done to increase the amount of bicalutamide that could be absorbed through the oral route. The primary objective of this effort was to develop a simple formulation method that allowed for easy scalability in order to produce bilayer tablets that included two different kinds of medications.

Materials and Methods

Cipla Ltd. in Goa, India, generously provided us with several free samples of bicalutamide. As a complimentary sample from Helax Health Pharmaceuticals in Mumbai, we were given koenimbin in addition to other components (India). The donations of lactose monohydrate and sodium starch glycolate came from Aurobindo Pharma in Hyderabad, India. Both magnesium stearate and polyvinyl

pyrolidone were purchased from SD Fine Chemicals in Mumbai, India. Crospovidone was provided free of charge by Medibios Pharmaceuticals, which is located in Bhoisar, Mumbai (India).

Compatibility studies of drug and polymers

- Fourier transform infrared spectrometry (FTIR)
  After weighing around 300 mg of KBr and grinding it down to a fine powder, the pure drug or a mixture of drug-excipients was added and grinded well before being combined with the KBr. Next, an IR press set to a pressure of 8 tonnes was used to press this KBr mixer onto a palate (Denis et al., 1996).
- Differential Scanning Calorimetry (DSC)
  The DSC investigation demonstrated that the nanoparticles had the same physical characteristics as the intrinsic medicine. The sample was kept in situ and encased in a conventional aluminium pan. It was heated between 25 and 300 degrees Celsius at a rate of 10 degrees Celsius per minute while an environment of nitrogen was present. As a point of comparison (Furr et al., 1996), we have an empty aluminium pan.

Preparation and optimization of bilayer tablets

- Preparation of Immediate ReleaseKoenimbin Granules
  Wet granulation was used in the preparation of immediate granules of koenimbin so as to accelerate the process by which the drug begins to exert its effects. Koenimbin and a number of additional excipients, including Xanthan gum, Sodium starch glycolate, and Dicalcium phosphate, were carefully weighed before being filtered through sieve #40 and then blended in a polybag. A consistent particle size was achieved by passing the powders that had been filtered through sieve #40 a second time after first thoroughly mixing them for around five minutes. After the powder combination was put through sieve #40, magnesium stearate was added to it so that it would be easier to lubricate. Compression machines with ten stations were utilised in order to compact the granules. Table 1 contains the breakdown of the tablet's ingredients. The formulation and optimization of the instant release tablet of koenimbin have been completed. The final bilayer pills were made using the recipe that had been improved.

Table 1: Formula for the preparation of Koenimbine Granules

Sr. No.	Ingredients	N-1 (mg)	N-2 (mg)	N-3 (mg)
1	Koenimbine	150	150	150
2	Xanthan gum	55	50	45
3	Sodium starch glycolate	16	16	16
4	Polyvinyl pyrolidone	24	24	24
5	Microcrystalline cellulose	55	60	65
	Total weight	250	250	250

- Preparation of Sustained Release Bicalutamide solid dispersions Tablets
  In the first step of the process, Bicalutamide solid dispersions were made using the solvent evaporation method. During this step, polymers (PEG-

20000) were dissolved entirely in ethanol in a beaker using a variety of various ratios. The drug bicalutamide was distributed throughout the solution at a ratio of 1:4 drug to polymer. To remove the solvent from the final combination, the resultant solution was left on the water bath, which was maintained at a temperature of 60 degrees Celsius plus or minus 0.50 degrees Celsius. The bulk that was collected was then dried. A glass mortar and pestle were used to grind the resulting material into a fine powder. After passing the crushed material through a number 60 sieve, it was then weighed before being put into the glass vials. In the second stage, a sustained release layer of bicalutamide solid dispersions was created using the wet granulation technique. This was done by adding lactose monohydrate, sodium starch glycolate, polyvinyl pyrolidone, and xanthan gum to the mixture. After carefully weighing the required quantities of bicalutamide solid dispersions and other excipients, the ingredients were filtered through sieve #40, completely combined, and then a suitable volume of binding agent was added slowly to create a cohesive mass. After that, the material was sent through filter #20 so that the granules could be obtained. Next, the granules were baked in an oven at a temperature of 50 degrees Celsius with hot air until they were dry. The dried granules were lubricated uniformly with magnesium stearate, and then talc was added and thoroughly mixed in. The granules were punched through with a 9 mm punch on a 10-station tablet compression machine (Mini Press I, Karnavati, and Gujarat, India) to create tablets (Panda et al., 2015; Abu-Huwaij et al., 2011; Freudenreich et al., 2002 and Smolen et al., 2005)

Table 2: Formula for the preparation of Sustained Release Bicalutamide solid dispersions Tablets

Sr. No.	Ingredients	NA-1 (mg)	NA-2 (mg)	NA-3 (mg)	NA-4 (mg)	NA-5 (mg)
1	Bicalutamide	50	50	50	50	50
2	Lactose monohydrate	60.30	70.30	65.30	65.30	65.30
3	Sodium starch glycolate	20.80	10.80	20.80	15.80	10.80
4	Polyvinyl pyrolidone	2.40	2.40	2.40	2.40	2.40
5	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5
7	Crospovidone	15	15	10	15	20
	Total Weight	150	150	150	150	150

- Preparation of Bilayer Tablets (Felson et al., 1994)

  Formulation of a tablet with a double layer the formulation of the bi-layer tablet uses the optimized formulation N-2 of the instant release layer (Koenimbine), as well as the optimized formulation NA-4 (Bicalutamide) for the control release. Wet granulation was used as the method of preparation for the optimized immediate layer of koenimbine. The wet granulation process was utilised in the preparation of an optimized sustained release layer of bicalutamide. After that, a layer of immediate release koenimbine was positioned in the lower die cavity and punched using a light amount of

compression force. After that, the sustained-release Bicalutamide solid dispersions tablets were inserted into the die cavity, and once again, the process was repeated. To create bilayer tablets, an immediate release layer of koenimbine was inserted in the upper chamber of the die, and this enabled for punching with an optimally hardness of between 6 and 8 kg/cm2. Punches of 10 millimeters were utilised in order to achieve compression (Mini Press I, Karnavati, and Gujarat, India). The total weight of each bilayer tablet was increased to 400 mg, and it contains 100 mg of koenimbine in the layer designed for immediate release and 50 mg of bicalutamide in the layer designed for extended release. After compression, the prepared bilayer tablets were tested for a number of different characteristics, and *In vitro* dissolving tests were performed (Abu-Huwaij et al., 2011 and Freudenreich et al., 2002).

Characterization parameters

- Appearance:
  The appearance was acknowledged visually through proving the colour variance.
- Hardness:
  When a tablet is put on its side, the amount of weight or pressure that is necessary to crush it is used to determine how hard it is. A tablet's tensile strength is also directly related to its hardness. At the moment, a variety of convenient hardness tests are being utilised. Some examples of these testers are those made by Mosanto and Pfizer. It is recommended that uncoated tablets have a minimum hardness of roughly 5 kg in order to ensure their mechanical stability. The hardness of the granules is determined by the granules' physical qualities, such as their hardness and their deformation under load, the binders, and most importantly, the compressional force. Because hardness has a role in how long it takes for a substance to disintegrate and dissolve, it is one of the factors that might potentially affect bioavailability.
- Thickness:
  It was decided that a Mitutoyo Digital Vernier calliper would be used to standardize the thickness of the 10 tablets that were randomly labelled (Smolen et al., 2005). A micrometer may be used to measure the thickness of individual tablets; this makes it possible for reliable measurements to be taken and provides information on the variance that exists between tablets. The thickness should be managed such that it does not deviate from a specified value by more than five percent.
- Friability:
  A Roche friabilator was utilised in order to ascertain the tablets' level of friability. The tablets are placed in a plastic chamber that rotates at a speed of 25 revolutions per minute. On each revolution, the chamber drops the tablets from a height of 6 inches, which combines the effects of abrasion and shock on the tablets. A sample of tablets, which had already been weighed, was put into the friabilator and spun for a total of one hundred times. After being wiped off with a delicate muslin towel, the tablets were reweighed after having the dust removed.

The friability (F%) is given by the formula

$$F\% = W_{0\,/}\, W \times 100$$

Where,
F% = Friability in percentage
W_0 = Initial weight of the tablets before the test
W = weight of the tablets after the test

- Weight variation:
  After determining the average weight of the 20 pills that were chosen at random, the standard deviation was determined by weighing each tablet separately.
- Drug content:
  Twenty pills are still intact despite being crushed. An amount of powder standing that corresponded to the quantity of a single tablet (50 mg) was carefully weighed, and then it was reallocated to a 100 ml volumetric flask. In a volumetric flask with 100 ml of capacity, the volume was brought up to the streak with methanol, and then the flask was sonicated for 10–15 minutes. According to UV spectroscopy, the drug's potency may be confirmed at a wavelength of 223 nm for koenimbine and 272 nm for bicalutamide (Mominet al., 2007).
- *In vitro* disintegration test for immediate release Koenimbine tablets
  Six tablets were selected at random from each batch to participate in the disintegration test. The disintegration test was carried out with the disc absent in simulated stomach fluid at a temperature of 37 degrees Celsius and an expenditure of disintegration apparatus.

***In vitro* dissolution studies (Patra et al., 2007)**

- Immediate release Koenimbine tablets
  It remained stationary on the type II apparatus until the paddle was completely depleted. a dissolve media consisting of 500 ml of pH 1.2 buffer (0.1N HCl) to be carried out at 37 ± 0.5 degrees Celsius with a rotating speed of fifty revolutions per minute. The drawings are kept covert for a predetermined time interval of up to forty minutes, and then they are evaluated using an ultraviolet spectrophotometer at 425 nm(Singh et al., 2019).
- Controlled-release tablets of Bicalutamide
  It is still being tried out on type II apparatus that makes use of the paddle. 900 cc of a buffer with a pH of 1.2 (0.1N HCl) was used as the dissolving media while the temperature was maintained at 37 ± 0.5 °C and the rotating speed was set to 50 rpm. The sample was examined using an ultraviolet spectrophotometer set at 272 nm after it had been left to rest in the dark for the allotted time period of 24 hours.
- Bi-layer tablet of Koenimbine and Bicalutamide
  On a type II equipment with a paddle, the dissolution of the bilayer tablets is still being carried out. 900 cc of a buffer with a pH of 1.2 (0.1N HCl) was used as the dissolving media, and the temperature was maintained at 37 degrees Celsius with a rotating speed of 50 revolutions per minute. The

sample was allowed to stand in the inverted position for the predetermined time interval of up to 12 hours before being assessed using the simultaneous estimation technique on a UV spectrophotometer (Maddiboyina et al., 2020).

- Statistical analysis of responses
  The Surface response plot, Contour plots were drawn using Design Expert Software v 8.0.6.1 (STATEASE).
- Stability studies
  The increased preparation was tested for its stability according to ICH requirements at a temperature of 40 ± 2 degrees Celsius and a relative humidity of 75 ± 5 percent relative humidity in a Thermo lab TH 90S stability chamber for a period of three months. The transported substances have to be analyzed for their drug content, their ability to float, and there *In vitro* drug release profile (Kotla et al., 2016).

Result and Discussion

Compatibility studies of drug and polymers

- Fourier transform infrared spectrometry (FTIR)
  According to the information shown in Figure 1, it was discovered that there was no possibility of an interaction between koemimbine and super disintegrant in either their pure or mixed forms.

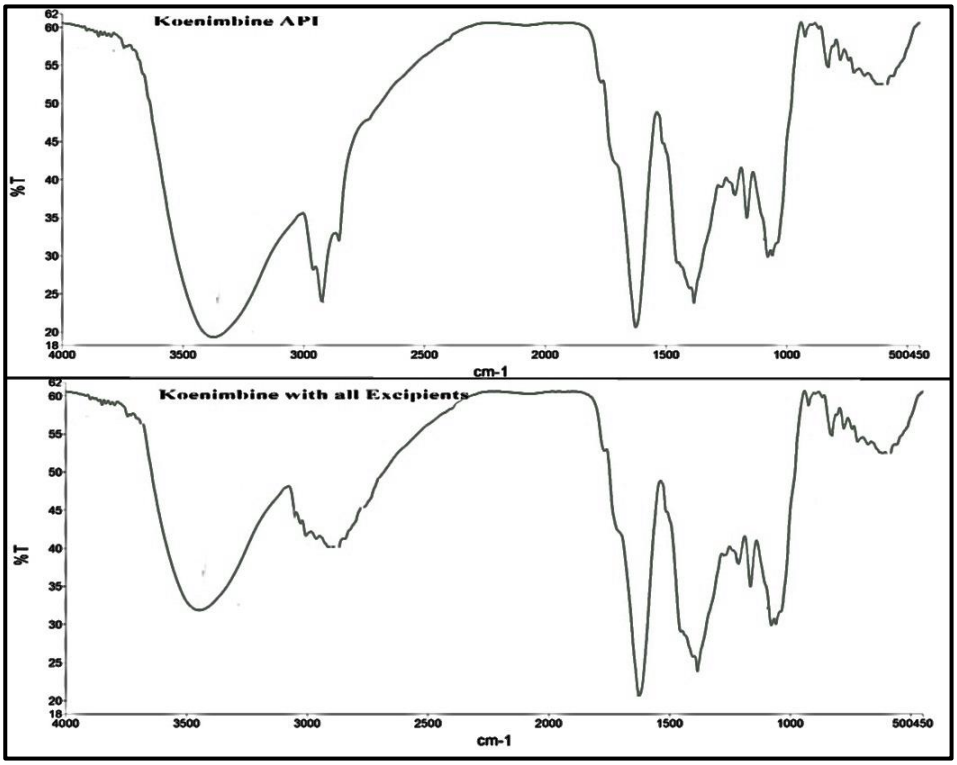

Figure 1: FTIR spectra of Koenimbine and Koenimbine along with all excipients

As can be seen in Figure 2, it was discovered that there was no possibility of an interaction between bicalutamide and disintegrant, both in their pure forms and in the forms in which they were mixed.

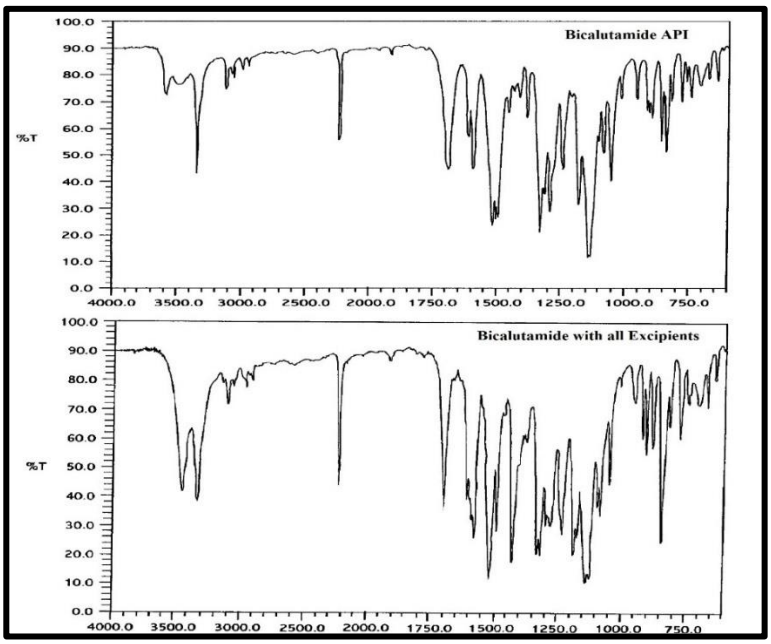

Figure 2FTIR spectra of Bicalutamide and Bicalutamide along with all excipients

- Differential Scanning Calorimetry (DSC)
  The use of DSC, a qualitative analytical method for examining the interactions, was equally successful in determining whether or not two substances are compatible with one another. According to the thermo grams, there was no discernible shift in the position of the Koenimbine endotherm peaks in the samples of the combination (as shown in Figure 3).

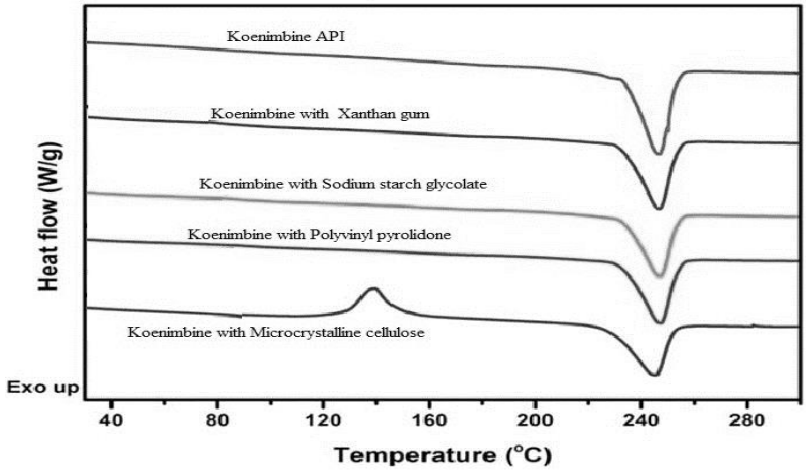

Figure 3: DSC Thermo-gram of Koenimbine and Koenimbine along with excipients

The use of DSC, a qualitative analytical method for examining the interactions, was equally successful in determining whether or not two substances are compatible with one another. As can be seen in Figure 4, the thermo grams did not exhibit any significant change in the peaks of the bicalcutamide endotherm in any of the mixed samples.

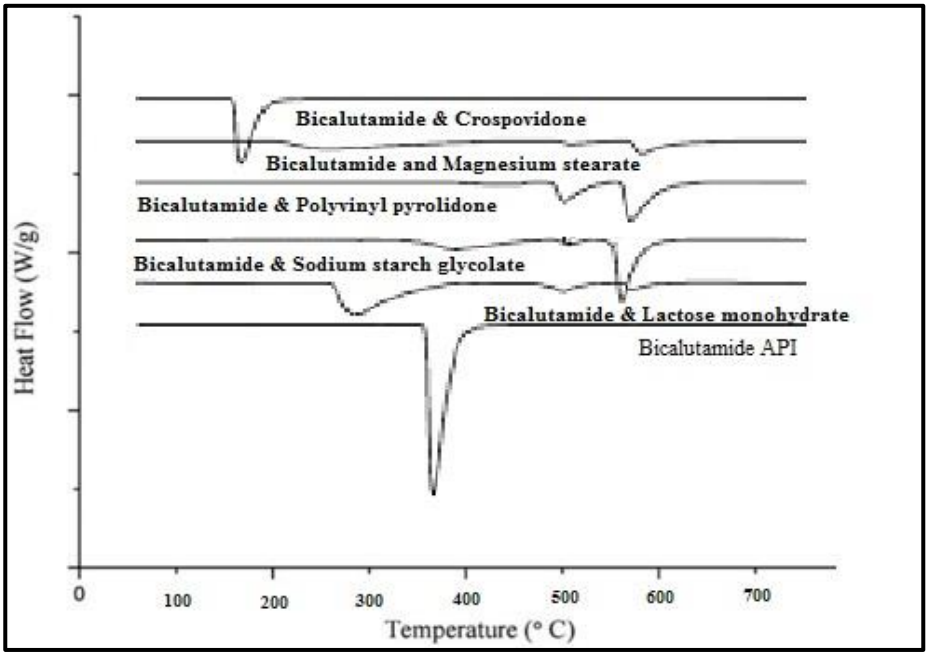

Figure 4: DSC Thermo-gram of bicalutamide and bicalutamide along with excipients

Preparation and optimization of bilayer tablets

The current problems were carried out to advance a bilayer drug release practice of KEN and BCT in order to increase absorption and bioavailability by accumulating the medication's stomach retention duration. Concerning the efficacy of this procedure, the most important thing that has to be done is to dissolve the tablet in a stomach environment first, and then go on to the next step, which is to create bilayer tablets. Preformulation studies are still being carried out, and they involve using sodium starch glycolate at a variety of concentration levels as a super disintegrant for both the immediate release layer and the hydrophilic matrix HPMC-K100. For the formulation of the bilayer pill, the optimized formulation N-2 from the immediate-release layer and NA-4 from the floating layer were employed. The direct compression approach that was used for all of the formulations was determined to be adequate. For example, the physicochemical assessment restrictions stayed within the allowed limits throughout the whole process.

Characterization parameters

- Characterization parameters for immediate release tablets of Koenimbine

The tablet that has been manufactured has a thickness that falls anywhere in the range of 3.124 ± 0.64 to 2.678 ± 0.67 millimeters. The hardness of the newly designed tablets has been maintained in the range of 3.4–3.8 kg/cm2 throughout production. Table 3 shows that the friability of all of the tablets falls within the range of 0.376 percent to 0.510 percent. This indicates that the friability of all of the tablets is less than 1 percent. Because of its inclination to inflate upon being wet, the formulation N-3 has the shortest disintegration time, which clocks in at 8.51 seconds.

Table 3: Evaluation of Immediate Release Koenimbine Tablets

Formulation	Thickness± S.D. (mm) (n = 10)	Hardness ± S.D. (kg/cm2) (n = 5)	Friability (%) (n = 10)	Avg. weight variation (n = 20)	Drug content (%)	Disintegration time (in sec) (n = 6)
N-1	3.124 ± 0.64	3.4± 0.4	0.509± 0.2	219.76 ± 0.52	98.21	09.43± 1.95
N-2	2.314 ± 0.21	3.8± 0.3	0.376± 0.3	282.87 ± 1.87	98.09	10.32± 0.12
N-3	2.678 ± 0.67	3.4± 0.6	0.510± 0.2	243.96 ± 0.76	99.12	08.51± 0.54

- Characterization parameters for floating tablets of BCT

  The created tablet maintains a thickness that falls anywhere in the range of 3.131 ± ± 0.23 to 3.645 0.32 millimeters. The rigidity of the formed GRDDS of bicalutamide has been kept within the range of 5.1–5.7 kg/cm2 throughout its establishment. The level of friability of whole tablets has been established as being less than one percent, specifically falling between the ranges of 0.195 percent to 0.321 percent as shown in Table 4.

Table 4: Evaluation of Sustained Releasebicalutamide Tablets

Formulation	Thickness± S.D. (mm) (n = 10)	Hardness ± S.D.(kg/cm2) (n = 5)	Friability (%) (n = 10)	Avg. weight variation (n = 20)	Drug content (%)
NA-1	3.314 ± 0.43	5.7± 0.5	0.321± 0.2	145.76 ± 0.42	98.93
NA-2	3.565 ± 0.56	5.1± 0.3	0.264± 0.6	152.87 ± 0.11	97.31
NA-3	3.645 ± 0.32	5.7± 0.2	0.291± 0.1	154.96 ± 1.32	98.32
NA-4	3.432 ± 0.58	5.4± 0.3	0.195± 0.6	150.96 ± 1.01	99.76
NA-5	3.131 ± 0.23	5.7± 0.6	0.311± 0.4	151.87 ± 0.71	98.31

- *In vitro* dissolution studies

  A comparison was made between the dissolution contours of the preparations that contained both of the disintegrant. Therefore, formulation N-2, which contains xanthan gum at a concentration of 25% and disintegrates extremely quickly in 08.51 seconds and releases more than 100.37 percent of the medicine in 45 minutes, continues to be recognised as

the optimum formulation, as shown in Table 4 and Figure 5. Consequently, N-2 of an immediate-release layer in a batch.

Table 5: *In vitro* drug release study for Koenimbine immediate-release tablets

Time (Minutes)	N-1	N-2	N-3
3	40.54	44.04	54.61
5	46.54	47.82	58.26
10	50.23	54.06	62.62
15	57.89	61.37	69.36
20	66.17	74.71	79.85
25	71.98	80.84	84.41
30	78.42	85.71	90.53
35	85.65	89.26	94.27
40	90.45	95.06	97.54
45	96.56	100.37	97.21

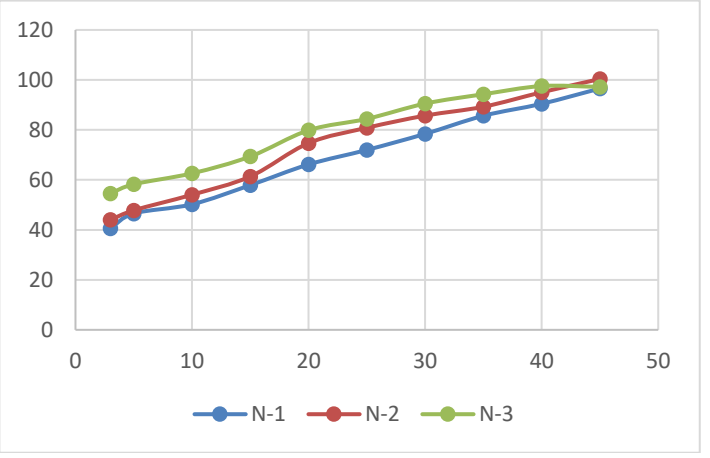

Figure 5: *In vitro* drug release study for Koenimbine tablets

As shown in Table 5 and Figure 6, the most drug was released from formula NA-4, which had the most gas-forming agents and the least amount of HPMC K4M. These changes to release showed that it was still important for release to happen. NA-2>NA-5>NA-1>NA-3>NA-4.

Table 6: *In vitro* drug release study for Bicalutamide Sustained-release tablets

Time (Minutes)	NA-1	NA-2	NA-3	NA-4	NA-5
0.5	13.15	13.41	16.40	19.55	10.09
1	19.75	16.89	25.39	27.99	15.96
2	28.91	20.83	34.19	36.42	22.00
4	36.78	24.73	41.88	44.11	27.68
8	51.98	35.94	62.20	62.61	47.46
10	63.89	48.94	72.28	74.51	61.19
12	71.39	55.35	77.59	79.09	66.69
16	76.34	62.86	82.17	87.33	71.45

20	84.22	67.44	87.11	93.00	75.84
24	89.16	71.83	91.50	98.32	79.87

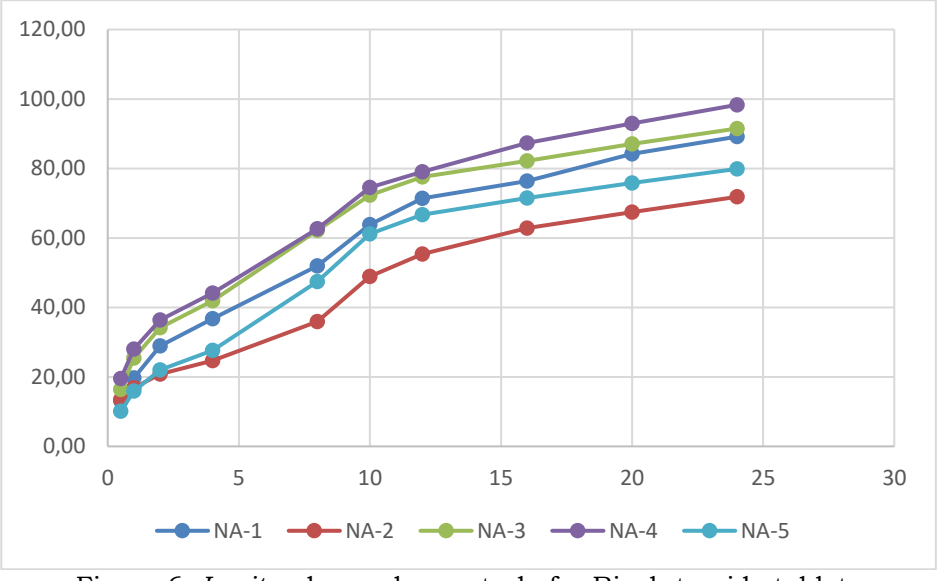

Figure 6: *In vitro* drug release study for Bicalutamide tablets

- For bilayer tablets
  A floating tablet's composition consists of an immediate-release layer (N-2 Batch) and a controlled-release layer that floats on top of it (NA-4 Batch). The prepared tablet has been measured to have an average weight of 400 milligramme, a thickness of 4.9 millimeters, and a hardness of 5.1 kg/cm2 respectively. The *In vitro* drug release of the primed bilayer tablets has been measured and found to be 99.53 percent (Koenimbine for 45 Min) and 100.32 percent respectively (Bicalutamide in 24 Hrs.).
- Stability studies
  A stability analysis was carried out for the improved bilayer tablet formulation at a temperature of 40 ± 10C and relative humidity of 75% for a period of three months. The drawings are still being reviewed for any adjustments to their hardness, % drug content, and *In-vitro* drug release. Table 12 presents the findings in their entirety. There was not a discernible considerable variation seen for the beyond parameters.

Table 7: Stability Data for optimized bilayer tablet formulation

Time (Month)	Evaluation parameters				
	Hardness (kg/cm2)	Drug content (%)		*In-vitro* drug release	
		Koenimbine	Bicalutamide	Koenimbine	Bicalutamide
0	5.0	99.86	100.11	99.42	100.46
1	5.1	99.84	100.01	100.31	99.86
2	4.9	99.61	99.97	100.06	100.11
3	5.1	99.11	99.31	99.53	100.32

Discussion

It was still being worked on to make the oral administration of the fixed-dose combination of koenimbine and bicalutamide simpler by developing a dosage form that would remain in the stomach for a longer period of time. This is still accomplished by developing a medication delivery system that is capable of maintaining the drug's presence in the stomach for an extended period of time. The precise tablets are still designed to maximize the bioavailability of the pharmaceuticals by making use of them to the fullest degree possible while avoiding needless dosage and, as a consequence, first-pass metabolism. This is accomplished by employing the drugs to their greatest extent. In order to treat prostate cancer, a combination of koenimbine and bicalutamide is typically used. The bioavailability of koenimbine is exceedingly poor, and several investigations have demonstrated very low or even undetectable amounts in blood and tissue outside of the intestines. The liver is responsible for the breakdown of bicalutamide, and its half-life is seven to ten days, which is a fairly lengthy period of time. It was recommended that a bilayer tablet of this fixed-dose combination be developed as a means of encouraging people to take their medication and maintaining long-term management of their blood pressure (Suryavanshi P.S., 2022).

Both the bilayer and the rapid release layers of the tablet went through their own individual optimization processes. Super disintegrant used to be composed of sodium starch glycolate. In order to create a matrix, a gelling agent made of microcrystalline cellulose was utilised. Crospovidone is added to substances in order to improve their ability to float and to slow down their release. In addition to lactose monohydrate, other fillers included sodium starch glycolate, magnesium stearate, polyvinyl pyrrolidone, and polyvinyl pyrrolidone. FTIR and DSC thermo grams demonstrate that there are no interfaces between the drug, polymers, and excipients in the formulation. The FTIR spectrum analysis was used in order to investigate a physical combination of medication and polymer for each and every physical and chemical distinction present in the medicine. The findings made it abundantly evident that there was no interference between the functional groups; this was demonstrated by the fact that the primary peaks of koenimbine and bicalutamide were still present. This indicated that they were compatible from a chemical standpoint. In addition, DSC, which is a qualitative method for analyzing interactions, was utilised in the compatibility experiments that were carried out. The thermo grams demonstrated that there was not a significant shift in the drug endotherm peaks within the mixed samples. The incorporation of water into the samples was the root cause of the shape shift as well as the variations in the peak of the drug combination. Direct compression is still utilised in the production of tablets since it helps manufacturers save money and reduces the total number of processes that must be carried out. Hardness, weight variation, thickness, drug content uniformity, *In vitro* disintegration duration, and *In vitro* dissolving experiments still need to be performed on the sustained release tablet, immediate release tablet, and bilayer tablet that have been created (Rajmane A., 2022). Compressing the floating, instantaneous, and bilayer tablets required the use of a RIMEK I multi-station rotary punching machine equipped with circular flat-faced punches measuring 9.5 mm, 4 mm, and 9.5 mm respectively. According to the findings of the reevaluation of the floating property,

all of the formulations exhibited satisfactory floating qualities. Because the gel layers produced by the investigated polymers were so effective at encasing the gas bubbles that were produced, none of the formulas failed after more than 24 hours of testing. The floating lag time increases in proportion to the quantity of HPMC-K100 present. This is due to the fact that at high concentrations, HPMC-K100 may impede access to the tablet matrix, which in turn lengthens the lag period. N-2 and NA-4 were selected as the most suitable components for a bilayer tablet after being subjected to a number of various assessment criteria. Following this, the tablet underwent an *In vitro* release modification as well as a stability study. The optimized bilayer tablet demonstrated that it was stable, and its values remained within the permissible range throughout the experiment.

Conclusion

We have created a bilayer tablet that has a layer designed for fast release of koenimbine and another layer tailored for sustained release of bicalutamide. The tablet demonstrates pre- and post-compression characteristics that are adequate. Because of the pharmacokinetics and the requirements of the treatment process, the approach of dividing the release of the drug into two distinct stages is one that is highly common. This applies to both the delivery level and the proportion of the dose portions. Within the immediate-release layer, sodium starch glycolate exerts a powerful influence on the breakdown and discharge of the medication when tested *In vitro*. According to the findings of our study, bilayer tablets containing Koenimbine and bicalutamide have the potential to be an effective therapy for migraines. These tablets provide the sequential release of the two medications. It was determined that by assuming a systematic preparation advent, it would be possible to acquire conveyance of two drugs out of a distinct dosage practice, which would potentially expand bioavailability, patient compliance, and provide restored disease supervision. This conclusion was reached as a direct result of the findings.

Declaration of competing interest

The authors declare no conflict of interest pertaining to this manuscript.

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