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Mathematical Approach of Functional ANOVA Method to the study of triblock copolymer of Poly(Crystal violet) drug release Mechanism

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Abstract

The core intention of this work is to bring into play a novel method that coupled Experimental design and Functional data analysis within drug release system, Functional ANOVA for a two mode behavior to assure the control of adding together a known drug namely Folic acid on the drug delivery system of Poly (crystal violet) base triblock copolymer. To achieve this, the experimental design by means of a treatment aspect (the quantity of FA-PCV, FA-PCV-PCL, FA-PCV-PCL-PTHF) at different time intervals (0,15,30,45 minutes, 1,2,4,6,12 hours) is performed. The efficient ANOVA can be used in all the information of every curvature or functional statistics. The outcome collected by means of this method through the conductivity and Relative humidity data indicate that the quantity of Folic acid adding with poly crystal violet based triblock copolymer significantly influences the drug delivery ability in the system. In addition, pair wise comparisons in conductivity and Relative humidity of poly crystal violet based triblock copolymers using the functional ANOVA method and other characterization tests such as FTIR, UV visible spectroscopy, Fluorescence study and FESEM study tests are carried out to discern the release of drug application of triblock copolymers of Poly(crystal violet). The outcome received at this point during the current exploration is decisively compared among the literature standards.

Keywords: Functional data analysis, Functional ANOVA, Drug delivery system, Conductivity, Relative humidity, Triblock copolymers

1. Introduction

Over the past three decades, researchers have shown great interest in improving drug treatment through delivery system (DDS) [1]. Hydrophilic matrix systems are one of the options for the extended release of pills and tablets containing a close combination of drugs and the release rate that regulates triblock co polymers such as PCV-PCL-PTHF and adjuvants in a defined component [2]. Polycrystal violet (PCV) based on triblock copolymers has been identified as one of the most suitable polymers in the construction of a hydrophilic matrix system due to its low cost, the presence of soluble components in water and the availability of different viscosity ranges [3]. Therefore, this polymer has acknowledged significant consideration in the restricted release of the drug [4]. Extensive opportunities for the development of advanced substances in the field of drug delivery / release based on molecular pathology are demonstrated. Polymeric compounds and composites of various organisms have been tested for the development of plants, tissue engineering, biosensors, scaffolds,wound healing, and uninterrupted drug delivery [5 - 9]. Among the desirable features of DDS are toxicity, high drug loading, and targeting, thereby reducing adverse effects on unintended tissues, continuous delivery of therapeutic molecules, physicochemical stability,ability to protect drugs from degradation, fertility, and high productivity [10–13].

1.1 Analysis of Variance (ANOVA) study

ANOVA is a statistically based decision-making tool for finding any differences in performance between groups of tested items. ANOVA assists in assessing the value of all key components and their interactions by comparing the median square with the measurement of test errors at certain confidence levels [14]. Statistically, there is a tool called F test, named after Fisher to determine which design parameters have a significant impact on the quality factor [15]. In the analysis the F value is the square root error of the residual error and is usually used to determine the value of a factor. When data is active, another method of classification of variance (ANOVA) is called active ANOVA (FANOVA) [16]. Covariates are factors while the response is active. This method, compared with the old one, has the advantage of using all the information in curves, instead of the specific numbers in it [17-19].

The integration of electronic copolymers with ABA or ABC-resembling structures is widely used in the field of Science and Engineering especially in the medicinal field [20 - 23]. In a recent study a component of the PTHF connected PCL-PCV-PCL (ABA) block copolymer was compiled to i) improve PCV processing, ii) improve the absorption and release properties of drugs, iii) increase fluorescence output. intensity (FEI) for the detection of cancer cells in the bioimaging field. Poly (caprolactone) (PCL) is an important bio-medical polymer due to its bio-compatibility and bio-degradation without any incytotoxic effect. Such a biomedical candidate can be synthesized using various chemical agents such as cellulose, calcium methoxide, hexynol, diphenylzinc and hydroxyl butyl vinylether [24-28]. Poly (tetrahydrofuran) (PTHF) is a tetrahydrofuronium end capped polyether in the midst of hydrophilic coating. Cationic initiating THF Ring opening polymerization leads to the configuration of PTHF [29, 30].
In the current investigation, modified PTHF-binding material connected to the PCL-PCV-PCL triblock co-polymer using a macro initiator. PCV based on the first novel was used to improve the analysis and coherence of the same bio- compatibility in the bio-medical field [31]. In addition, polymer synthesis incorporates a one-step eco-friendly process with a low cost and an economically viable route. Above all, the FEI behavior and drug release of each polymer were not carefully compared in the literature. So in the current study, we took this task as a challenge and combined the same successes and deeply compared the outcome especially to DDS using the ANOVA method.

2. Experimental section

2.1 Materials

Crystal violet (CV) and Methanol were purchased from Spectrum, India. Caprolactone (CL) was purchased from Sigma Aldrich, India. Chloroform (CHCl3) and tetrahydrofuran (THF) are purchased from S.D. Stannous octoate (SO) was purchased in Merck, India. Diethyl ether, India and so used.

In the present study, the final targeted polymer products were assembled in three steps as follows.

2.2 Methods

2.2.1 Poly(Crystal violet) (PCV) Synthesis.

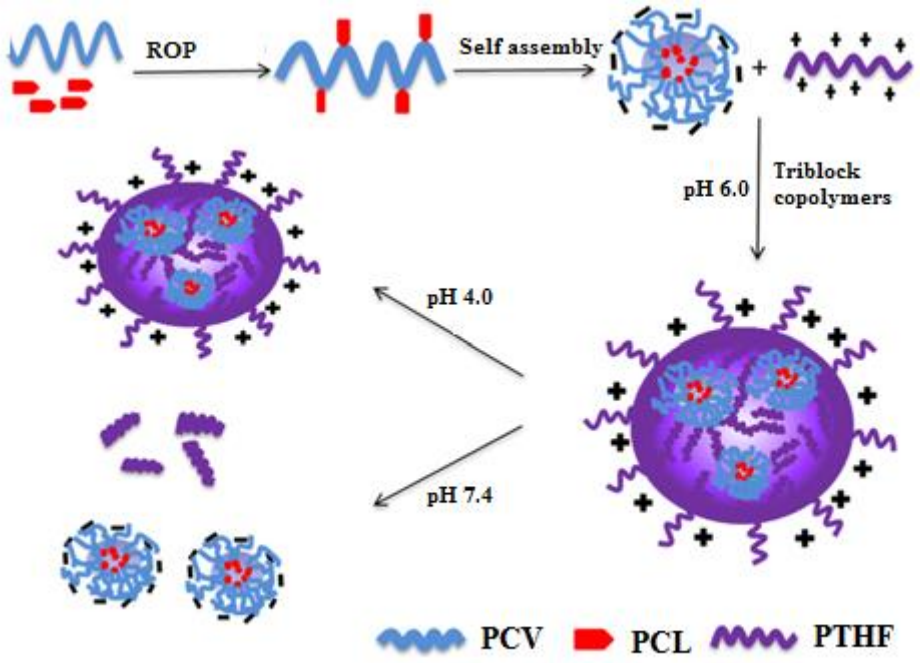
4g Crystal violet dye dissolved in 100 mL ethanol and dissolved in 250 mL 1M HCl under intense and continuous stirring. 2g FeCl3 in 100 mL of double purified water (DD) can be added slowly under a gentle stirring condition with N_2 purification at 0-5^{o}C. The reaction medium color was dark brown marked. This color formation ensured a reduced dimerization reaction. For about 6 hours the wrapping continued. At the end of the medium reaction a brownish-yellow was observed and dried at 110oC for 8 hours. The built-up rain was measured and eventually stored in a zip lock cover. Yield was marked as 90%. During the chemical polymerization of Crystal violet, Fe3 + was reduced to Fe0 (i.e.) particles of iron nano.

2.2.2 Synthesis of Poly (caprolactone)-b-Poly (Crystal violet) -Poly (caprolactone) triblock copolymer.

The 0.3g PCV was taken from a 25 mL round bottomed (RB) flask fitted with a N_2 inlet and outlet. Here PCV serves as a great start. 2g CL was accurately weighed and discharged into the RB flash. 0.001g Stannous Octoate catalyst was added and the [M / C] ratio was kept to 1000. The temperature of the reaction compounds was increased to 1600C with minimal stirring. The reaction is allowed to continue for the next 2 hours. During the polymerization reaction, the medium became very viscous due to the high polymerization of caprolactone. After two hours of ROP, a low-key low flask was taken from the oil bath and cooled. The content was dispersed in CHCl3 (25 mL) and re-added by adding 200 mL ether taken from a 500 mL bucket. The goat was kept under a steam lid for about 12 hours to dry the sample. Yield was marked as 99%. So a clean sample (triblock copolymer) was weighed and stored in a zipper lock cover.

2.2.3 PTHF end functionalized triblock copolymer Synthesis

The polymer produced in the second phase was dissolved in 25mL of THF (and acts as a co-monomer). The polymerization of the THF ring opening was initiated with the addition of 0.001g PAH. The course of this polymerization reaction was performed at 45oC below the N2 atmosphere for 8 hours. At the end of the polymerization reaction, the unresponsive THF was allowed to evaporate. 20 mL of double-filtered water is immersed in the contents of the flask and reheated at 110oC. Due to the evaporation process, all unresponsive THF has been removed. The yield of triblock copolymer was marked at 65% .So the pure polymer was weighed and stored in a zipper lock cover.



Scheme 1. Schematic representation of FA/ PCV-PCL-PTHF triblock copolymer preparation and application

3. Instruments for Characterization and testing

Combined samples are identified by the following strategies. FTIR view of the samples was recorded with the help of the Shimadzu 8400 S, Japan tool in the form of KBR pelletization from 400 to 4000 cm − 1. The Jasco V-570 tool was used to study drug extraction using a visual UV spectrum measurement. A cyclic voltammetry study was conducted at CH Instruments 660cc, USA. The four-probe method was used to study the conductivity characteristics of composite samples [43]. The molecular weight measurement of triblock copolymer samples was made with the non-chromatography (SEC) Perkin Elmer Series 200 exclusion size. The surface morphology and constituent part size of the connected samples are determined by FE-SEM, a tool of Hitachi S4800 Japan.

4. Results and discussion

FTIR spectral study

The FTIR spectrum confirmed the functionality of the system. FTIR spectrum for PCV (Figure 1a) is revealed. O-H extensions of water molecules appeared at 3406 cm-1. CH symmetric and anti symmetric stretching have been identified at 2861 and 2938 cm-1 respectively. The fragrant CH extension extends from 761 and 809cm^{-1}. The CN extension can be seen at 1353 cm-1. The C-Cl extension appeared at 579 cm-1.

PCV-PCL diblock copolymer (Figure 1b) is represented. O-H and NH extensions appeared at 3427 and 3533 cm-1 respectively. Aiphatic C-H symmetric and anti symmetric stretching was detected at 2874 and 2941 cm-1 respectively. The carbonyl stretch on the PCL segment can be seen at 174 cm-1 [33]. CH from the vibrating plane can be seen in 721cm-1.C-O-C ether linkage (1182 cm-1), CN stretching (1364 cm-1), quinonoid stretching (1593 cm-1), CH stretch (833 and 775 cm-1) can be seen.The appearance of carbonyl expansion and C-O-C bonding ensured the opening of the Caprolactone polymerization ring with Polycrystal violet.

The FTIR spectrum of triblock copolymer (Figure 1c) is enumerated.The tetrahydrofuronium cation stretch appeared at 1602 cm^{-1}.The remaining peaks were explained before. The appearance of a peak corresponding to tetrahydrfuronium ion confirmed the ROP of THF in the presence of diblock copolymer which can act as a successful initiator.

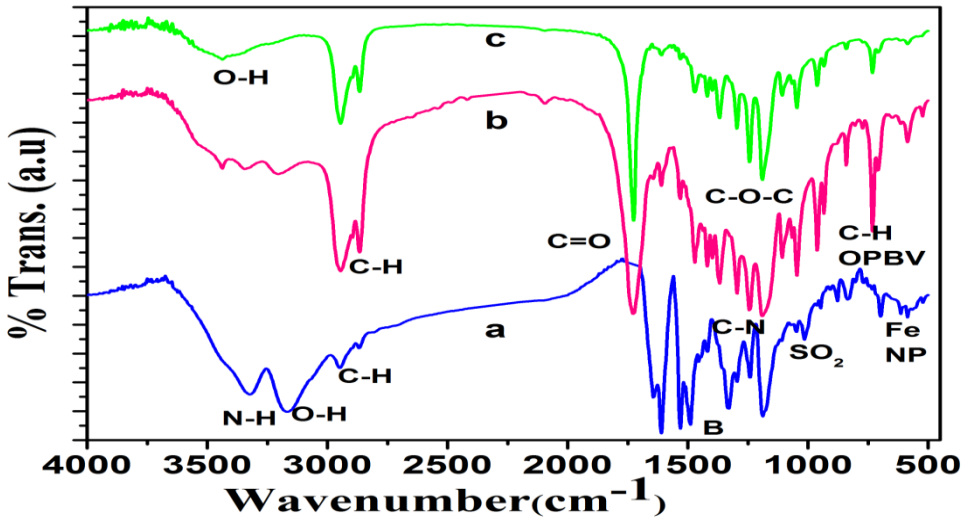


Figure 1. FTIR spectrum of (a) PCV, (b) PCV-b-PCL, (c) PCV-b-PCL-b-PTHF

UV visible spectroscopy

UV Visible absorption of PCV is showed (Figure 2a). The spectrum showed two humps at 583 and 545 nm corresponding to the monomeric and dimeric structure of PCV [34]. structure. The red switch at the top ensured the opening of the Caprolactone polymerization ring using PCV as a chemical launcher. Perhaps quaternary ammonium carbon may be involved in the ROP of Caprolactone. As a result the peak red was changed to 590.2 nm (Figure 2b). The visible UV spectrum of triblock copolymer is shown (Figure 2c). And the spectrum shows two humps at 599.2 and 543 nm. Another red switch at the top to 599.2 nm secured ROP for THF by using diblock copolymer as a chemical launcher. UV effects can also be supported by Fluorescence spectroscopy.

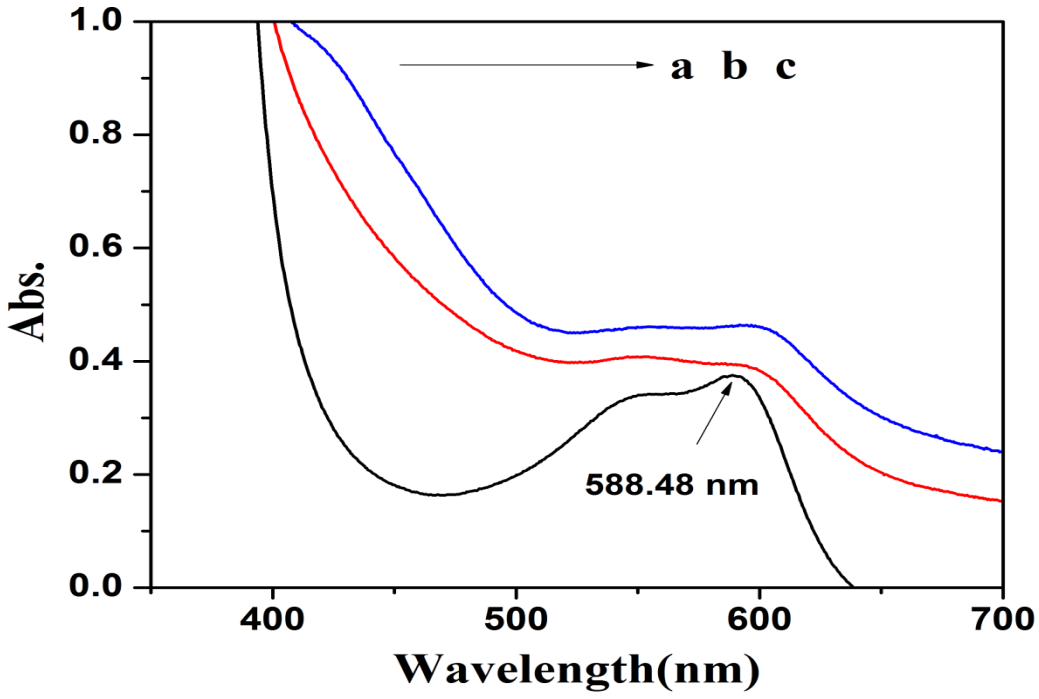


Figure 2. UV visible spectrum of (a) PCV, (b) PCV-b-PCL, (c) PCV-b-PCL-b-PTHF

Fluorescence study

A unique feature of dyes is their fluorescence release. It (Figure 3a) shows the fluorescence emission spectrum of PCV. The spectrum shows a single wide wavelength with a value of λmax of 603.5 nm. After diblock copolymerization with caprolactone units the blue discharge spectrum was

changed to 5846 nm due to the depression of the plasma resonance effect (Figure 3b). Represents (Figure 3c) fluorescence emission spectrum of triblock copolymer.After triblock copolymer formation. the output height and redness were adjusted to 600.9 nm [35]. The red shift in the discharge peak explains the role of tetrahydrofuronium ion. Compared to total PCV system showed a high value λmax.

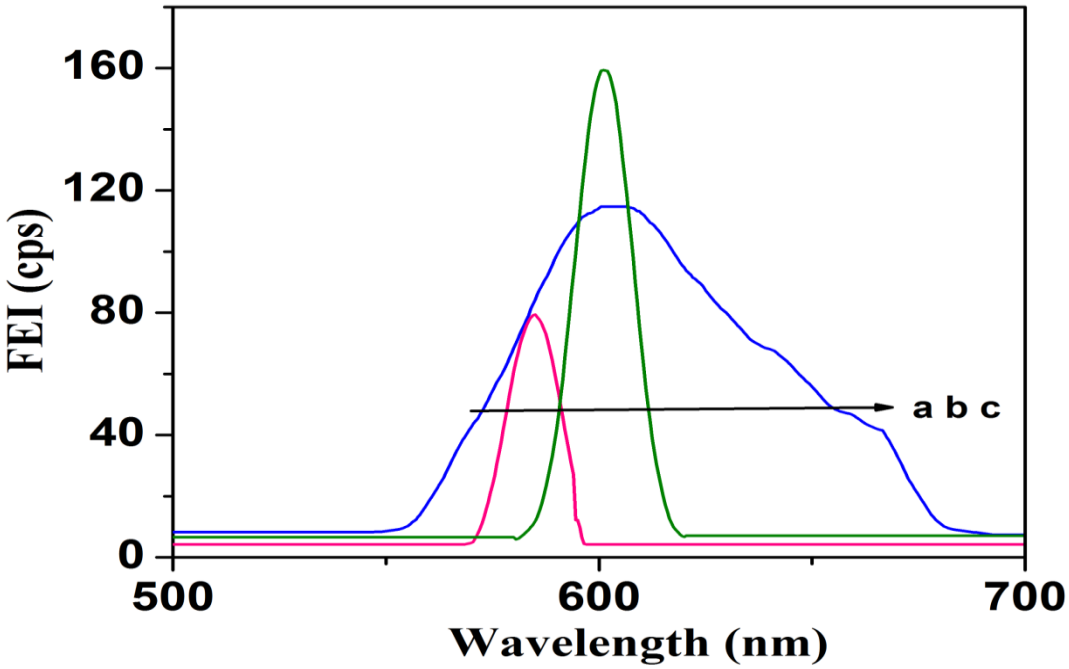


Figure 3. Fluorescence Emission spectrum of (a) PCV (b) PCV-b-PCL (c) PCV-b-PCL-b-PTHF

Field Emission Scanning Electron Microscopy (FESEM) Analysis

The surface morphology of PCV is (Figure 4a) given internally. Nanovoid materials are very useful in the biomedical field as a drug carrier and other iron nano particles are present in the surface of PCV. Represents (Figure 4b) FESEM image of diblock copolymer. Here again one can see nano sized particles with broken stone as morphology [36-39]. Similarly (Figure 4c) the upper morphology of the triblock copolymer is represented by a certain void on its surface. During the drug loading process the drug can be added to the voids. So such a thing is very useful in the field of biomedical as a drug transporter [40].

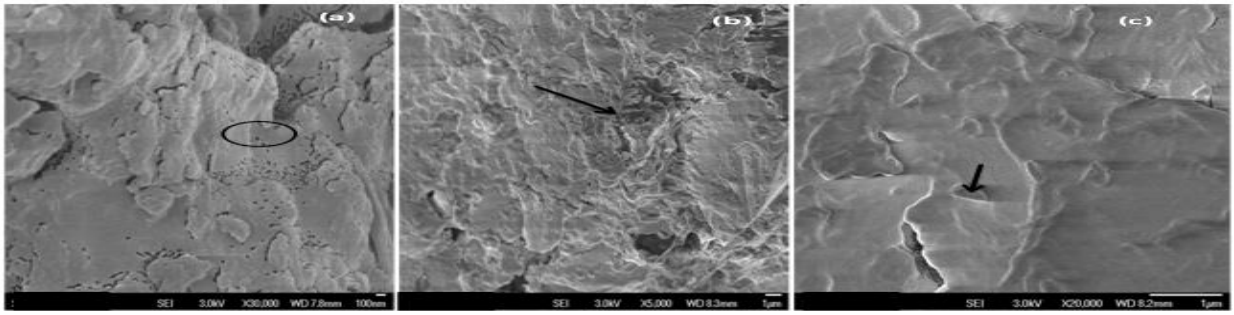


Figure 4. Field Emission Scanning Electron Microscopy images of (a) PCV (b) PCV-b-PCL (c) PCV-b-PCL-b-PTHF

Conductivity study

The effect of temperature on the electrical conductivity studied in all three systems individually and showed in Figure 9a, b, c. It has been found that though increasing the temperature the amount of conductivity increases linearly and that depends on the condition of the polymer [41-43]. As PCL is an electrical insulator it has therefore shown very low conductivity while increasing the temperature [44]. Due to the presence of tetrahydrofuronium ion triblock copolymer showed a very high degree of electrical conductivity relative to temperature and this can be explained on the basis of low melting temperatures. Compared to PANI the current system produced lower power transmission.

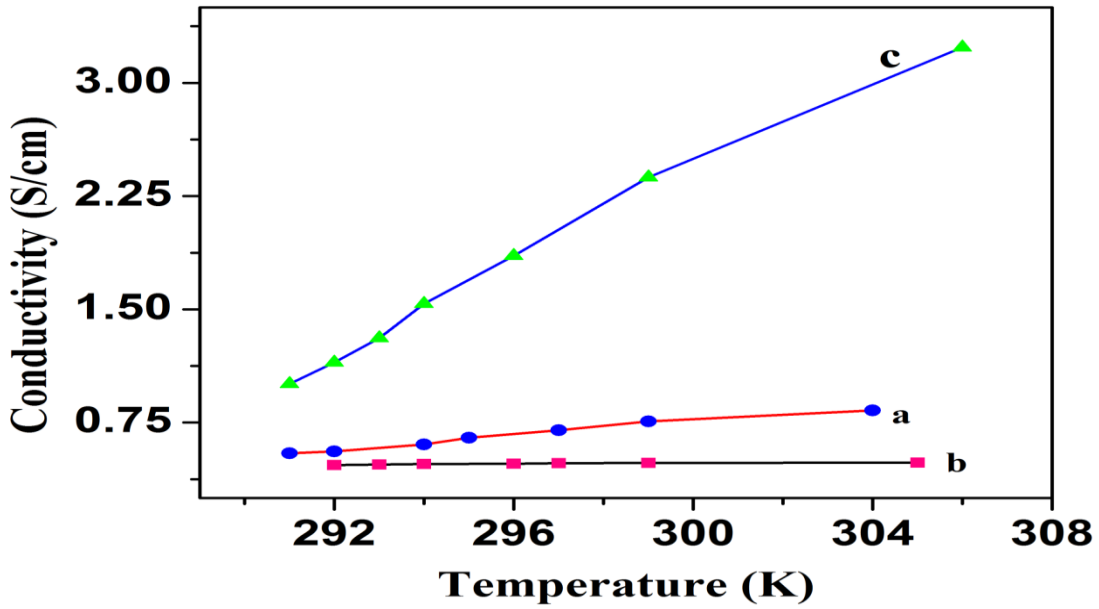


Figure 5. Temperature Vs. conductivity plot of (a) PCV (b) PCV-b-PCL (c) PCV-b-PCL-b-PTHF

TABLE 1: Effect of Temperature (K) on Conductivity (S/cm) of FA-PCV,FA-PCV-PCL and FA-PCV-PCL-PTHF drug delivery system:

	PCV		PCV-PCL		PCV-PCL-PTHF	
	Temperature	Conductivity	Temperature	Conductivity	Temperature	Conductivity
Sl.No	Kelvin	S/cm	Kelvin	S/cm	Kelvin	S/cm
1	292	0.4685	291	0.5459	291	1.007
2	293	0.4714	292	0.5589	292	1.1482
3	294	0.4749	294	0.6045	293	1.3089
4	296	0.4775	295	0.6495	294	1.5361
5	297	0.4805	297	0.6992	296	1.8553
6	299	0.4823	299	0.7581	299	2.3753
7	305	0.4849	304	0.8306	306	3.2362

ANOVA Study in Temperature (K) Vs Conductivity (S/cm):

TABLE 2: ANOVA (Two way classification) applied for the analysis in the effect of Temperature on Conductivity of FA-PCV,FA-PCV-PCL and FA-PCV-PCL-PTHF drug delivery system :

Sl.No	PCV	PCV-PCL	PCV-PCL-PTHF
1	0.4685	0.5459	1.007
2	0.4714	0.5589	1.1482
3	0.4749	0.6045	1.3089
4	0.4775	0.6495	1.5361
5	0.4805	0.6992	1.8553
6	0.4823	0.7581	2.3753
7	0.4849	0.8306	3.2362

H_{01} : There is no significant difference between rows.
H_{02} : There is no significant difference between columns.
H_1 : There is significant difference between rows and columns.
LOS: 5% level.

TABLE 3: ANOVA analysis:

Sl.	Columns X →	X_1	X_2	X_3	Total	X^2_1	X^2_2	X^2_3

No	Rows Y↓							
1	Y_1	0.4685	0.5459	1.007	2.0214	0.21949225	0.29800681	1.014049
2	Y_2	0.4714	0.5589	1.1482	2.1785	0.22221796	0.31236921	1.31836324
3	Y_3	0.4749	0.6045	1.3089	2.3883	0.22553001	0.36542025	1.71321921
4	Y_4	0.4775	0.6495	1.5361	2.6631	0.22800625	0.42185025	2.35960321
5	Y_5	0.4805	0.6992	1.8553	3.035	0.23088025	0.48888064	3.44213809
6	Y_6	0.4823	0.7581	2.3753	3.6157	0.23261329	0.57471561	5.64205009
7	Y_7	0.4849	0.8306	3.2362	4.5517	0.23512801	0.68989636	10.47299044
Total		3.34	4.6467	12.467	20.4537	1.59386802	3.15113913	25.96241328

Step 1 : N=21

Step 2 : T=20.4537

Step 3 : $T^2/N = (20.4537)^2/21 = 19.9216116$

Step 4 : $TSS = \sum X^2_1 + \sum X^2_2 + \sum X^2_3 - T^2/N$ (1)

$= 1.59386802 + 3.15113913 + 25.96241328 - 19.9216116$

$TSS = 10.78580883$

Step 5 : $SSC = (\sum X_1)^2 / N_1 + (\sum X_2)^2 / N_1 + (\sum X_3)^2 / N_1 - T^2/N$ (2)

$= 1.593657143 + 3.084545841 + 22.203727 - 19.9216116$

$= 6.960318384$

Step 6 : $SSR = (\sum Y_1)^2 / N_1 + (\sum Y_2)^2 / N_1 + (\sum Y_3)^2 / N_1 + (\sum Y_4)^2 / N_1 + (\sum Y_5)^2 / N_1 + (\sum Y_6)^2 / N_1 + (\sum Y_7)^2 / N_1 - T^2/N$ (3)

$= 1.36201932 + 1.581954083 + 1.90132563 + 2.36403387 + 3.070408333 + 4.357762163 + 6.905990963 - 19.9216116$

$SSR = 1.621882762$

$SSE = TSS - SSC - SSR$ (4)

$= 10.78580883 - 6.960318384 - 1.621882762$

$SSE = 2.203607684$

TABLE 4: ANOVA observed report:

Variation Source	Sum of squares	Degree of Freedom	Mean square	Variance	Table value
Between Columns	SSC=6.960318384	(C-1) =3-1 =2	MSC=SSC/C-1 =6.960318384/2 =3.480159192	F_c=MSC/MSE =18.95160865	F_c(-1)(r-1) F_c(2,12) =3.88
Between Rows	SSR= 1.621882762	(r-1) =7-1 =6	MSR=SSR/(r-1) =1.621882762/6 =0.270313793	F_R= MSR/MSE =1.472024967	F_R(C-1)(r-1) F_R(6,12) =3.03
Error	SSE=2.203607684	(C-1)(r-1) =2*6 =12	MSE=SSE/ (C-1)(r-1) =2.203607684/12 =0.183633973	-	-

Observed report:

Case (i) : Cal F_c > Tab F_c when $\alpha = 0.05$ (240.8725609>19.41)

So, H_{o1} is rejected.Therefore it is observed that there is significant difference between the rows.

Case (ii) : : Cal F_R < Tab F_R (5.532172151>4.00)

So, H_{o2} is accepted. Therefore it is observed that there is no significant difference between the columns. From the study of Functional ANOVA method and its two way treatment analysis, it is confirmed that the drug release activity of PCV based triblock copolymer is tremendously increased by decreasing the temperature of the system and increasing the conductivity nature of the triblock copolymer units.

Drug delivery study

The drug delivery activity of PCV, di and triblock copolymer were tested with Folic acid as a model drug. At a definite interval of time 2 ml of a liquot was pipette out and subjected to UV visible measurement. Based on the UV visible spectra the plots for different models were drawn (Figure 11(a-m)) and found that the Peppas model yielded the maximum R^2 value of 0.59 with (Figure 11n) the slope value of 0.05.If the slope value less than 0.5 that indicates the Fickian flow mechanism of drug.The same drug was

loaded onto diblock copolymer under identical experimental conditions.The similar plots were made (Figure 12(a-m)) and found the maximum R^2 value of 0.90 yielded by Peppas model. Again it was noted that the slope value of the Peppas model was calculated as 0.091 (Figure 12n) again established the Fickian flow of drug. In the case of diblock copolymer one hydrophobic segments were introduced. Even then the drug followed the regular release mechanism. The drug release mechanism of triblock copolymer was also tested (Figure 13(a-m)) under identical experimental conditions. In the system the maximum R^2 value of 0.91 was measured (Figure 13n) for the Higuchi model. This assured the dissolution of drug in the given medium and slowly deliver the drug through Higuchi model. This indicates that while changing the phase from hydrophilic to hydrophobic the drug release mechanism is also varied. This can be explained on the basis of solubility as well as the drug in the given solvent [42].

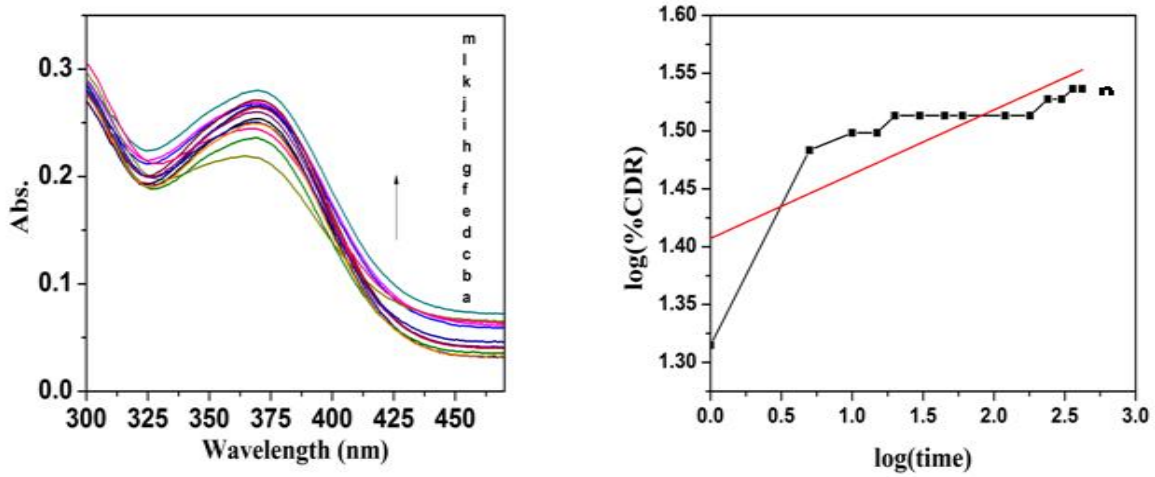


Figure 6. UV visible spectrum of FA-PCV system recorded during the drug release at various time interval of (a-m), (n) log (time) Vs. log (%CDR) plot

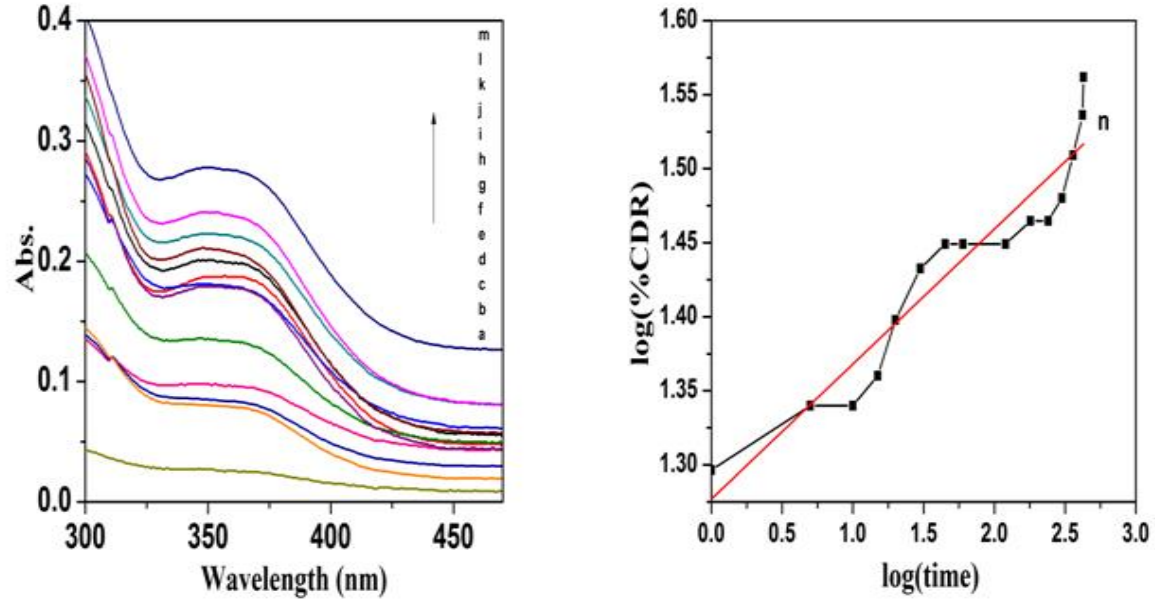


Figure 7. UV visible spectrum of FA-PCV-PCL system recorded during the drug release at various time interval of (a-m), (n) log (time) Vs. log (%CDR) plot

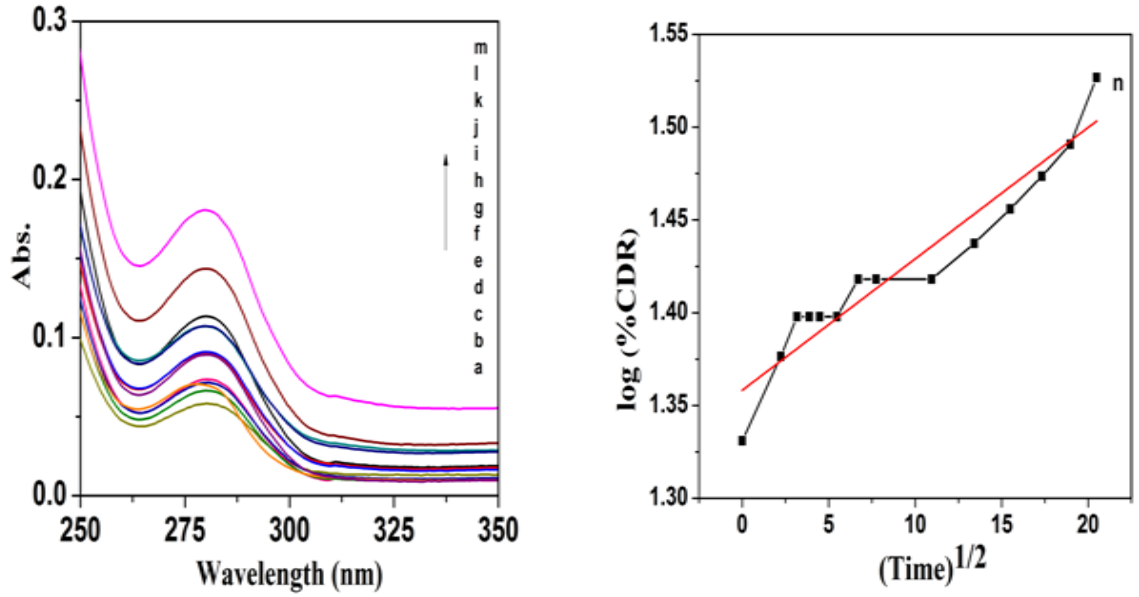


Figure 8. UV visible spectrum of FA-PCV-PCL-PTHF system recorded during the drug delivery at various time interval of (a-m), (n) $(Time)^{1/2}$ Vs. log (%CDR) plot

5. Conclusions

The important points from the above study is arranged here as conclusions.
i)The appearance of both benzenoid(1500 cm^{-1}) and quinonoid (1586 cm^{-1}) stretchings confirmed that the PCV is made up of a copolymer like structure. ii) The Ultraviolet (UV) visible spectrum of PCV exhibited a peak at 583 nm due to monomeric structure of PCV. The same was red shifted to 590.2 and 599.2 nmcorresponding to the di and triblock copolymer formation. iii)The triblock copolymer exhibited a fluorescence discharge peak at 600.9 nm with the red shift and confirmed the role of Tetrahydrofuronium ion iv) Broken stone like morphology appearance with microvoids set the diblock copolymer formation. v) Both the di and triblock copolymer showed the lowest electrical conductivity value than the homo polymer due to their non conducting nature and this behavior was analysed by applying the two way classification of functional ANOVA method. vii) Both the homo and diblock copolymer confirmed the Fickian flow drug release mechanism whereas the triblock copolymer exhibited the Higuchi model in which Functional ANOVA applied significantly.

Abbreviations

ANOVA: Analysis of variance
CV: Crystal violet
CDR: Cumulative drug release
DDS: Drug delivery system
FA: Folic acid
FEI: Field emission intensity
FTIR: Fourier transform infrared spectroscopy
FANOVA: Funtional analysis of variance
FESEM: Field emission scanning electron microscopy
LOS: Level of significance
MSC: Mean of squares value of columns
MSE: Mean of squares value of error
MSR: Mean of squares value of rows
M_n: Number average molecular weight
M_w: Weight average molecular weight
PCV: Poly (crystal violet)
PCL: Poly(caprolactone)
PTHF: Poly(tetrahydrofuran)
PD: Polydispersity
ROP: Ring opening polymerization
SSC: Sum of squares of columns
SSE: Sum of squares of error
SSR: Sum of squares of rows
TSS: Total sum of squares
UV: Ultraviolet

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

All authors contributed equally to this work.

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