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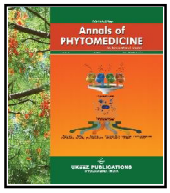

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Development of pulsincap of ivabradine hydrochloride by using some natural gums

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Abstract

The recent study aimed to develop a cost-effective natural gum-based pulsincap of ivabradine hydrochloride (IH) having 5 h of lag time in drug release for the chronotherapy of angina. Gums, from the plants such as *Terminalia elliptica* Willd., *Buchanania lanzan* Spreng. and *Albizia lebbeck* Benth. were collected and isolated from the trunk bark and successfully evaluated for their physicochemical parameters such as solubility, swelling index, pH, and flow properties. All the gums are found to be soluble in water, having slightly acidic pH, impressive swelling capacity, and good to excellent flow properties and compressibility. Around 22 (F0-F21) formulations (PULSINCAP) with (F1-F21) and without gums (F0) were developed using different thicknesses of the plug (0-60 mg) prepared by different gums. Results showed that formulation F13 having 50 mg of Saj gum as a plug successfully achieved the desired lag time of 5 h, followed by a quick release of more than 99% of the drug, hence considered as the optimized formulation. Drug release kinetic studies showed the exponent "n" >1, which indicates the non-fickian super case II transport mechanism in drug release. It suggested drug release by erosion. Optimized F13 also passed the stability test for 3 months as per ICH guidelines. The FTIR test of IH with each gum revealed no interaction. These parameters indicate the potential application of *T.elliptica* gum as novel pharmaceutical excipients in the design of pulsatile drug delivery system (PDDS) for the chronotherapy of angina pectoris.

1. Introduction

Angina is a disease that follows a circadian rhythm, where the peak occurs in the early morning before taking the medicaments (Muller, 1999; Takeda, 2011; Taylor *et al*., 1991). To deal with the same, it required chronotherapy or timed delivery of drug based on the circadian behavior of the disease (Somani *et al*., 2019). Novel PDDS releases a certain amount of drug after a predetermined lag time, provide the right amount of drug at right time and make sure the spatial and temporal delivery to achieve desired chronotherapy (Qureshi *et al*., 2009). PDDS are single or multiple-unit tablet capsules or osmotic systems designed by using many technologies such as rupturable membrane, erodible polymeric coating, pH-induced or externally controlled systems (Nayak *et al*., 2009; Imad *et.al*., 2020; Naikodi *et al*., 2021).

IH is an old antianginal drug that was used to treat chronic stable angina got approved by FDA in 2015 to manage chronic heart failure not managed by beta blockers (Yancy *et al*., 2016). It is the first specific heart rate-lowering agent used in the treatment of angina pectoris (Sulfi and Timmis, 2006). It reduces the heart rate by inhibiting the funny channel (Bucchi *et al*., 2006;Tardif *et al*., 2005). It is widely used when heart problems are not managed by beta blockers or calcium channel blockers (Ruzyllo *et al*., 2007). Its oral bioavailability is only 40 %, biological half-life is 2 h, pKa value is 8.6, T max is 2 h and first-pass metabolism through oral route is more than 50%. All these factors makes it an ideal candidate for PDDS. These days natural gums are widely being applied in pharmaceutical sectors due to their biocompatible, bioerodible, nontoxicity, costeffective, and easy availability from nature (Girish *et al*., 2009; Reddy *et al*., 2013).

Terminalia elliptica Willd. is a gum-yielding plant species, commonly known as Saj is belongs to the family, Combretaceae. The gum is reported as the matrix forming agent in the formulation of the sustained release tablets of alprazolam (Kumare and Shendarkar, 2021). *Buchanania lanzan* Spreng. is a gum-yielding species commonly known as Char or Chironji in Hindi and Charu in Odia. It belongs to the the family, Anacardiaceae (Rai *et al*., 2015). Mostly found in the States of India including Odisha (Siddiqui *et al*., 2014; Niraj *et al*., 2020). Gum of this plant previously has been used in designing spheroids of diclofenac sodium (Gaikwad *et al*., 2013). *Albizia lebbeck* Benth. is another gum yielding Indian species commonly known as Siris or Indian walnut. It belongs to the family Fabaceae. It is widely cultivated in tropical and subtropical regions of India (Yadav *et al*., 2011). Traditionally, many parts of the plants have been used medicinally as astringent, cough, ophthalmic infection, flu, gingivitis, lung problems, and abdominal tamers, inflammation, *etc*. (Wealth of India, 2006; Singh *et al*., 2012; Husain, 2021). The above literature indicating towards the safety of these gums to be used as pharmaceutical excipients. Keeping this in view, an attempt was made for the isolation and characterization of collected gums from trunk bark of *T. elliptica*, *B. lanzan* and *A. lebbeck* and apply these gums in the development of the orally

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administered time specific, pulsincap of IH for the management of early morning angina pectoris and heart failure. The main goal was to achieve the a lag time of 5-6 h, *i.e.*, the dosage form is to be taken at bedtime around 9.00-10.00 pm and is expected to release the active ingredient at around 2-3 am. As the t max of the IH is 1-2 h, its maximum plasma concentration would reach around 3.00-4.00 am and would be very effective to treat angina and other cardiovascular events.

2. Materials and Methods

Drug ivabradine hydrochloride and empty capsules shells (No.1) were purchased from Scientifiocity, Bhubneswar, Odisha, and all the other chemicals such as microcrystalline cellulose (MCC), crospovidone, magnesium stearate, Talc and acetone, formaldehyde, *etc.*, were purchased from the Yarrow Chem products, Mumbai, India.

2.1 Collection, extraction and isolation of gums

The fresh gums were collected separately during January and March by hand tapping method from the bark of the *T.elliptica*, *B.lanzan*, and *A. lebbeck* in the nearest forest of Barapahada, District Bargarh (Farroq *et al*., 2013; Jani *et al*., 2009). Gums were extracted using distil water (Sujitha *et al*., 2012; Malviya, 2011). Supernatants collected in the extraction procedure were treated with two times the volume of acetone to isolate the pure gums in the form of precipitate. Precipitated gums were separated by centrifugation and left in a hot air oven at 40-50°C, then passed through sieve number 100 and stored in desiccator for subsequent tests (Kadajji, 2011; Chatterji, 2019).

2.2 *In vitro* characterization and flow property of isolated gum

In vitro characterization of isolated gum powder is done by measuring various parameters such as percentage yield (Bhosale *et al*., 2014), solubility studies (Lala,1981), organoleptic properties (Rishabha *et al*., 2010), swelling index (Srivastava *et al*., 2010; Shankar, 2010) and pH (Shankar, 2010). The flow property of the gum was studied by tapped density and bulk density, hausner's ratio, compressibility or carr's index, and angle of repose (Srivastava, 2010).

2.3 Formulation of pulsincap

Pulsincaps are formulated after the preformulation (Rishabha *et al*., 2010) and compatibility studies of the drug with isolated gums by FTIR (Shankar, 2010; Meka *et al*., 2012).

2.3.1 Preparation of formaldehyde treated cross linked hard gelatin capsules body

Around 220 numbers of hard gelatin capsules of size No.1 were collected and bodies and caps were made separated. All the capsules bodies were spread on the wire mesh present in glass desiccators as a single layer having 25 ml of 37% formaldehyde solution taken in a beaker and kept below the wire mesh. Then 2.5 g of potassium permanganate solution was added to it. Closed the lid of the desiccators and let the bodies to expose to the formaldehyde vapor for 4 h. Removed all the bodies of the treated capsules after 4 h and kept them in the filter paper and air dried for the subsequent 48 h in an open atmosphere to make sure the complete removal of formaldehyde. All these treated capsules bodies were rejoined with their untreated cap and stored in an air-tight container for further use (Srinivas *et al*., 2013; Khan *et al*. 2011; Bhat *et al*., 2011; Veerendra *et al*., 2021; Christy *et al*., 2016).

2.3.2 Testing of physical parameters of treated and untreated capsules body

Formaldehyde-treated and untreated capsules body was tested manually for various parameters such as color, odor, stickiness, and shape. Also, the physical parameters such as average length, external diameter, and thickness of the treated and untreated capsules were measured by using slide calipers (Khan *et al*., 2011).

2.3.3 Solubility study of treated and untreated capsules body

The solubility of the 5 treated and 5 untreated capsules bodies having untreated cap was tested using 0.1N HCl in a disintegration apparatus (Electrolab) and the time at which the capsule dissolved or form a fluffy mass was noted (Jagdale *et al*., 2013; Salunkheak *et al*., 2011).

2.3.4 Qualitative test for free formaldehyde in empty capsules body

20 µg/ml formaldehyde solution of distilled water was prepared as the standard reference solution. Around 25 capsules, bodies treated with formaldehyde were taken after 48 h of air drying and cut into small pieces and dropped in the 40 ml of distilled water in a beaker, and stirred for 1 h with the help of a magnetic stirrer to let the residual formaldehyde to mix with the distilled water. The stirred solution was then filtered into a 50 ml volumetric flask and made up the volume with distilled water. From it, 1 ml solution was withdrawn in a test tube. To it, 4 ml of water and 5 ml of acetylacetone were added and the test tube was kept in a water bath at 40°C for 40 min as a sample solution. The same procedure was repeated by taking 1ml of the 20 µg/ml formaldehyde solution in a test tube. The intensity of color produced in the test solution was compared with the standard solution (Christy *et al*., 2011; Khan *et al*., 2011).

2.3.5 Formulation and preparation of the pulsincaps using treated capsules body

Around 22 formulations of pulse release capsules (pulsincap) from F0 to F21 as given in Table 1, were prepared by manual filling. First, the untreated cap and treated bodies of the capsules were separated. Then the required amount of the IH (Table 1) was properly blended with the specified amount of MCC (diluents and disintegrant), crospovidone (super disintegrants), magnesium stearate (lubricant) and talc (anti-adherent and lubricant) powders in a mortar and passed through the sieve No 60. Each of the treated capsule bodies was manually filled with the variable weight of powder blend carrying 7.5 mg of the IH in each. Each gum of *T. elliptica*, *B. lanzan* and *A. lebbeck* as given in Table 1, were separately weighted and filled in the capsule bodies and tightly pressed with the help of a glass plunger to get the variable thickness of plugs to achieve the desired lag time. The filled treated body was then merged with the untreated cap to get ready for further evaluation (Christy *et al*., 2011; Khan *et al*., 2011).

Table 1: Composition of different formulation for pulsincap

F.N	IH (mg)	MCC (mg)	CP (mg)	Talc (mg)	Mg.Stearate (mg)	Gum (mg)	Concentration of gum for plug (mg)	Total weight of the pulsincap (mg)
F0	7.5	142.5	6	2	2	-	-	160
F1	7 .5	122.5	6	2	2	*T.elliptica*	20	160
F2	7 .5	122.5	6	2	2	*B.lanzan*	20	160
F3	7 .5	122.5	6	2	2	*A.lebbeck*	20	160
F4	7 .5	112.5	6	2	2	*T.elliptica*	30	160
F5	7 .5	112.5	6	2	2	*B.lanzan*	30	160
F6	7 .5	112.5	6	2	2	*A.lebbeck*	30	160
F7	7 .5	102.5	6	2	2	*T.elliptica*	40	160
F8	7 .5	102.5	6	2	2	*B.lanzan*	40	160
F9	7 .5	102.5	6	2	2	*A.lebbeck*	40	160
F10	7 .5	97.5	6	2	2	*T.elliptica*	45	160
F11	7 .5	97.5	6	2	2	*B.lanzan*	45	160
F12	7 .5	97.5	6	2	2	*A.lebbeck*	45	160
F13	7 .5	92.5	6	2	2	*T.elliptica*	50	160
F14	7 .5	92.5	6	2	2	*B.lanzan*	50	160
F15	7 .5	92.5	6	2	2	*A.lebbeck*	50	160
F16	7 .5	87.5	6	2	2	*T.elliptica*	55	160
F17	7 .5	87.5	6	2	2	*B.lanzan*	55	160
F18	7 .5	87.5	6	2	2	*A.lebbeck*	55	160
F19	7 .5	82.5	6	2	2	*T.elliptica*	60	160
F20	7 .5	82.5	6	2	2	*B.lanzan*	60	160
F21	7 .5	82.5	6	2	2	*A.lebbeck*	60	160

FN-Formulations, IH- Ivabradine hydrochloride, MCC- Microcrystalline cellulose, CP- Crospovidone

2.4 Evaluation of pulsincap

2.4.1 Percentage drug content

Capsules were selected randomly from each batch of the prepared pulse release capsule (pulsincap) of IH and removed the content and powdered in a mortar. The quantity of powder equivalent to 7.5 mg of the drug was accurately weighed and transferred into a 100 ml volumetric flask and made up the volume with pH 7.4 phosphate buffer and shaken well. Then the resultant solution was filtered in 0.45 µm filter paper. Drug content was determined in triplicate by using a double-beam UV visible spectrophotometer at 285 nm (Sharma *et al*., 2012; Srinivas *et al*., 2013).

2.4.2 *In vitro* release profile

The *in vitro* release of all the formulations of pulsincap was performed using USP type I dissolution apparatus (Basket type) (Electro lab model-TDT-08L USP) according to Sharma *et al.* (2012); Lachman (2013); Jagdale *et al*. (2014).

2.4.3 Drug release kinetic study of optimized pulsincap

To understand the mechanism of drug release optimized formulation was fitted with the most popular models such as Zero order, 1st order Higuchi model, Hixson Crowell, and Korsmayere pappa's model and determined the coefficient correlation (R^2) values (Robinson, 2010; Dash *et al*., 2010).

2.4.4 Stability study of optimized pulsincap

A stability study was performed by storing a few samples of optimized formulation (F13) at 40ºC and 75% relative humidity in a stability chamber for 3 months and observing the various stability parameters such as shape change, color change, % drug content and lag time initially at 24 h, followed by 1st, 2nd and 3rd month (Singla *et al*., 2012).

3. Results

3.1 Physicochemical and bulk characterization of isolated gum powders

As given in Table 2, pH of the 1% (W/V) solutions of each gum was found to be in the range of 4.4 -5.9, 4.3-4.9, and 4.3-4.8 , swelling index found to be 17.00 ± 1.69, 15.42± 1.93 and 22 .94 ± 2.02, bulk density found to be 0.476 ± 0.02 g/cm^3, 0.525 ± 0.03 g/cm^3 and 0,501 ± 0.03 g/cm^3, tapped density found to be 0.588 ± 0.06 g/cm^3, 0.623 ± 0.02 g/cm^3 and 0.575 ± 0.01 g/cm^3, hausner's ratios found to

be 1.23 ± 0.06, 1.12 ± 0.03 and 1.18 ± 0.05, compressibility Index found to be 19.04 ± 1.01 %, 15.73 ± 0.96 %, and 12.86 ± 0.94 % and angle of repose found to be as 23.37 ± 0.03^0, 16.04 ± 0.15^0 and 13.37 ± 0.21^0, respectively for *T. elliptica*, *B. lanzan* and *A. lebbeck* gum.

Table 2: Physicochemical and bulk characterizations of isolated gum powders

Sl. No.	Properties of gums	*T. elliptica* gum	*B. lanzan* gum	*A. lebbeck* gum
1	Ph (1% W/V solution)	4.23 - 5.58	4.20 - 5.05	4.89 - 5.29
2	Swelling index	17.00 ± 1.69	15.42 ± 1.93	22.94 ± 2.02
3	Bulk density (g/cm^3)	0.476 ± 0.02	0.525 ± 0.03	0,501 ± 0.03
4	Tapped density (g/cm^3)	0.588 ± 0.06	0.623 ± 0.02	0.575 ± 0.01
5	Hausner ratio	1.23 ± 0.06	1.18 ± 0.05	1.12 ± 0.03
6	Carr's index (%)	19.04 ± 1.01	15.73 ± 0.96	12.86 ± 0.94
7	Angle of repose (0)	23.37 ± 0.03	16.04 ± 0.15	13.37 ± 0.21

Values given as mean ± Standard Deviation (SD), (Number of observation, n=3).

3.2 Preformulation studies

IH is the BCS I classified drug (Assessment report/EMA/263015/2017) having better aqueous solubility hence suitable for oral administration. The procured drug sample of IH was soluble in water, ethanol (95%), methanol, and chloroform but not soluble in acetone and benzene. The melting point of the drug sample was found to be 192^{0}C, which meets with the melting point of the standard drug mentioned in IP.

3.3 Spectrophotometric analysis of drug

From the results shown in Figure 1 for the UV spectrophotometric study, the lmax of the drug was found to be 285 nm which meets with the official value of the pure drug compound mentioned in IP. The correlation-coefficient value (R^2) of the standard graph of IH in pH 7.4 phosphate buffer (Figure 2) was found to be 0.999 and yields a straight line, which shows that the drug obeys Beer's law in the concentration range of 10-50 mcg/ml using maximum wavelength 285 nm.

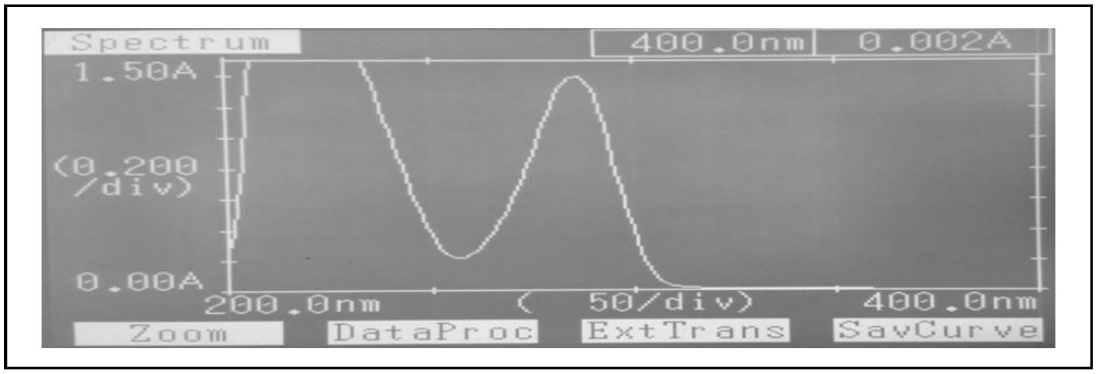

Figure 1: Determination of λ max of IH.

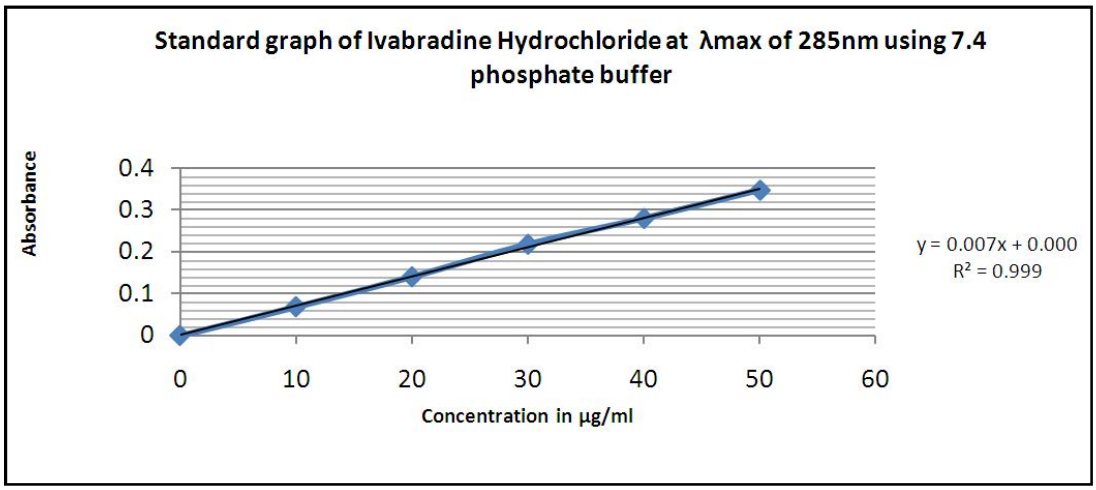

Figure 2: Standard graph of IH using 7.4 phosphate buffers.

3.4 Drug identification and its compatibility with isolated gums by FTIR

The characteristics peaks obtained from the FTIR profile of the drug (Figure 3) obtained its characteristics peak at 3338.2 cm^{-1} (N-H Stretching), 2944.6 cm^{-1} (Symmetric C-H stretching), 1632.8 cm^{-1} (C=O stretching), 1520.8 cm^{-1} (C=C stretching), 1468.6 cm^{-1} (C-C stretching bands), 1248.7 cm^{-1} (O-CH_3 stretching), 1107.0 cm^{-1} (C=C stretching bands), 1058.8 cm^{-1} (O-CH_3 stretching and C-N stretching of tertiary aliphatic amine). The results show that peaks obtained from the FTIR profile of the pure drug were found to be completely matched with the standard spectrum of IH. From Figures 4, 5, 6, it was observed that the peaks of the drug did not shifted or changed when mixed with *T. elliptica*, *B. lanzan* or *A. lebbeck* gum, hence concluded to be no interaction between IH and these gums.

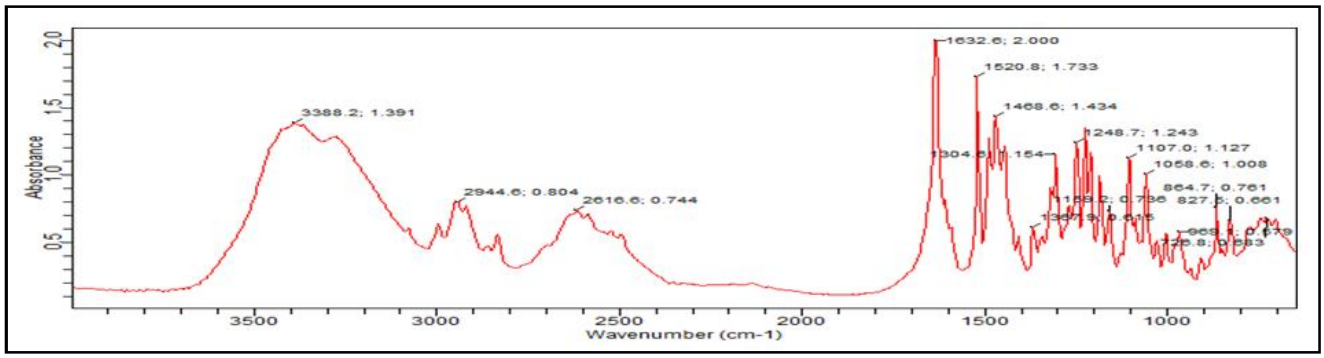

Figure 3: FTIR profile of IH (Drug).

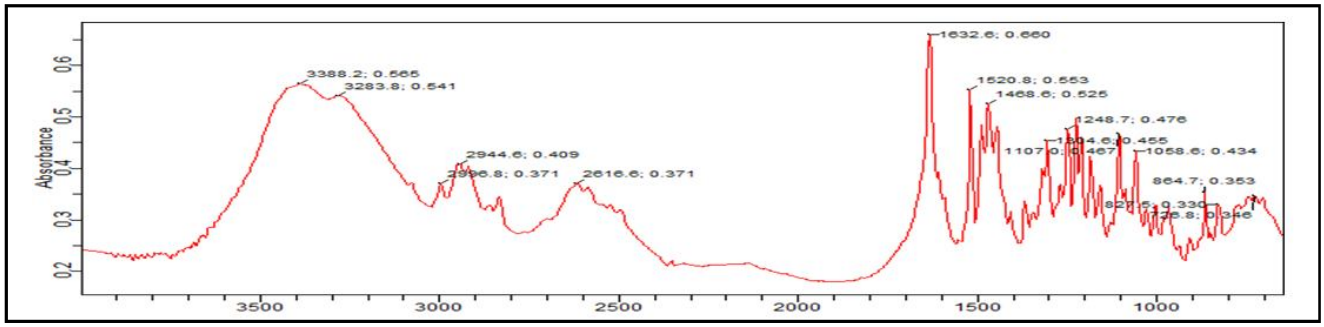

Figure 4: FTIR study of IH and *T. elliptica gum* mixture.

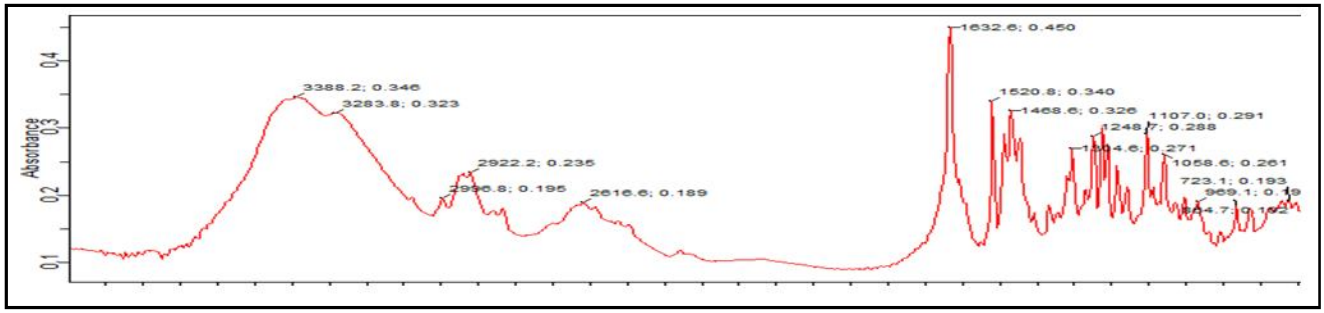

Figure 5: FTIR profile of IH and *B. lanzan* gum mixture.

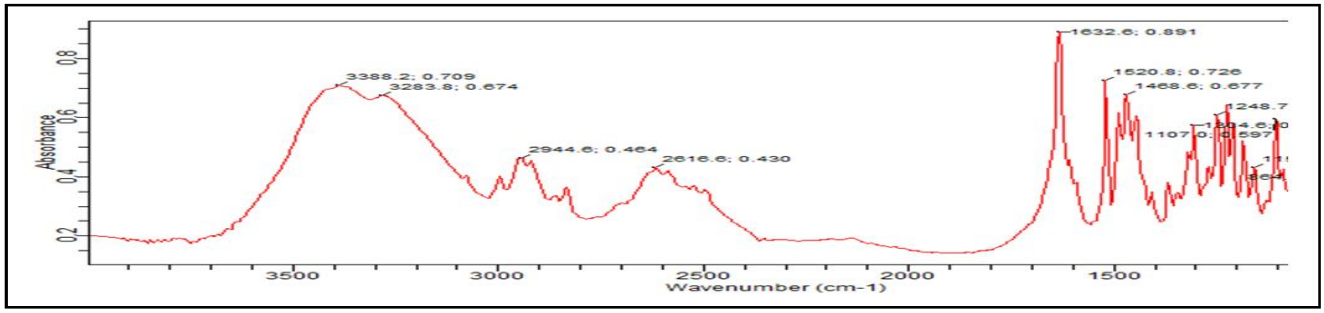

Figure 6: FTIR study of IH with *A. lebbeck* gum mixture.

The results showed that peaks obtained from the FTIR Profile of the pure drug were found to be completely matched with the standard spectrum of IH. Figures 4, 5, 6 show that the peaks of the drug did not shift or change in the presence of *T.elliptica*, *B.lanzan* and *A.lebbeck* gum, hence could be concluded that, there was no interaction between IH and respective gums.

3.5 Analysis of physical parameters of formaldehyde-treated and untreated empty gelatin capsule bodies

Previous literature revealed the 4 h of exposure of an empty capsule body with the formaldehyde vapor as the favorable period of treatment for the development of a cross-linked hard gelatin capsule. Keeping this in view the capsules body was treated with formaldehyde vapor for 4 h. After 4 h of treatment, it was found that the treated capsule bodies did not dissolve or not formed any floppy mass in distilled water for more than 24 h, while all the untreated capsule bodies and caps completely disintegrated or dissolved in the 1st h of the study. It could be due to the reaction of formaldehyde with the gelatin shell to form an irreversible complex which made it hard enough to remain stable in the dissolution fluid. Hence, the 4 h treated capsule bodies were selected for the formulation of the various formulations of pulsincap. The physical parameters of formaldehyde-treated and untreated capsule shells were determined and results are given in Table 3. Before the treatment, the color of the capsule bodies was milky white in appearance. No significant color change was noticed in the capsule body before and after treatment (Table 3). The shape of very few capsule bodies was found to be slightly deformed but usable. None of the bodies were sticky before or after treatment. The average external diameter and length of the capsule body as given in Table 3 was slightly increased after treatment with formaldehyde vapour. This could be due to the chemical reaction between formaldehyde vapour and gelatin shell which leads to a change in the flexibility of the polymeric chain leading to an increase in the average length and diameter of the capsule bodies. Before the treatment the capsule's bodies were odorless. But just after the treatment with formaldehyde it is given a characteristics order which was completely deodorized after air drying for 48 h. The average weight of the empty gelatin capsule bodies was found to be increased after the treatment with formaldehyde vapor.

Table 3: Parameters of empty gelatin capsules with and without treatment

Parameters	Non treated	Treated
Colour	White	White
Average external diameter (mm)	6.8 ± 0.3	7 ± 0.3
Average length	17.6 ± 0.2	18.2 ± 0.3
Thickness	0.1 ± 0.0	0.1 ± 0.0

Values are given in Mean ± SD (n= 3), n= number of observations.

3.6 Qualitative test analysis for free formaldehyde in the treated capsule body

From the qualitative test for free formaldehyde (Khan *et al.*, 2011), it was observed that the intensity of the color produced by the test solution was less than the standard solution which state that the test solution has less than 20 µg/ml of free formaldehyde in 25 numbers of treated capsules body.

3.7 % drug content of formulated pulsincaps

The results obtained from the % drug content of all the formulations were found between in the range of 97.33 % to 101.78 % (Table 4). The values were found to be within the specified pharmacopoeial limit.

Table 4: % Drug content study of F0 to F21

Pulsincap formulation	% Drug content
F0	99.67 ± 1.33
F1	98.81 ± 2.89
F3	100.21 ± 1.32
F4	99.10 ± 3.89
F5	97.33 ± 1.77
F6	101.01 ± 0.89
F7	99.55 ± 3.01
F8	101.78 ± 1.66
F9	98.43 ± 2.41
F10	99.92 ± 2.02
F11	99.22 ± 1.33
F12	97.50 ± 1.09
F13	98.93 ± 1.51
F14	100.82 ± 1.44
F15	97.66 ± 3.56
F16	98.07 ± 2.86
F17	99.64 ± 1.41
F18	101,67 ± 2.67
F19	100.03 ± 3.12
F20	99.30 ± 1.55
F21	98.42 ± 2.19

Values are given in Mean ± SD (n= 3), n= number of observations.

3.8 *In vitro* drug release study of pulsincaps

In vitro dissolution study of the 22 formulations of pulsincap such as F0 to F21 was performed using USP Type I (IP) basket type dissolution apparatus at variable pH medium at 37 ± 2°C and the results were summarized in Table 5 and Figures 7 and 8. The objective was to achieve a lag time of 5 h in drug release, followed by a quick release of the drug. From Figure 7, it could be observed that formulation F0 having no plugging materials of gum released more than 95% of the drug from the capsules within 1st h of the study. As observed in Table 5 formulations F1, F2, and F3 having 20 mg of each gum as the plug, quickly released more than 85% of the drug within 1st h of the study. While the plug concentration of the gums increased from 20 to 30 mg, F4, F5, and F6 released 83.44 %, 89.90 %, and 97.78 % of the drug, respectively, in the 1st h of the study (Table 5), hence could not able to produce the desired lag time. The quick erosion of the plugging layer in these formulations might be due to the lack of concentration of these gums to withstand the

hydrodynamic pressure created by the dissolution medium, hence it became easier for the dissolution fluid to penetrate the plugging membrane and come in contact with the drug and super disintegrates (crospovidone), which leads to bulk erosion and fast release of the drug from the dosage form. It was observed that formulation F7 containing 40 mg of *T. elliptica* as the plugging material (Table 1) produced a lag time of 2 h in drug release, followed by a bulk release of more than 95% of the drug within the next 2 h. In contrast to it, formulations F8 and F9 having the same amount (40 mg) of *B. lanzan* and *A. lebbeck* gum, respectively, did not produce any lag time and released more than 85% of the drug within 1st h of the study. Increasing the concentration of all the gums from 40 to 45 mg (F10, F11, and F12), it was observed that the lag time of the formulation F10 having 45 mg of *T. elliptica* gum as plug increased up to 3 h, followed by a quick release of more than 90% of drug within 1 h after lag time (Table 5). The formulation F11 (45 mg *B. lanazan* gum as plug) and F12 (45 mg *A. lebbeck* gum as the plug) released 67.51% and 98.17% of the drug, respectively, in the 1st h of study without any lag time. Again increasing the concentration of *T. elliptica* gum from 45 to 50 mg (F13), the drug release was prevented for up to 5 h (lag time), followed by a quick release of more than 99% of the drug within the next 2 h (Table 5 and Figure 8), while F14 having 50 mg of the *B. lanzan* gum could produce only 3 h of lag time, followed by 90% of drug released from the dosage form within 2 h (Table 5 and Figure 8). Formulation F16 (50 mg of *A. lebbeck* as plug) did not produce any lag time and released more than 90% of the drug within the 1st h of the study (Table 5 and Figure 8). Formulation F16 (55 mg of *T. elliptica* gum as plug) and F17 (55 mg of *B. lanzan* as a plug) increased the lag time up to 8 h and 6 h, respectively (Table 5), which are more than the desired lag time of 5 h. At the same time formulation F18 (55 mg of *A. lebbeck* gum as plug) not seems to be affected by the increase in the gum concentration and released more than 96% of the drug within 1st h. Increasing the concentration up to 60 mg of all the gums, it was observed that the F19 (60 mg of *T. elliptica* gum as a plug) and F20 (60 mg *B. lanzan* gum as a plug) produced a lag time of more than 8 h and 7 h, respectively, which were far beyond the desired lag time (Table 5). No lag time was observed by F21 having 60 mg of *A. lebbeck* gum as the plug.

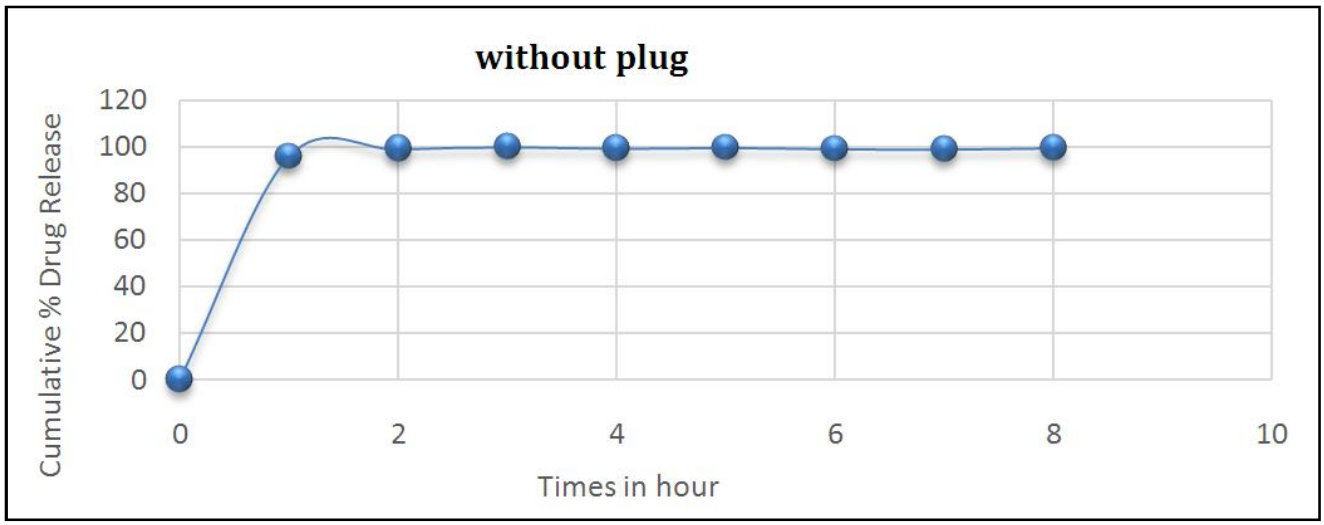

Figure 7: Cumulative % drug release of normal capsule (F0) .

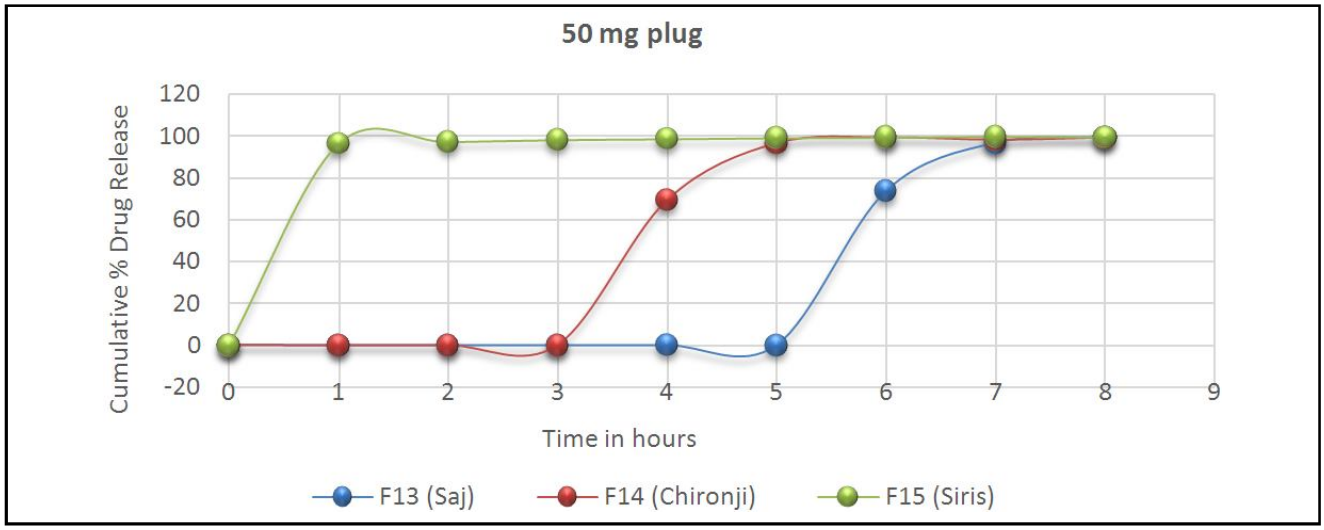

Figure 8: Cumulative % drug release of pulsincap (F13-F15) .

Table 5: ***In vitro*** **drug release study of pulsincap**

FN	Medium	0.1N HCL		pH 7.4 Phosphate buffer			6.8 Phosphate buffer		
	time (h)	1	2	3	4	5	6	7	8
F0		96.0±1.2	98.06 ±1.34	99.95±1.56	99.36 ±0.41	99.72±0.67	99.16±0.9	99.01±1.21	99.55±1.71
F1		85.07±3.21	93.73±2.15	96.18±0.99	97.37±0.61	98.43±1.90	99.32±1.67	99.78±1.75	99.56±1.76
F2		92.12±2.33	96.78±3.12	96.69±1.33	97.61±1.54	99.55±2.56	99.89±1.33	99.01±0.90	99.67±1.32
F3		97.09±1.14	98.01±1.33	98.66±1.32	99.31±2.10	99.47±1.42	99.01±1.34	99.88±1.9	99.31±3.2
F4		83.44±2.11	88.01±1.91	91.78±1.2	93.32±1.9	98.03±1.34	99.89±1.19	99.56±2.7	99.46±1.89
F5		89.90±2.11	92.12±1.34	93.24±3.12	94.08±1.70	99.78±1.77	99.51±1.56	99.90±2.9	99.81±2.33
F6		97.78±2.45	99.90±1.71	99.23±1.56	99.32±0.91	99.67±1.56	99.01±0.51	99.38±3.12	99.62±2.10
F7		0	0	81.77±	90.77±1.34	95.98±1.81	97.67±	99.57±3.12	99.06±1.70
F8		85.55±1.8	91,32±1.56	93.04±3.12	96.67±	97.71±1.66	98.06±1.55	98.40±1.89	99.09±1.78
F9		93.99±1.55	99.84±1.41	97.09±1.70	98.21±1.81	99.32±1.77	99.89±	98.98±1.78	99.10±1.45
F10		0	0	0	91.13±3.12	96. 45±1.97	98.56±1.56	99.60±1.38	99.41±3.10
F11		67.51±2.3	82.13±	94.09±	95.68±1.77	97.47±	99.43±	99.71±3.12	99.55±0.99
F12		92.17±1.77	97.58±2.46	98.41±1.56	99.08±1.45	99.21±1.99	99,09±0.92	99,93±1.51	99,73±0.17
F13		0	0	0	0	0	78.58±0.45	99.33±2.44	99.89±2.1
F14		0	0	0	69.19±1.47	96.39±2.10	99.12±1.81	98±2.12	99.10±2.5
F15		96.22±0.39	97.14±1.81	98.10±1.34	98.49±1.77	99.02±1.34	99. 24±1.77	99.66±3.12	99.36±1.70
F16		0	0	0	0	0	0	0	33.70±0.71
F17		0	0	0	0	0	0	93.14±3.23	98.35±0.82
F18		96.92±1.70	98.07±1.70	98.80±3.14	99.12±2.21	99. 24±2.33	99.55±1.87	99.27±1.78	99.60±2.34
F19		0	0	0	0	0	0	0	0
F20		0	0	0	0	0	0	0	71.05±3.1
F21		98.62±1.33	98.75±1.45	98.53±1.31	99.78±1.09	99.43±2.4	99.89±0.97	99.01±0.88	99.59±2.1

Values are given in Mean ± SD (n= 3), n= number of observations.

3.9 Kinetic profile of optimize formulation (F13)

As per the result, the coefficient correlation (R^2) values of the zero-order model, 1st order, Higuchi model Korsmeyer Peppas model and Hixson Crowell model were found to be 0.698, 0.634, 0.482, 5.621and 0.687, respectively (Table 6). The data of the Higuchi plot (R^2 value 4.482) indicates that the drug release pattern does not obey Fick's law of diffusion and follows the non-fickian mechanism of drug release kinetics. Here the exponent "n" value of the Korsmeyer Peppas model was found to be 2.060 which is >1, hence it indicates the non-fickian super case II transport mechanism of drug release by the dosage form. As the release start after a specified lag time, no kinetics model is strongly fitted for this release pattern and none of the values goes near to one, which indicates the mixed order release kinetics of drug release from this dosage form.

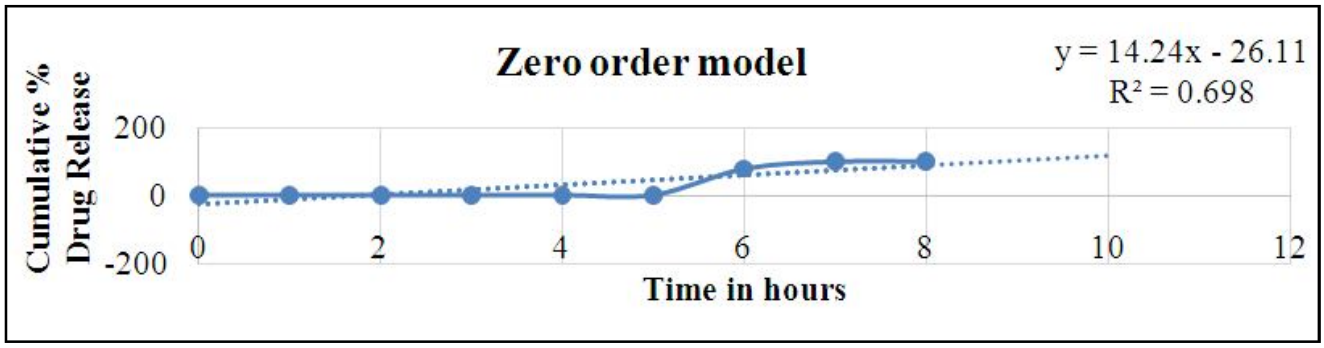

Figure 9: Zero order release kinetics of optimized formulation (F13).

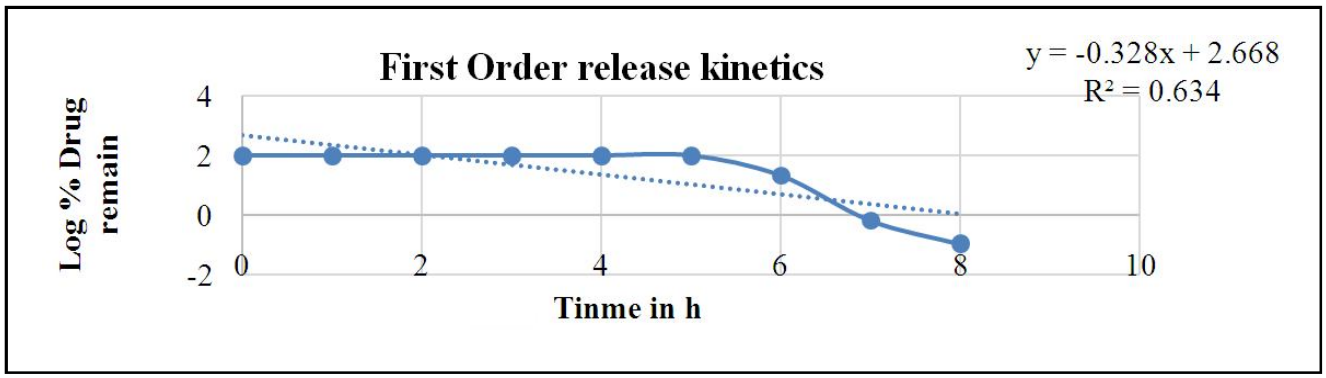

Figure 10: 1st order release kinetics of optimized formulation (F13).

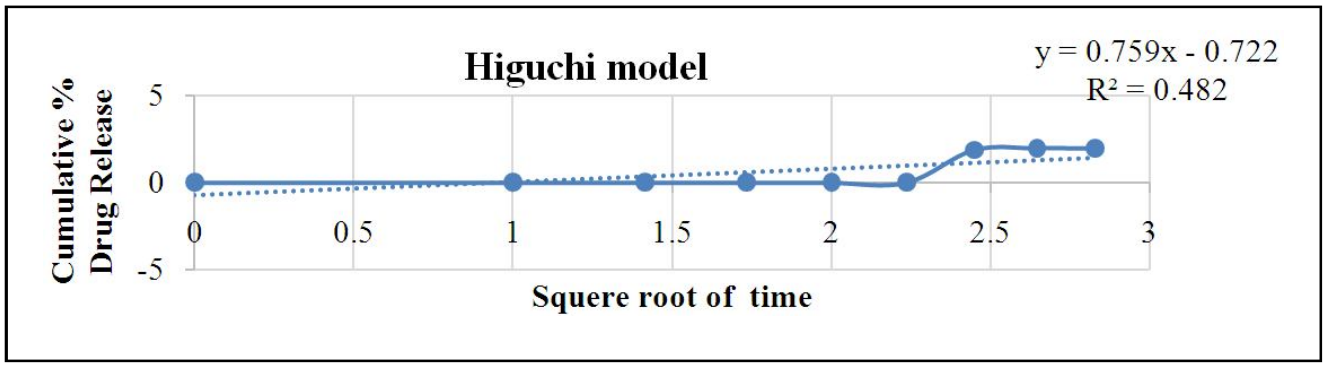

Figure 11: Higuchi release kinetics of optimized formulation (F13).

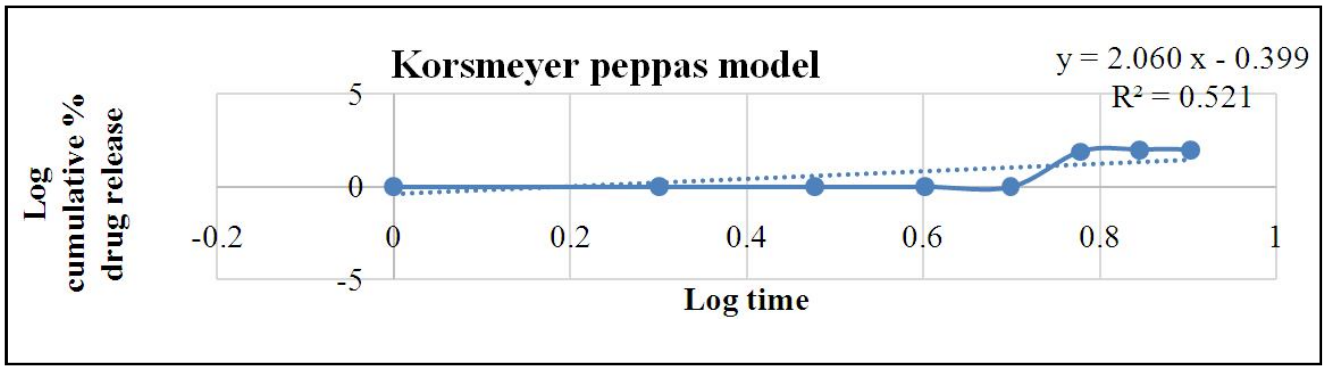

Figure 12: Korsemayer pappas model of optimized formulation (F13).

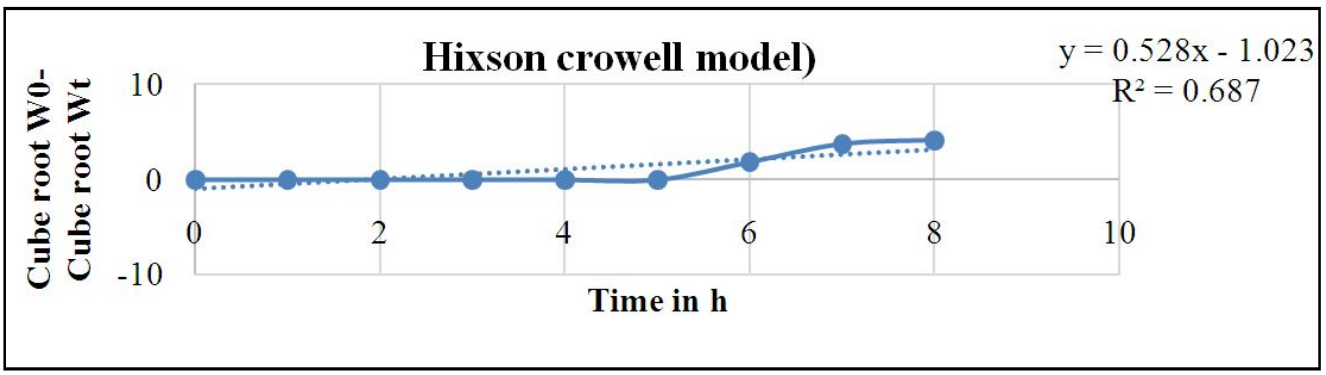

Figure 13: Hixson crowell model of optimized formulation (F13).

Table 6: Comparison of coefficient correlation (R^2) values

Various release kinetic model of drug	Coefficient correlation (R^2) value
Zero order kinetics	0.698
1st order kinetics	0.634
Higuchi model	0.482
Korsmeyer Peppas model	0.521
Hixson Crowell model	0.687

3.10 Stability study of optimized formulation as per ICH guidelines

Stability study was performed by storing samples of optimized formulations of F13 at 40°C and 75 % RH for three months and stability parameters like change in shape, color, drug content, and lag time in drug release were thoroughly observed. The sample was analyzed initially and followed by 1st, 2nd and 3rd month. The results of the stability test given in the Table 7 showed no significant change in the stability parameters of the optimized formulation after 3 month.

Table 7: Stability study of the optimized formulation (F14) by storage at 40^0 C/75 RH

Parameters observed	Initial	After one month	After two month	After three month
Physical change in shape	No change	No change	No chance	No change
Colour	White	White	White	White
Drug content (%)	99.56 ± 1.35	99.21 ± 2.81	98.68 ± 1.05	97.16 ± 1.05
Lag time of drug release	5 h	5 h	5 h	5 h

4. Discussion

The pH of the 1% (W/V) solution of *T. elliptica*, *B. lanzan* and *A. lebbeck* gums indicates the slightly acidic nature. Hence, the pH may need to be adjusted while preparing these gums for oral or buccal drug delivery system. The swelling index states that all the gums had excellent swelling properties, and hence could be used as a drug release modifier in pharmaceutical dosage form designing. The swelling index of *A. lebbeck* gum was found to be the highest among the three. Though, it had a very good swelling index, the gel strength of the same was not up to the mark as the other two gums such as *T.elliptica* and *B. lanzan* .

The bulk density, tapped density, Hausner ratio, and Carr's index state that the *T. elliptica* gums were more compressible than the other two gums but the compressibility properties of *A. lebbeck* gum were less than the other two gums. The angle of repose results indicates the good to excellent flow properties of these isolated gum powders. The FTIR study showed no interaction between IH and respective gums.

Dissolution data indicates the increase in the concentration of *T. elliptica* and *B.lanzan* gum as the plug leads to the increase in lag time. It could be due to the increase in thickness and gel strength of the plugging membrane which creates more time for the surrounding dissolution medium to penetrate the drug compartment of the pulsincap. On the other hand, increasing the concentration of *A. lebbeck* gum could not produce any lag time and released most of its drug within 1st h of the study which may be due to the quick swelling and erosion, low gel strength, and low compressibility nature of this gum which leads to bulk erosion. The change in pH of the medium did not seem to produce any effect on the drug release from the dosage form, which indicates the pH-independent nature of all these gums. While comparing, *T. elliptica* and *B. lanzan* gum, both found to have a good effect on producing the lag time but *T. elliptica* gum had a slight advantage over *B. lanzan* gum to produce it at very less concentration. On the other hand, all the formulations of *A. lebbeck* gum irrespective of its concentration released more than 95% drug in the 1st h without having any lag time, hence not found to be a suitable candidate for plugging agent in the formulation of pulsincap, especially at the directly compressible form. From the overall study, the formulation F13 having 50 mg of *T. elliptica* gum as the plug was found to be suitably matched with the desired lag time of 5 h, followed by a quick release of more than 99 % of the drug within a short period, which could be considered as the optimized formulation of pulsincap for further study. The kinetic study of optimized formulations F13 shows non-fickian super case II mechanism, *i,e.,* erosion mechanism of drug release. Stability analysis shows that the color of the optimized formulation of the pulsincap remains intact and the % drug content was under the specified limit of IP, BP, or USP. The lag time of the pulsincap under storage was able to maintain its 5 h of lag time in drug release within 3 months. The above finding indicated good stability of the optimized pulsincap.

5. Conclusion

Gums were successfully isolated from their crude source and met their physicochemical specifications. The preformulation studies by FTIR confirmed no interaction between the drug and isolated gums. 21 formulations (F1-F21) having 20 mg, 30 mg, 40 mg, 45 mg, 50 mg, 55 mg, and 60 mg of each gum as plug and one formulation F0 (without plug) were successfully formulated using formalin treated (4 h) capsules body. The % drug content of all the formulations was under the specified limit. Among all the formulations of pulsincap, F13 having 50 mg of *T. elliptica* gum as the plug was able to match with the predetermined lag time of 5 h showed a non-fickain erosion mechanism of drug release kinetics and also passed the stability test by retaining all its important characteristics while kept under 40°C and 75% RH for 3 months. The results concluded the potential chronopharmaceutical applications of a natural polysaccharide such as Saj (*T. elliptica*) gum as a novel excipient in the development of novel drug delivery system in the future.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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