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Original Article

The Development, Formulation, and Assessment of Polyelectrolytic Complexes of an Anticancer Compound (Vinorelbine Tartarate)

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ABSTRACT

Introduction: Vinorelbine tartrate is used as a first-line treatment in conjunction with conventional treatments, especially advanced disease including cancer patients. **Objectives:** The objective of the study was to develop a polyelectrolyte complex carrier system for Vinorelbine tartarate used for the treatment of Cancer. **Materials and Methods:** Polyelectrolyte Complex (PEC) was prepared using entrapment method using gum Kondagogu and chitosan as polymers. Materials and Methods: Vinorelbine tartarate was best complexed with gum Kondagogu and chitosan. Various formulations were developed by changing the gum Kondagogu and chitosan ratios and optimized. The optimized formulations were further characterized for their complex formation, loading efficiency, entrapment efficiency, particle size, FTIR studies, *in vitro* release, swelling studies. **Results:** At Gumkondagogu concentrations exceeding 80%, the highest output of PEC was noted. In comparison to phosphate buffer (pH 6.8), the PEC revealed a reduction in the discharge of vinorelbine tartarate in 0.1 N HCl. Increased medication release and swelling were caused by increasing the Kondagogu gum concentration in PEC. Due to chitosan's greater degree of swelling in an acidic medium, PEC 1:3 ("Gumkondagogu: chitosan") having a greater amount of chitosan demonstrated 98% release in just 4.5 hr. **Conclusion:** The observation made in the present investigation conclusively proves that the novel hydrogels prepared from gum Kondagogu/chitosan holds a great potential as a natural polymer based delivery device for controlled delivery of drug like Vinorelbine tartarate for the reason to reduce dosing frequency.

Keywords: Anticancer agent, Polyelectrolyte complex, Vinorelbine tartarate, Gum Kondagogu and Chitosan.

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INTRODUCTION

The fact that the fight against cancer is in its fourth decade, researchers are still looking for better targeted treatments that can eliminate tumour cells while sparing healthy organs. Each year, more than ten million people get a cancer diagnosis, and it is predicted that by 2020, there will be approximately 15 million cases reported every year. Cancer is a primary cause of death.[1] The majority of today's anticancer medications do not distinguish between diseased and healthy cells, despite the fact that chemotherapy is somewhat effective. Chemotherapeutic drugs thus cause systemic toxicity and undesirable side effects by damaging healthy tissues while killing cancer cells. Furthermore, due to quick clearance and extensive distribution into the specified organs and tissues, substantial doses of the drug must be delivered, which is costly and frequently leads to unfavorable toxicity.[2] Using therapeutic chemicals more efficiently by better directing them to tumour tissues is the first crucial step in enhancing treatment regimens. If high quantities of anticancer medications could be specifically delivered to malignant tissues only, their therapeutic efficacy and toxicity would be considerably increased. The aforementioned fact justifies the necessity for the development of innovative therapies for cancer and drug delivery systems that allow precise targeting of tumour cells.

Drug Profile

The Vinca alkaloid vinorelbine, which is obtained from the *Vinca rosea* leaves are used to treat a various cancers, like Lung, breast, ovarian, and bladder cancers. It is also used to treat Hodgkin's disease, lymphomas, and acute leukemia. Vinorelbine binds to tubulin and prevents it from polymerizing into microtubules and spindles, which causes cancer cells that are susceptible to it to undergo apoptosis. Vinorelbine prevents the cell from dividing normally. The growth and metastasis of cancer cells throughout the body are slowed or stopped by vinorelbine. Alkaloids from

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plants and other naturally occurring substances are frequently used as mitotic inhibitors. They can stop cell division-related processes like mitosis or stop enzymes from making vital proteins. These functions occur within the M phase of the cell cycle, but they can harm cells at any stage. While suppression of axonal microtubules appears to be correlated with vinorelbine's neurotoxicity, suppression of mitotic microtubules coincides with anticancer activity. Vinorelbine is superior on mitotic than axonal microtubules *in vitro* compared to comparable vinca alkaloids, which would explain why it has less neurotoxicity. This substance also increases radiation sensitivity. Peripheral nerve injury is a side effect of these medications that is well-known to have a dose-limiting effect.[3]

The term "hydrogel" describes three-dimensional network structures built of a collection of synthetic and/or natural polymers that possess a high capacity for absorbing and holding onto water.[1] The hydrogel structure is created when hydrophilic groups or domains within a polymeric network are hydrated in an aqueous environment. A capacity for water absorption, the propensity to swell, and the immobilization of proteins, peptides, and other biological components are all characteristics of hydrogels. These gels can resemble biological tissue due to the amount of water they contain. Many types of Hydrogels were reported like; Temperature-sensitive hydrogels: These hydrogels swell and de-swell when the temperature of the surrounding fluid changes. Light-sensitive hydrogels: These gels undergo transdermal photo-polymerization after subcutaneous injection and used as drug release devices. Glucose-sensitive hydrogels: The responses of these hydrogels to the presence of the glucose around the surrounding fluid.[4] These gel-like substances used to target certain cells because they allow the medication that is held inside by swelling brought on by changes in the pH of the environment around them. They are nano-scale, typically between 20 and 30 nm. Hydrogels those are pH-sensitive. The pH-trigger method of regulated release is the most appealing. The GI-tract of human has a pH gradient that spans from 1-7.5 (saliva pH is 5.6-5.6, stomach pH is 1-3, small intestine pH is 6.6-7.5, and colon pH is 6.4-7.0). The polymers which are pH-sensitive have acidic or basic groups that receive and release protons when exposed to changes in the pH of the surrounding environment.

Methods of Hydrogels Preparation

Polymerization with cross-linking agents present and covalent cross-linking of water-soluble polymers are two examples of chemical cross-linking methods. Permanent or chemical hydrogels result from this process.[2,5,6] The solid-state radiation technique and grafting are included. In grafting, a monomer is polymerized onto the skeleton of a premade polymer. High energy radiation therapy or the chemical reagents both work to activate the polymer chains. Radical production in molecular chains is induced by solid-state radiation when hydrocolloids are exposed to it, thanks to the radiation's direct impact. The two main activities that take place here are the formation of fundamental radicals as an outcome of the existence of water and direct energy transport to the macromolecule to produce macro radicals. Due to the relative simplicity of manufacture and the benefit of not utilizing cross-linking chemicals, physical or reversible gels have seen an increase in interest in physical cross-linking methods. These chemicals have an effect on the integrity of the components to be captured (e.g. cells, proteins, etc.,) and require their removal before application. The following are the numerous techniques reported for making physically cross-linked hydrogels: To warm or chill a polymer solution: When heated solutions of gelatin or carrageenan being cooled, physically cross-linked gels are created. The creation of connection zones, helix association, and helix association all contribute to the gel's formation.[7] Method for Complex Co-Acervation: Combining a poly-anion and a poly-cation can result in the formation of complex co-acervate gels. The basic idea behind this process uses polymers with opposing charges attract one another and depending on the concentration and pH of the relevant solutions, they interact to create soluble or insoluble complexes. Positively charged proteins are more likely to combine with anionic hydrocolloids to form poly-ion complex hydrogels when their isoelectric point is lower.[8] Using freeze-thaw cycles, a polymer can also be physically cross-linked to create its hydrogel. The mechanism entails the structure forming microcrystals as a result of freezing and thawing. Polyvinyl alcohol and xanthan freeze-thawed gels are examples of this sort of gelation.[9,10] The high level of water content and resulting biocompatibility, hydrogels have found success in the biomedical field.

Polyelectrolyte Complexes

PEs has a propensity to develop PECs when they combine with one or more ions that have opposite charges. These are made when poly-ions with opposite charges contact electrostatically. Aqueous PE solutions with opposing charges are combined, cooperative electrostatic interactions between poly-cations and poly-anions, which are pre-dominative, form a PEC, which leads to the development of a separate state from the solvent-dense phase.[11] PE complexation primarily happens within substances that have opposite charges, such as PE-PE, drugs, nucleic acids, and surfactants. PECs provide significant benefits as pharmaceutical excipients since they are generally biocompatible, responsive to changes in environmental conditions and well-tolerated, such as regulating drug release. The formation and stability of PECs have been known to be influenced by a number of factors, including the degree of ionization of each of the oppositely charged PEs, the charge distribution over the polymeric chains, concentration, ratio, type and location of the ionic groups, polymer flexibility, m.w. temperature, the ionic strength, and the pH of medium.[12-14]

One opposite-charged PE solution gets added to a different PE solution as a titrant while being stirred.[15] During this, the titrant initially dilutes the opponent solution, and continued

titration results in the formation of complexes. The size of the complex is influenced by the concentration of PEs and the pace at which titrant is added.[16] Koetz and Kosmella provided a useful method of complicated synthesis[17] based on the amount of titrant consumed. At low titrant intake, small aggregates or particles of complex formation formed, whereas at high titrant consumption, larger aggregates or particles that possess a tendency to flocculate formed. There has recently been a lot of attention paid to PECs because of all the beneficial applications that they have. Charged particles also serve as medication delivery systems, enzymes, or DNA since they can be easily incorporated into the complex particles. Dialysis membranes, film coatings, membranes, protein isolation and fractionation, pharmaceutical product binding, targeted nucleic acid delivery, microcapsule preparation for drug delivery, enzyme imitators, contact lenses, medical applications, are some of their possible uses.

Gum Kondagogu (GKG)

Gum Kondagogu serves as a dried gum exudate made from *Cochlospermum gossypium* trees and other *Cochlospermum* species that belong to the plant Bixaceae family. It is a novel natural anionic biopolymer having good emulsifying properties and used as non-toxic polysaccharides. KG is a complex acetylated polysaccharide with a high m.w. that mostly comprised in D-galactose, D-galacturonic acid, and L-rhamnose.[18] It absorbs water instead of dissolving it like other water-soluble gums to create a thick colloidal solution.[19] Cold water causes powdered KG to swell to the point where a 3-4% solution will result in a gel with a consistent smoothness and texture. Additionally, Kondagogu gum has been successful in biosorbing nickel and total chromium from water-based solutions.[20] In the making of floating delivery of drugs devices, it was also employed as a carrier.[21] Furthermore, it can be combined with chitosan to form polyelectrolyte complex.[22] Although Kondagogu gum is a major forest product, its economic application has been restricted by the absence of scientific evidence, particularly with regard to its use in pharmaceutical preparations.

Chitosan

There is a lot of chitosan, a naturally occurring polymer, in nature. A linear co-polymer polysaccharide is chitosan. Chitosan is employed in a wide range of sectors, including those involved in biochemical engineering, biomedical engineering, water treatment, metal extraction and recovery, food, chemicals, cosmetics, and medicine, because of its advantageous physicochemical properties and distinctive biological properties. However, one significant drawback that prevents chitosan from being widely used in biological systems is poorly soluble in aqueous solutions.[23] Chitosan does, however, possess several functional groups that permit graft modification, which gives the changed chitosan unique features. Chemically altering chitosan in this way can increase its solubility and broaden the applications for it.

The study involves the formulation of drug loaded hydrogels for treatment of various types of cancer. The hydrogels were made by using chitosan and gum Kondagogu in different ratios. The hydrogels were evaluated for complex forming efficacy between gum Kondagogu and chitosan. Following that, hydrogels containing vinorelbine tartarate were made and tested for a number of factors, including particle size, drug content, zeta potential, entrapment effectiveness, and dissolution.

The Research hypothesis was, vinorelbine is a lipophilic member of the vinca alkaloids, class of remedies have higher cytotoxicity and therapeutic effectiveness due to prolonged exposure. We are attempting to establish a link between vinorelbine tartrate formulation and efficacy.

MATERIALS AND METHODS

Materials

All Pharmaceutical-grade chemicals and reagents were employed in the experiment. Gum kondagogu (Grade-I) procured from A.P. Girijan Cooperative Corporation, Hyderabad, Vinorelbine Tartartate from Dr. Reddy's labs, Hyderabad, Chitosan from Bright labs, Kothapet, Hyderabad, and Acetic acid from SD fine chemicals, Mumbai, India

Methods

Development of UV spectroscopic method

Procedure

Stock solution is made by dissolving 10 mg of pure drugs in a volumetric flask filled with distilled water and then adding water to fill the remaining 100 mL. The stock solution was appropriately diluted to create a 10 g/mL solution for the working standard Vinorelbine tartarate solution. Pipette 5 mL of this stock solution, and then use a double-beam UV-VIS spectrophotometer to subject the sample to UV scanning in the 200-400 nm range.

Calibration Curve

For the concentration range of 1 to 9 g/mL, an absorption maximum standard curve was produced. Various portions of standard stock solutions containing 1 to 9 mg of medication per mL had been placed to 10 mL volumetric flasks, and the flasks were then filled with distilled water. At 267 nm, the absorbance was calculated in comparison to the matching reagent blank. By using a UV spectrophotometer at 267 nm, the concentrations of vinorelbine tartarate were calculated.

Preparation of Polymer Solutions

To get a fine and consistent sample, Gumkondagogu was ground in a high-speed mechanical blender and then sieved through a

bin (mesh size: 250 lm). 0.25% w/v powder of Gumkondagogu was precisely weighed and added to deionized water in a beaker. The entire solution of gum was left at room temperature and slowly stirred overnight using a magnetic stirrer. The remaining undissolved material was subsequently separated by allowing the gum solution to stand at 25°C for 12 hr. The solution of gum was passed via filter paper, and the resulting clear solution was applied to further applications.

Analyzing the Development of Polyelectrolyte Complexes between Gumkondagogu and Chitosan

Kondagogu as well as Chitosan A mechanical stirrer (REMI, India) was used to mix the appropriate quantities of 0.02 to 0.18% (w/v) Gumkondagogu solutions in the flask. Then, 50 mL of the prescribed Gumkondagogu/chitosan weight ratio (% w/w) and 0.18 to 0.02% w/v chitosan in a 1% (v/v) solution of acetic acid were added. Each flask contained a precipitate that appeared to be gel-like. Centrifugation of the flask's contents was place for 15 min at 5000 rpm. The precipitate was supposed to be dried at 45°C, and its yield (percentage) was calculated[24] The zeta potential[25,26] and viscosity[27-29] of the resultant supernatant obtained after centrifuging PEC were measured in order to assess the effectiveness of polyelectrolyte complex formation.

$$Yield\ (\%\, w/w) = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

Developing a Drug-Loaded Polyelectrolyte Complex with Chitosan and Gumkondagogu

0.2% (w/v) of Vinorelbine tartarate was gradually added to a 0.25% (w/v) solution of Gumkondagogu in deionized H_2O. Following complete drug dissolution, several weight ratios (%w/w) of chitosan 0.25% (w/v) in acetic acid 1% (v/v) were added to the combination of Gumkondagogu and Vinorelbine tartarate solution to produce PECs of 5:1, 3:1, 1:1, and 1:3. Finally, deionized H_2O was added to each formulation to bring the amount up to 100 mL. The mixes were then agitated for a further 15 min using a mechanical stirrer before being set aside for 30 min. Centrifugation at 5000 rpm was used to separate the product which got the precipitated from the solution. After that, it was rinsed with ds.H_2O, dried at 40°C for 12 hr, pulverized in a mortar, and put through sieves #40 and #85. For subsequent research, those particles that made it past filter #40 but remained on sieve #85 were utilized.

Evaluation of PEC

Drug entrapment efficiency

Accurately weighed 10 mg in drug loaded PEC with various polymer ratios was dissolved in 10 mL of 1 N NaOH for 24 hr. The liquid was sonicated for three min with a probe sonicator after being diluted to 30 mL at ambient temperature with 0.1 M PBS, pH 6.8. The solution's pH was raised to 6.8 using 0.1 N HCl, yielding a final volume of 50 mL. The resulting solution was filtered using a syringe filter, and the UV technique was used to calculate the drug concentrations. The % of drug released from each formulation was calculated using the amount of drug entrapped in the PEC as measured by this approach.

$$\%EE = \frac{\text{Total amount of drug} - \text{Free drug in the supernant}}{\text{Total amount of drug Loaded}} \times 100$$

Swelling Studies

The equilibrium weight approach was used to accomplish the water uptake into PECs. Briefly, a hydraulic press was used to form pellets out of dried PECs with various gum Kondagogu/chitosan ratios. These pellets were put in the dissolution equipment's baskets. Both 0.1 N HCl, pH 1.2 and a 0.1 M PBS, pH 6.8 were applied to these baskets. At regular intervals, baskets were taken out of the swelling media, blotted with blotting paper, and then immediately weighed.

$$Water\ uptake\ (\%) = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In vitro Drug Release Studies

A measured quantity 20 mg of PEC that had been loaded with vinorelbine tartarate was put in a cellulose bag and submerged in a beaker containing 200 mL of 0.1 N HCl buffer, pH 1.2 before being incubated for 2 hr at 37°C and 100 rpm.[30] A 0.1 M PBS, pH 6.8 was placed to the acidic solution after 2 hr. Amounts of 2 mL were withheld every 30 min until 100% of the medication was released. To keep the dissolving fluid volume constant, an equivalent volume of buffer solution was added. The samples' drug content was assessed using the UV technique.

Particle Size Analysis

Particle size analysis was performed with a Nikon microscope at a 100x magnification in order to determine the size of the particles.

FTIR Studies

FTIR spectra obtained on Bruker FTIR were used to determine the compatibility between pure drugs and polymers. The KBr press was used to make the pellets of potassium bromide. The solid powder sample was combined with 100 times the amount of KBr in a mortar to make the pellets, and the finely ground powder was added to a stainless-steel die. In the die, polished steel and powder were sandwiched.

Effect of pH and Ionic Strength on Complex Formation between Gumkondagogu and Chitosan

By comparing the ideal GKG and CS ratio for efficient complex formation, the effect of pH was ascertained. A breaker was filled with the necessary amount of GKG and CS solution made from 0.25% (w/v) stock. By applying diluted HCl or NaOH, the pH of the aforementioned solution was changed to range from 2 to 10. The appropriate amount of 0.25% (w/v) CS in 1% (w/v) of

acetic acid was then added, giving 50 mL of a total volume, and carefully mixed to achieve the desired GKG/CS ratio of 80/20 (%w/w). After 15 min of stirring, this mixture was centrifuged for 10 min at 5000 rpm. The resulting precipitate was separated, and then dried at 40ºC. Based on the weight of hydrogel, percentage yield was calculated. The effect of ion strength was determined by taking different concentrations of (0-100 mM) of NaCl were added to gum solution at pH 5, and the remaining procedure was repeated as specified above.[31]

Statistical Analysis

The data were evaluated using One-way ANOVA, followed by Excel and Graph Prism 5.0.

RESULTS AND DISCUSSION

The data were displayed in Table 1 along with the absorption maxima, which were obtained at 267 nm with a distinctive peak (Figure 1). The calibration curve of Vinorelbine tartarate was performed and R^2 was found to be 0.999 (Figure 2). The GKG/CS hydrogels are loaded with vinorelbine tartarate using the entrapment method. Beginning with 0.1, 0.2, 0.3%, and 0.4% w/v of drug concentration with constant CKG/GS ratios (80/20% w/w), the maximum quantity of vinorelbine tartarate that could be loaded into the hydrogels was optimised. It was discovered that vinorelbine tartarate at concentrations of 0.1 to 0.4% w/v had different entrapment efficiencies. As a result, we chose 0.2% w/v as the optimal medication concentration for further research. With 0.2% w/v of vinorelbine tartarate, hydrogels with various CKG/CS ratios were made. Measurements of particle size, entrapment efficiency, and flow characteristics were made in response to the decline in gum Kondagogu concentration and the results are reported in Table 2. Following swelling in an acidic solution, vinorelbine tartarate-loaded hydrogels with varying GKS/CS ratios (% w/w) were transferred into a 0.1 PBS, pH 6.8. According to Table 3, the amount of water uptake by these hydrogels has been plotted versus time. When compared to pH 1.2 buffers, it was found that water intake was at its highest at pH 6.8, 0.1 PBS. The change in the ionization and solubility of the polymers at different pHs can be used to explain the variation in hydrogel swelling between pH 1.2 and 6.8. It turned out that, PEC 5:1 and PEC 1:3 shown less swelling at pH 1.2 buffers. This is because the -COO group of GKG undergoes protonation from -COOH in HCl environment, which reduces the polymer's solubility. PEC 5:1 and PEC 3:1 showed low swelling in HCl conditions due to decreased GKG solubility, whereas PEC 1:3 showed considerable swelling in acidic conditions due to higher chitosan solubility at this pH. As seen in PEC 5:1 and PEC 3:1, this hydrogen bonding could additionally tighten the PEC network, reducing its capacity to swell. 5:1 PEC and 3:1 PEC had the most swelling at pH 6.8 buffer as the -COOH group of GKG becomes ionized to -COO, increasing the solubility of the polymer. As a result, PEC 5:1 and 3:1 hydrogels absorb more water, increasing their swelling properties at pH 6.8. However, because PEC 3:1 contains a high fraction of CS and is unionized at this pH, there is no swelling in this hydrogel. Table 4 and Figure 3 display the vinorelbine tartarate release profile from hydrogels with various GKG/CS (%w/w) ratios. Vinorelbine tartarate's realization profile has a sigmoidal shape, and the particles provide an effective mechanism for regulating the release of donepezil HCl. Regression equations were used to compute the concentration of vinorelbine tartarate using the standard graph of vinorelbine tartarate in 0.1N HCl, 1.2, and 0.1 M, pH 6.8 PBS (Table 5). It came to light that the cumulative release of vinorelbine tartarate in acidic pH was minimal due to (i) the drug's limited solubility in HCl solution and (ii) the fact that GKG and chitosan are both significantly

Table 1: Standard Curve of Vinorelbine Tartarate in Purified Water.

Parameters (Units)	Values
	Vinorelbine tartarate
λ_{max}/nm	267 nm
Linearity Range (µg/mL)	1-25
Molar Absorptivity(1/mol/cm)	0.21 x10^5
Correlation coefficient (r2)	0.999
Regression equation (y)	0.031x+0.014
Intercept, c	0.014
Slope, b	0.031
LOD (µg/mL)	0.61
LOQ (µg/mL)	0.185
Sandell's sensitivity (ng cm^{-2})	1.95×10-2
Relative standard deviation	0.189

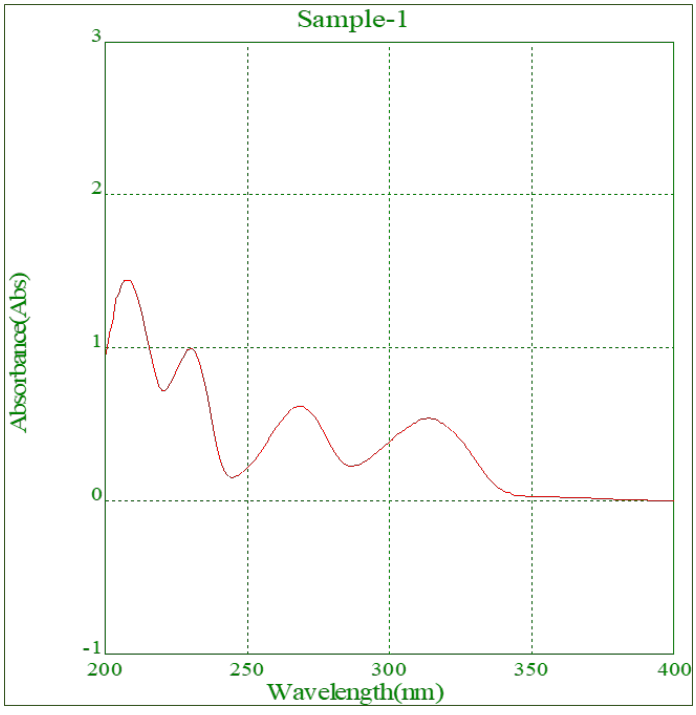

Figure 1: Max peak of Vinorelbine tartarate. The absorption maxima were obtained at 267 nm.

Table 2: Showing the % Yield, Angle of Repose, Entrapment Efficiency of PEC's.

Sl. No.	Formulations GKG: CS	Yield (%)	Angle of repose	Entrapment Efficiency (%)
1	5: 1	94.9	24.5	97.9
2	3: 1	90.27	30.2	96.2
3	1: 1	64.1	39.5	94.4
4	1: 3	55.03	43.2	94.1

Maximum yield of PEC (polyelectrolyte complex) was observed at gum Kondagogu concentrations above 80%.

Table 3: Showing the % of Water Uptake of PEC's.

Time in (hr)	Formulations (GKG:CS)			
	5: 1	3: 1	1: 1	1: 3
1	1.2	1.5	1.5	1.7
2	1.4	1.7	2.8	3.8
3	2.1	2.3	3.6	4.1
4	2.7	3.4	3.7	4.4
5	3.9	4.4	4.2	4.7
6	4.6	5.8	4.6	4.9
7	5.2	5.9	5	5.3
8	5.6	6.5	5.4	5.7

The PEC showed lower release of Vinorelbine tartarate in 0.1 N HCl as compared to phosphate buffer (pH 6.8). Increasing the concentration of gum kondagogu in PEC led to an increase in drug release and swelling.

Table 4: Showing *in vitro* Drug Release of Drug Loaded PEC's.

Time in (hr)	Formulations (GKG:CS) PEC's % Cumulative drug Release			
	5: 1	3: 1	1: 1	1: 3
1	0	0	1	0
2	1	1	3	2
3	17	18	20	39
4	38	35	43	62
5	56	64	59	83
6	74	78	63	90
7	89	90	92	95
8	90	94	96	99

PEC 1:3 (gum kondagogu: chitosan) with higher concentration of chitosan showed 98% release within 4.5 hr, owing to the fact that chitosan has a higher degree of swelling in acidic medium.

ionized, which tightens the network in the PEC. Less edema as a result of this impact delays the release of the medication. PEC-3:1 hydrogel particles released 100% of the drug during the first 4 hr at pH 6.8, whereas PEC- 5:1 and PEC- 3:1 hydrogel particles didn't release 100% of the drug until 8 hr had passed. As CS has a pKa of 5.3-6 and vinorelbine tartarate has a pKa of 4, the rise in the concentration of vinorelbine tartarate reduced the ionization of CS.[2,25,32] The burst release of Vinorelbine tartarate for PEC 1:3 Polyelectrolytic complexes are due to less-than-ideal NH_3-COO ionic interaction, larger percentage (w/w) of CS results in increased degree of swelling in acidic conditions. With increase in GKG (5 w/w) concentration in the Polyelectrolytic complexes, GKG is a hydrophilic polymer and can facilitate the entry of solution into the particles, generating maximum swelling, vinorelbine tartarate was found to be enhanced. Additionally, the carboxylate ions of vinorelbine tartarate and GKG were found to repel one another. This entire process significantly improves the drug's solubility and hastens its dissolution. Hence, Vinorelbine tartarate burst release for PEC 1:3 Polyelectrolytic complexes are caused by an increased percentage (w/w) of CS, which increases

Table 5: Mathematical Equations for the Models Used to Describe Release Characteristics of Vinorelbine Tartarate PEC's.

Mathematical equations for the models used to describe release characteristics of Vinorelbine tartarate using CS and GKG	
Zero order	$Q_t=Q_0+K_0 t$
First order	Log C=Log C0- $k_1 t/2.303$
Higuchi	$Q_t=Q_0+K_H t^{1/2}$
Korsemeyer-peppas	$Q_t=K_{KP} t^n$

It was found that the *in vitro* drug release from hydrogels was best explained by higuchi"s equation as the plot showed highest linearity (r 2>0.9) followed by zero order indicating that the concentration was near independent of drug released. To find out the release mechanism, the corresponding plot (log cumulative percent drug release vs time) for korsemeyer-peppa"s equation indicate a good linearity (r 2>0.9) except for PEC-1:1 and PEC-1:3. The release exponent "n" for PEC-5:1 and PEC-3:1hydrogels was in between 0.5 to 0.8.

Table 6: Showing Effect of Ionic and pH Effect On GKG:CS Complexes.

Sl. No.	pH of GKG solution	% yield	Ionic strength (mM)	% yield
1	2	54.9	0	93.8
2	3	64.3	10	88.9
3	4	82.9	20	82.7
4	5	89.6	40	70.8
5	6	80.8	60	54.4
6	8	64.7	80	48.2
7	10	48.8	100	35.0

5.0 pH of GKG solution has the maximum % Yield i.e. 89.6 and 10 pH is having lowest % Yield i.e. 48.8. Zero Ionic strength mM has the maximum Yield i.e. 93.8 and 100 ionic strength is having lowest % Yield 35.0.

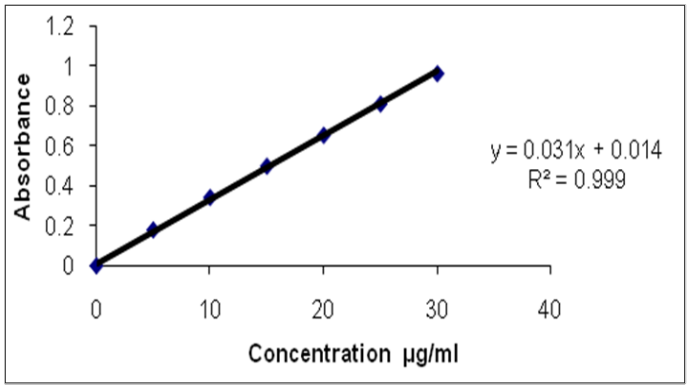

Figure 2: Calibration curve of Vinorelbine tartarate.

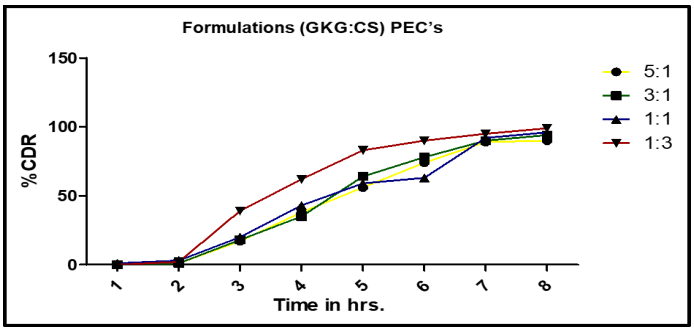

Figure 3: % CDR of drug loaded PEC's. *In vitro* drug release study of Vinorelbine from Vinorelbine loaded PEC showed higher release in Phosphate buffer pH 7.4 than in deionized water indicating that drug was released by ion exchange process. The drug molecules that are bound to surface of the polymer aggregates by ionic Complexation can be rapidly released in the presence of counter ions in the buffer. In case of PLN, lipid acts as barrier and retard rapid release of the drug in presence of counter ions. This finding once again confirms the importance of the lipid in the formulation.

swelling in HCl conditions due to an inefficient NH_3-COO ionic interaction. The release of vinorelbine tartarate was found to be enhanced with an increase in 5 w/w concentration GKG in the Polyelectrolytic complexes because the hydrophilic polymer GKG may make it easier for solution to enter the particles, promoting maximum swelling, and the carboxylate ions in vinorelbine tartarate and GKG are mutually repulsive. This entire process dramatically increases the drug's solubility and hastens its dissolution. As a result, PEC 5:1 exhibits a higher percentage of release than PEC 3:1 and 1:3.

Effect of ionic strength in terms of mM, yield, and PH on GKG in Table 6, CS complexes, and % yield were displayed. The maximum yield for a GKG solution at 5.0 pH is 89.6, whereas the maximum yield for 0 mM of ionic strength is 93.8. FT-IR spectra of GKG, CS, GKG-CS hydrogel (Figures 4 to 7), and donepezil-loaded GKG-CS hydrogel were used to characterised vinorelbine tartarate-loaded GKG/CS hydrogels (PEC 5:1). Chitosan's spectra displayed the recognizable absorption bands at 1594, 1384.42, and 1376.86 cm^{-1} (amide groups and -CH_2 bending), respectively. The distinctive bands of the saccharide structure were the absorption bands at 1035.17 cm^{-1}. The characteristic absorption bands at 3434.05 cm^1 (OH stretching) and 1731-40 cm^{-1} (ester carbonyl group) were visible in the spectra of GKG. The typical peaks of both GKG and CS were visible in the spectra of the GKG-CS hydrogel, with just a slight shift. The CS used in this study's FTIR analysis revealed the doublet peak at 1594, 1384.42 cm^{-1}, which was produced by the chitin's deacetylation. However, with increasing peak sharpness, these doublet peaks in GKG-CS hydrogel were somewhat altered into a practically single band measuring 1642.79 cm^{-1}. When compared to the GKG, the peak diminished at the ester carbonyl groups, at 1731.40 cm^{-1}. The likelihood of a relationship between GKG and CS due to electrostatic contact may be to blame for this variation in the IR spectra of the complex. Vinorelbine tartarate showed spectra of drug-loaded hydrogels that revealed the distinctive peak of both GKG-CS hydrogels with a minor shift in the C-N stretching at 1317 cm^{-1} in Vinorelbine tartarate, which was determined to have been moved towards 1420 cm^{-1}, and the

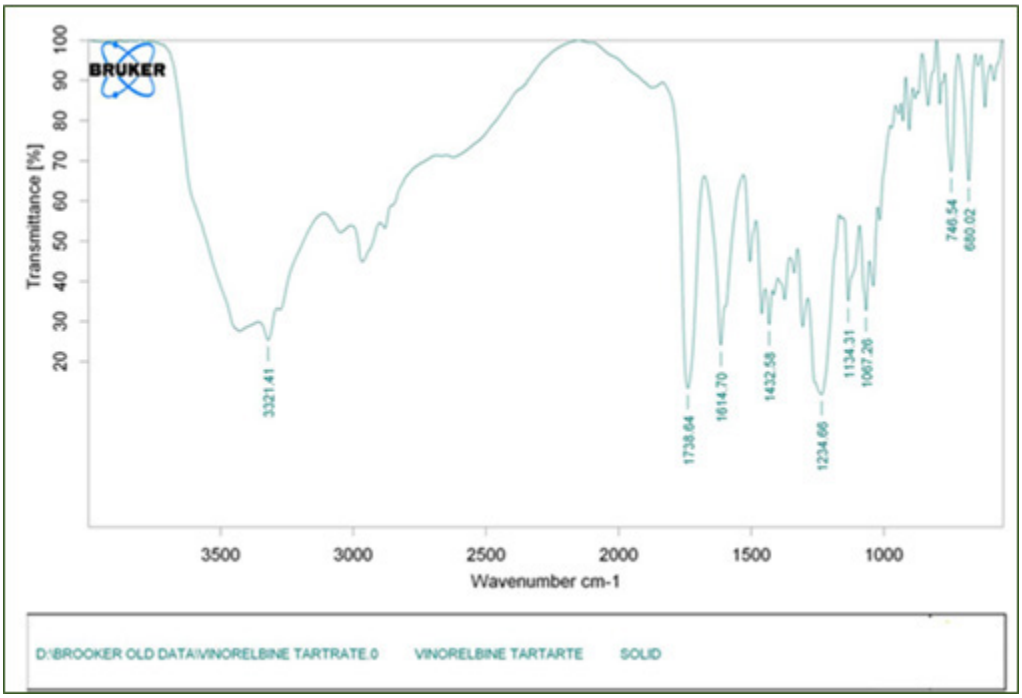

Figure 4: FTIR spectroscopy of Vinorelbine tartarate.

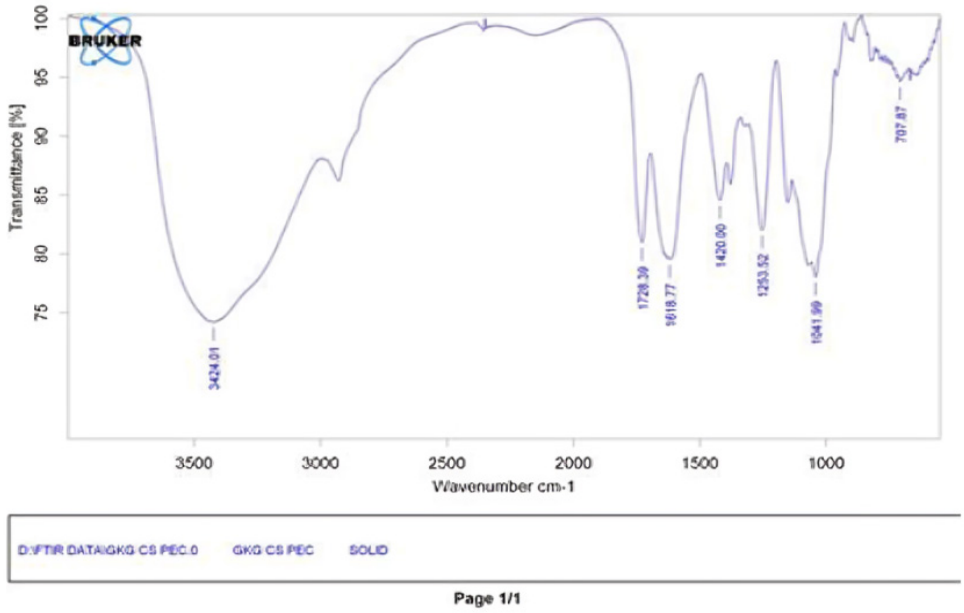

Figure 5: Gum Kondagogu and chitosan loaded PEC'S.

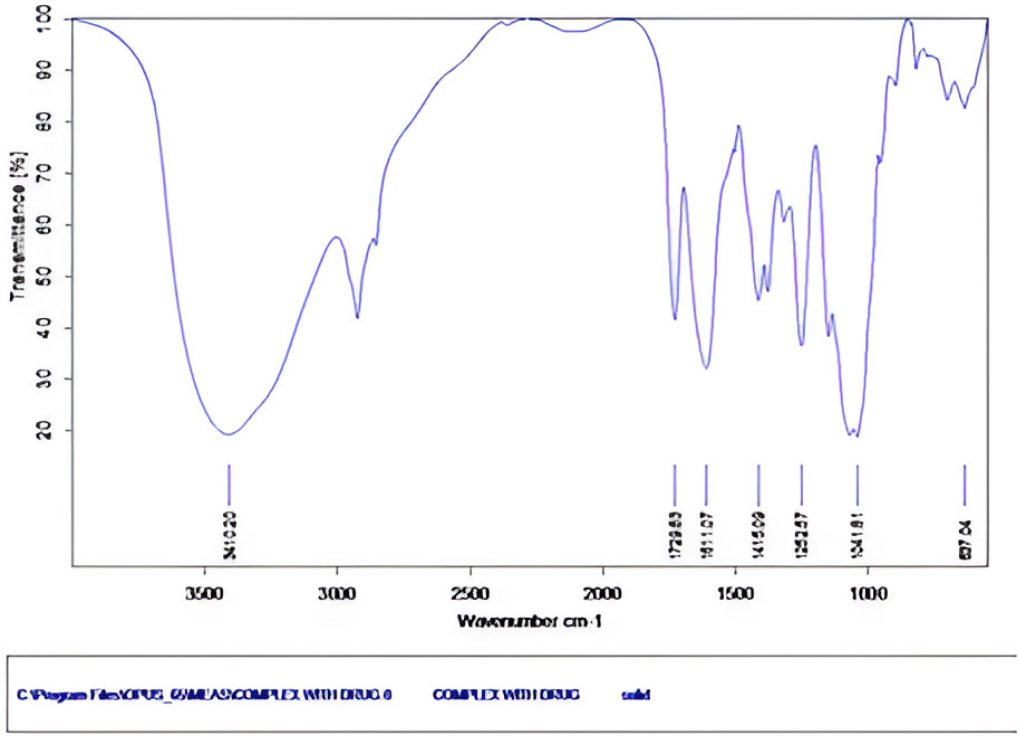

Figure 6: FTIR spectroscopy of Vinorelbine tartarate loaded PEC's.

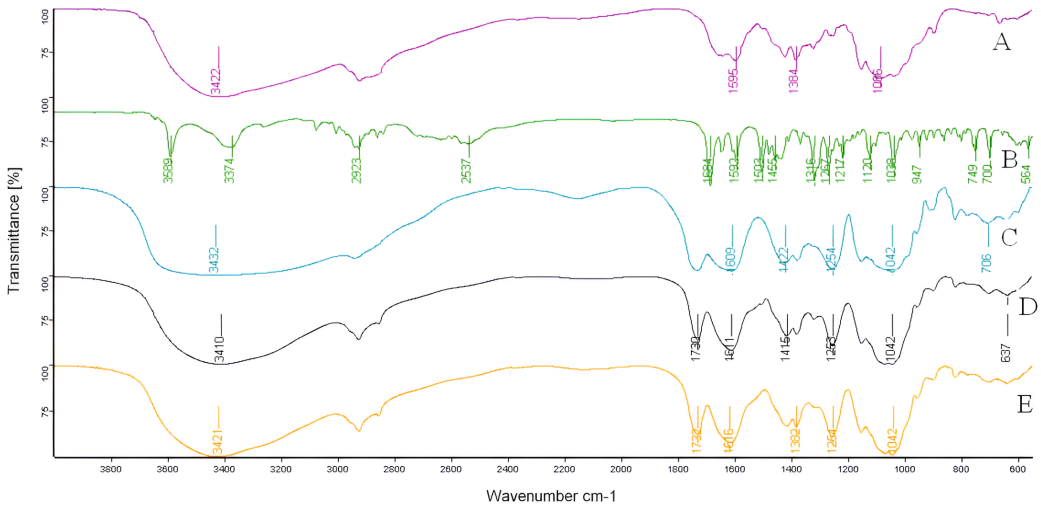

Figure 7: Comparative spectrum. A=complex without drug, B=donepezil hydrochloride, C=Chitosan, D=complex with drug, E=Gumkondagogu. FTIR spectra data showed the absence of chemical interaction between the drug and the excipients.

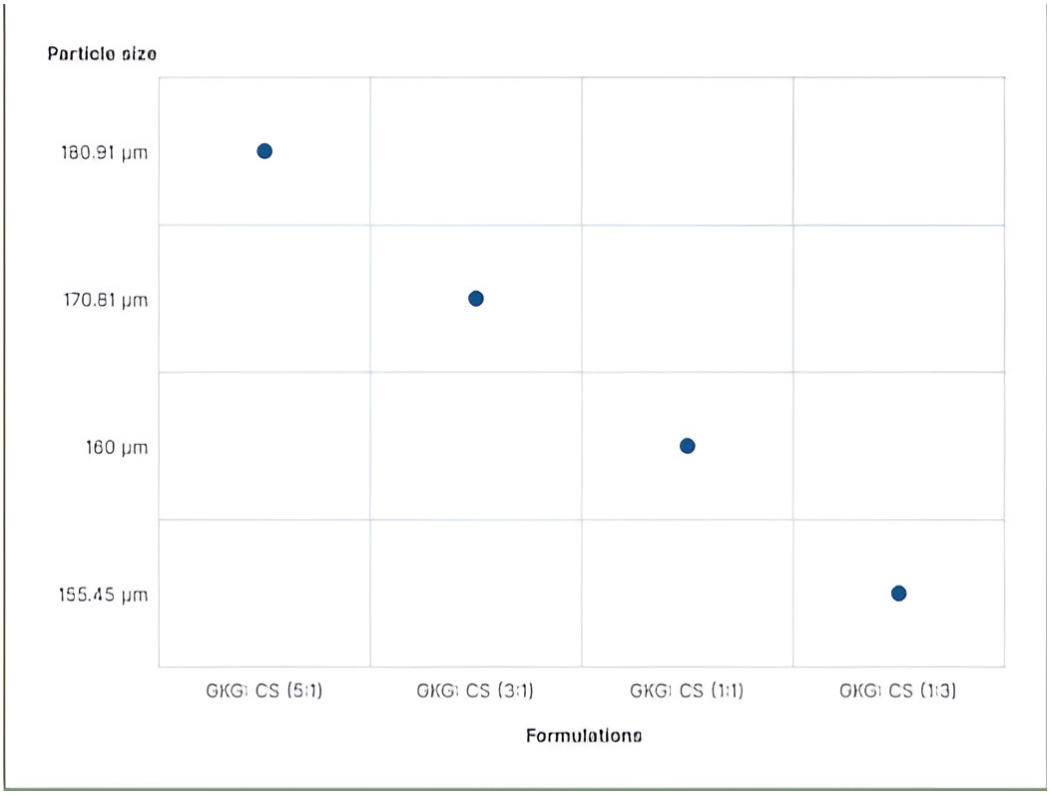

Figure 8: Particle size of various formulations. GKG: CS (5:1) Formulation was the highest particle size and GKG: CS (1:3) Formulation was having the lowest particle size i.e. 180.91 µm and 155.45 µm respectively.

peak due to amino groups in the hydrogel was diminished. This indicates that the chosen polymers did not interact chemically to create the GKG/CS hydrogel and vinorelbine tartarate. Following is a list of the particle sizes for the different formulations (Figure 8). GKG: The average particle size of 100 particles in the CS (5:1), (3:1), (1:1), and (1:3) formulations was 180.91 mm, 170.81 mm, 160 mm, and 155.45 mm, respectively.

CONCLUSION

The study's objective was to employ the complex co-acerbation method or the polyelectrolyte approach to create a novel pH-sensitive Polyelectrolytic complex between GKG and CS. The carboxyl group of Gumkondagogu and the amide group of chitosan engage electrostatically to create the complex between GKG and CS. The GKG:CS ratio of 5:1 was shown to be the optimal one for complex formation. Vinorelbine tartarate hydrogels (5:1, 3:1) were demonstrated to modify their drug release rate *in vitro* in response to pH changes. Due to the complex expanding more at higher pH levels than it did at pH 1.2, the drug release was higher at pH 6.8. The findings of the present study unequivocally demonstrate the great potential of the novel Polyelectrolytic complexes made from the gum Kondagogu/chitosan as a natural polymer-based delivery system for the precise delivery of medications like vinorelbine tartarate in order to decrease dosing frequency.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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