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FORMULATION AND EVALUATION OF CURCUMIN COATED CENTRAL VENOUS CATHETERS IN THE ERADICATION OF CATHETER-RELATED BLOOD STREAM INFECTIONS

Nissara Ahammed[1], Revathi Sundaramoorthi[1]*, Venkatesh Dinnekere Puttegowda[2], Umashankar Chikkanna[1]

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ABSTRACT
Background: Biofilm formation on catheters after implantation, leading to the development of catheter-related bloodstream infections, is a significant concern with the usage of vascular catheters, leading to the death of hospitalized patients. The research aimed to modify the catheter surface by developing a coating technique using PU, PVP, and curcumin. **Methodology:** A dip coating technique with a base coat of PU and a top coat of PVP was used on 7 French triple-lumen Polyurethane CVCs with the antimicrobial agent Curcumin. Based on the concentration of polyurethane used, 5 formulations were prepared and evaluated as per ISO guidelines. **Results and Discussion:** Dip coating was successful in coating the catheters. All the physical parameters were within the ISO limits. The process parameters that produce uniform coating were studied. The coated catheters were radiopaque. At the end of 24 hours, all formulations displayed an initial burst release due to the top coat of PVP. Formulation E demonstrated a sustained release of 94.17% of the drug over 21 days. The amount of polyurethane included in the base coat determines how long the sustained release lasts. The formulation follows zero-order kinetics and fits the Higuchi model with quasi-Fickian release, indicating that the release is diffusion-controlled. **Conclusion:** The dip coating technique proved to be a successful method for developing drug-coated central venous catheters. Coating with curcumin reduces bacterial colonization, growth on the catheter surface, and biofilm formation, thereby preventing CRBSI, which in turn enhances patient outcomes and lowers healthcare expenses.

INTRODUCTION

Central venous catheter (CVC), (Figure 1), is a type of medical device that contains an open, flexible tube implanted into a central vein, such as the femoral, subclavian, or internal jugular vein, and progresses until the end point of the lumen is located in the right atrium, superior vena cava, or inferior vena cava [1]. Single-, double-, and triple-lumen catheters are the names given to catheters with one, two, and three tubes, respectively.

[1]*Department of Pharmaceutics, School of Pharmacy, Sri Balaji Vidyapeeth, Deemed to be University, Pillaiyarkuppam, Puducherry, India*
[2]*Department of Pharmaceutics, Acharya & BM Reddy College of Pharmacy, Bengaluru, India.*

For Correspondence:** **revathis@sbvu.ac.in
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Catheters can be implanted for weeks, months, or even years. CVCs facilitate the collection of blood samples and the administration of intravenous fluids, medications, nutritional solutions, blood, and blood products [2]. Plasma proteins, especially fibrin, cover the CVC's surfaces as soon as it is implanted. The bacteria get attached to this protein sheath after migrating from the skin along the catheter tube. This leads to the establishment of biofilm on the catheter surface. The biofilm is composed of yeast and gram-positive and gram-negative bacteria. These biofilms, once formed, lead to the development of catheter-related bloodstream infections (CRBSI). CRBSI is a frequent, fatal, and costly side effect of using CVC. These biofilms enable the bacteria to proliferate throughout the body, and the microorganisms of biofilms rapidly develop antimicrobial resistance [3-5]. The biofilm results in the development of CRBSI and prolonged hospital stays. Catheters carry a frighteningly high chance of developing infection and subsequent death, more so than any other kind of medical device. A compromised host immune response to an infection can develop sepsis and can result in multiple organ failure. The mortality rate that is indicated ranges from 3 to 25% [6-9]. The percentage of patients admitted to intensive care units with implanted catheters is around 90%, among which 18% are central venous catheters [10]. Numerous technological advancements are being researched to reduce CRBSI, including antimicrobial coatings, alterations to the catheter's polymeric surface, antimicrobial lock therapy, bacteriophage therapy, electrical enhancement of antimicrobial activity, and antimicrobial peptides. Coating or blending central venous catheters with antimicrobial agents is a novel research project. In addition to standard preventative hygiene measures, coating or impregnating catheters with antimicrobial chemicals shows significant promise in reducing catheter-associated issues [11-12]. Numerous research studies have been conducted by coating the catheter surface with silver, chlorhexidine, 5-fluorouracil, rifampin, and minocycline, among others. However, the development of drug resistance in microbes has rendered many antimicrobial drugs ineffective [13]. Curcumin is the choice of antimicrobial agent in the current study, as it is an indigenous, natural substance with broad-spectrum antibacterial activity that is safe, affordable, non-hemolytic, and non-cytotoxic. Curcumin has encouraging prospects for preventing implant infection [14-15]. Curcumin is a plant-derived polyphenolic active constituent extracted from the rhizome of Curcuma longa. Curcumin has been shown to possess antibacterial, anticancer, anti-inflammatory, and antioxidant properties. Curcumin inhibits the growth of bacteria by targeting their cell walls, membranes, proteins, DNA, and other cellular components. It prevents the germs from adhering to host receptors and inhibits the production of bacterial biofilms [16]. Curcumin is recognized for its ability to counteract antimicrobial resistance [17]. By reducing the MICs of failed antibiotics, curcumin restores their efficacy [18]. The most promising and extensively utilized polymers in medical devices are polyurethanes (PU) and polyvinylpyrrolidone (PVP). Due to their excellent mechanical properties, biocompatibility, hemocompatibility, and non-cytotoxicity, they are utilized in implantable medical devices [19-22]. They are used in many biomedical applications, including wound dressings, drug delivery systems, implants, and artificial organs [23]. PVP is appropriate for developing immediate-release devices, whereas polyvinyl alcohol (PVA) is appropriate for developing systems for sustained-release drug delivery [24].

Pellethane™ 2363-80AE is a polyurethane elastomer that belongs to the USP Class VI material with a medical grade. It has superior resilience, low-temperature properties, resistance to microorganisms, low extractables, excellent hydrolytic stability, and exceptionally smooth surfaces. It allows sterilization by dry heat, ethylene oxide, or gamma radiation. Due to the property of immediate release, polyvinylpyrrolidone was used in the top coat to achieve burst release of curcumin, and polyurethane was used in the base coat to achieve sustained release of curcumin till the duration of implantation. The dip coating technique is used to encapsulate antimicrobial agents in polymers, which in turn exhibit controlled and sustained drug release with good antimicrobial activity [25-27]. Phosphate buffer pH 7.4 can be used as an equivalent to artificial blood for determining the in vitro release of drugs [28-30]. The rate of release of water-insoluble drugs can be significantly enhanced by the use of surfactants such as Tween 20, which has higher HLB values [31]. The concentrations of surfactants used to improve the solubility in phosphate buffers are usually fixed just above their CMC values. If the concentration of surfactant is much greater than the CMC, there are chances of interaction with the polymer, and it may impact drug release. A good sink condition can be obtained by using Tween 20 at concentrations below 1% [32].
Incompatibility with the drug and polymers can be evaluated using various physicochemical methods like thermal estimation like differential scanning calorimetry (DSC), thermogravimetric

analysis (TGA), spectrophotometric methods like Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction, nuclear magnetic resonance (NMR), and chromatographic separations like high-pressure liquid chromatography (HPLC) [33-35]. There is no primary research on coating CVC with indigenous herbal, broad-spectrum antimicrobial agents. The goal of the current investigation was to develop a coating technique and coat the CVC with herbal antimicrobial agents, such as curcumin, to establish immediate burst release and subsequent controlled release of curcumin throughout the implantation duration. This approach aimed to combat the emergence of antimicrobial resistance and thereby prevent the formation of biofilm and subsequent CRBSI.

MATERIALS AND METHODS

Materials

Curcumin and the curcumin reference standard were obtained from the Sami Sabinsa Group Limited, Bengaluru. Catheter tubes from S3V Vascular Technologies, Mysore. Pellethane grade polyurethane and polyvinylpyrrolidone were obtained from Majik Medical Solutions Pvt. Ltd., Hyderabad. Tetrahydrofuran [THF], disodium hydrogen orthophosphate, and potassium dihydrogen orthophosphate were obtained from Thermo Fisher Scientific India Ltd., Mumbai. Sodium chloride was procured from Nice Chemicals (P) Ltd. Potassium hydroxide was obtained from SD Fine Chem Ltd. Tween 20 was obtained from Thomas Baker. Ethanol was obtained from the Drugs Testing Laboratory, Bengaluru.

PREFORMULATION STUDIES

Solubility of Curcumin, PU, and PVP

The solubility of curcumin was investigated in water, ethanol, tetrahydrofuran, dimethyl sulfoxide, acetonitrile, and phosphate-buffered saline (PBS) at pH 6.8 and pH 7.4, as well as in PBS with 1% Tween 20 at pH 6.8 and pH 7.4. The solubility of polyvinyl pyrrolidone and Pellathane Polyurathane-2363-80 AE was carried out in water, ethanol, and tetrahydrofuran.

Melting point of Curcumin

The melting point of curcumin was determined using the Lab India visual melting range apparatus as per the United States Pharmacopeia (USP) open capillary tube method.

Antimicrobial Activity of Curcumin

Antimicrobial activity of curcumin using the disc diffusion method against 6 CRBSI-causing organisms, *P. aeruginosa*, *E. coli*, *S. aureus*, *A. baumanii*, *K. pneumoniae*, *S. mutans*, *and C. albicans* was carried out. The positive control used was Ciprofloxacin, and the blank was phosphate buffer pH 6.8 with 1% of Tween 20.

Assay & identification of Curcumin

The identification and assay of total curcuminoids were performed using a newly developed HPLC method. The developed method was validated as per ICH guidelines. The chromatographic condition is given in Table 1.

Table 1: Chromatographic conditions for the estimation of Curcumin by HPLC

CHROMATOGRAPHIC CONDITIONS	
HPLC system	Shimadzu UFLC DGU–20A 5R
Column	250X4.6 µm Octadecylsilane column
Wavelength	425 nm
Detector	UV
Flow rate	2 ml/min
Mobile phase	Acetonitrile & 2% Acetic acid [400:600]
Inject. volume	20 µl
Temperature	30ºC
Solvents	Phosphate Buffer pH 6.8, DMSO, Tetrahydrofuran, Acetone, Acetonitrile, and Dimethylformamide.

COMPATIBILITY OF CURCUMIN WITH SOLVENTS AND POLYMERS

The compatibility and stability of curcumin when mixed with PU and PVP were assessed using chromatographic techniques (HPLC), scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) [33,34,36,37].

Chromatographic Technique (HPLC)

Curcumin, polyvinylpyrrolidone, and PU were dissolved in tetrahydrofuran. The solution was further diluted with PBS (pH 6.8) containing 1% Tween 20. The samples were stored for 5 days. The samples were analyzed using the HPLC method on days 1 and 5, as described in the Assay of Curcumin. For assessing compatibility, the chromatograms of the mixtures were compared with those of the pure component, focusing on peaks, retention time, and the area of the curcumin peaks, as well as the peaks of curcumin mixed with polymers.

Scanning Electron Microscopy [SEM]

The drug-mixed polymers were coated onto the CVC tubes made of polyurethane using the dip-coating technique. The uncoated & coated catheters were visualized using a SEM electron microscope with an accelerating voltage of 100 KV and magnification up to 10.00KX to observe morphological features.

Fourier-Transform Infrared Spectroscopy (FTIR)

The IR spectra of Curcumin, PU, PVP, Curcumin mixed with PU, and Curcumin mixed with PVP were recorded on a Shimadzu, Japan, in the wave band from 400 to 4000 cm^{-1} by accumulating 32 scans at a resolution of 4 cm^{-1}.

Combined Differential Scanning Calorimeter and Thermogravimetric Analysis [DSC-TGA]

The thermograms of curcumin, polymers, uncoated PU catheters, and coated ones were recorded in a DSC-TGA instrument TA module (Waters) SDT 650. The thermograms were determined under nitrogen gas at temperatures ranging from 25°C to 600°C with a heating rate of 10°C/min. Enthalpy, peak temperature, weight loss, and residue obtained were determined to assess the compatibility between the drug and polymers.

Optimization of drug and polymer concentrations

Various concentrations of PVP and PU were tried, keeping the concentration of the drug constant. Based on the initial screening studies, the parameters focused on are coating uniformity, various concentrations of coating solution of drug and polymer, uniformity in the dispersion of coating solution, dipping, withdrawal speed, and contact time of catheter in the coating solution, intermittent stirring of coating solution, drying procedure, and drying temperature, etc.

FORMULATION OF DRUG-COATED CATHETERS

In the formulation of drug-coated catheters shown in Figure 1, a two-layer coating was adopted. One is a base coat of PU and a top coat of PVP over the base coat. Five formulations were developed using the dip coating technique by changing the polymers and concentrations [38-42]. PU granules and Curcumin were dissolved in tetrahydrofuran separately. PVP was dissolved in ethanol. The curcumin solution was transferred dropwise to the PU solution and PVP solution with constant stirring. The mixtures were stirred to form uniform solutions. Seven French triple-lumen catheters, each 17 cm in length, were given a base coat of PU and Curcumin with the help of a metallic guide wire. The dried catheters were given a top coat of PVP & Curcumin over the base coat of PU and Curcumin similarly. The concentration of curcumin and polymers is given in Table 2.

EVALUATION OF COATED CATHETERS

Coating uniformity with microscope & Surface texture by scanning electron microscopy [SEM]

The coated catheters were evaluated according to the requirements outlined in ISO guidelines [43-44]. Any pinholes or physical deformities on the coated surface were assessed under a high-resolution microscope. The surface texture and uniformity of the coating were evaluated using SEM. The uncoated and coated catheters were visualized using a SEM with an accelerating voltage of 100 kV and magnification of up to 10,000X to observe their morphological features.

Table 2: Details of the formulations with concentration of Curcumin, PU & PVP in top coat and base coat

Formulation	Weight Of PVP (Top Coat) (Gram)	Weight Of PU (Base Coat) (Gram)	Weight Of Curcumin In Top Coat (Gram)	Weight of Curcumin In Base Coat (Gram)
A	5	10	5	10
B	5	15	5	10
C	5	17.5	5	10
D	5	20	5	10
E	5	25	5	10

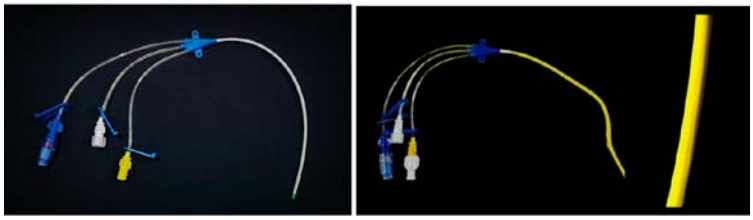

Figure 1: Uncoated catheter and Catheter coated with top coat of drug & PVP, base coat of drug and PU.

Coating thickness by laser measuring head

The thickness of the catheter tubes at the distal, middle, and proximal ends was measured before and after coating using a sophisticated laser head measuring instrument [43].

Tensile strength by a universal testing machine

A universal testing machine was used to measure the tensile strength of the coated catheters [44].

Radio opacity of the catheter with X-ray

One of the catheter's key characteristics is its capacity to be located by X-rays through the circulatory system. The Pellathane grade polyurethane contains 20% barium sulfate, which acts as a radiopaque agent and aids in finding the catheter during insertion and implantation within the blood vessels. The coated catheters were subjected to radio-opacity testing according to ISO guidelines and ASTM guidelines using an X-ray machine [44-46].

Drug content estimation by ultraviolet spectrophotometer.

The amount of the drug loaded onto the coated catheter was estimated using a UV spectrophotometer [47]. The coated catheters were cut into small pieces and dissolved in THF. Further dilutions were made using PBS with 1% Tween 20, pH 6.8, and the standards and samples were estimated by UV spectroscopy at 425 nm.

***In vitro drug release studies and* estimation by UV spectrophotometer**

The amount of drug released in vitro was estimated using a UV spectrophotometer from day 1 till almost 90% of the coated drug is released from the catheter [39-42, 48-52]. The coated catheter was cut into small pieces. PBS with 1% Tween 20, pH 6.8, was added and continuously stirred using an auto-shaker at room temperature at a lower rpm. At the end of every 24 hours, the solution was filtered using a 0.22 µm Whatman filter paper. Fresh media was added to maintain sink conditions. The standard and sample solutions were estimated by UV spectroscopy at 425 nm. The procedure was repeated every 24 hours till all the drug released was calculated. Cumulative drug release was calculated.

Statistical analysis

The mathematical models, including the zero-order, first-order, Higuchi model, and Korsmeyer-Peppas model, were fitted to the data to study the kinetics of in vitro drug release.

RESULTS AND DISCUSSION

Preformulation Studies

The melting point of curcumin was found to be 183°C. The developed HPLC method conformed to the parameters outlined in the ICH guidelines and was instrumental in studying the compatibility of the drug and polymer. Zone of inhibition studies of curcumin demonstrated antimicrobial activity against all six major blood infection-causing organisms. The antibacterial effects of curcumin are attributed to a range of molecular mechanisms. Cell membrane degradation, changes in the plasmid gene expression, inhibition of DNA replication, and decreased motility are a few examples of these mechanisms [14].

This antimicrobial action is attributed to the inherent ability of Curcumin to suppress the QS system, thereby acting on host receptor cells to prevent bacterial adhesion of *P. aeruginosa, S. aureus, A. baumannii, H. pylori*, and other organisms in biofilms [53]. The changes in the lipid content of the fungal membrane induced by curcumin ultimately lead to the generation of reactive oxygen species, causing early apoptosis of C. albicans. In C. albicans, curcumin damages the cell wall and causes membrane permeabilization by downregulating genes involved in the cell wall integrity pathway [54]. Solubility studies helped in selecting suitable polymers and corresponding solvents for the research.

Compatibility of curcumin with solvents and polymers

By high-performance liquid chromatography

The physical and chemical stability of the drug and excipients, when determined using RP-HPLC, was found to be satisfactory [37, 55]. There is no difference in colour and texture between the test samples and those stored under ambient conditions. HPLC studies indicated that there were no interactions between the drug and the selected excipients at a temperature of 40°C for 5 days, indicating the compatibility of all chosen excipients with the drug substance. The results are given in Table 3, and the chromatogram is shown in Figure 2.

By Scanning Electron Microscopy: SEM analysis confirmed the successful coating with a smooth and uniform surface in all the formulations. SEM analysis confirmed the maintenance of morphologies of both the drug and excipient particles, as well as the uniform dispersion of drug particles on the surface of polymer particles [37]. This indicates a high level of compatibility between drugs and polymers. Figure 3 represents the SEM images of coated catheters and uncoated catheters.

Table 3: Results of Compatibility studies of the drug when mixed with excipients by HPLC

PARAMETERS	RESULT
Peaks, RT, area of Curcumin	Peaks of Curcumin with polymers did not show a difference.
Deformity	No deformity was observed in the peaks of Curcumin and Curcumin mixed with polymers.
Interaction	No interaction between Curcumin & used excipients when stored at 40ºC for 5 days
Additional Peaks	No peaks were identified that could be associated with degradation products.
Recoveries and % RSD	The % RSD & recoveries were very much in agreement with that of the respective pure drug
Sharpness and symmetry	Established peaks' parameters were well maintained, endorsing the compatibility.

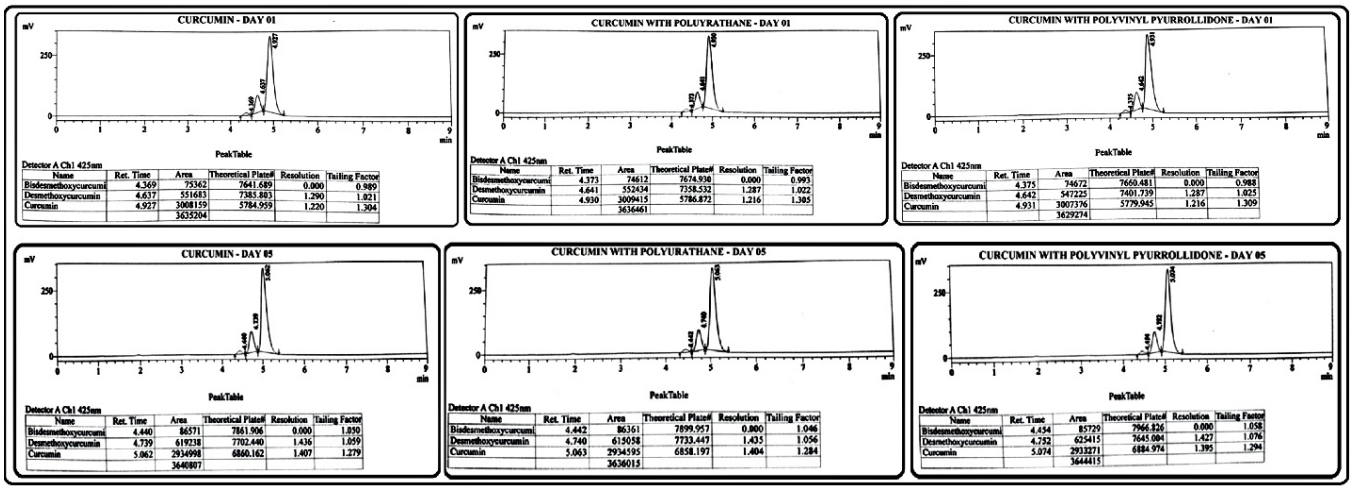

Figure 2: HPLC chromatograms of Curcumin, Curcumin mixed with PVP, and Curcumin mixed with PU on 1st and 5th day

By Fourier Infrared spectrophotometer: The FTIR spectra of curcumin, curcumin mixed with PU, and curcumin mixed with PVP showed OH stretching vibration and CH2 stretching observed at 3448 cm^{-1} and 2920 cm^{-1}, respectively. Mixed vibration of (C=O) and (C=C) showed a strong peak at 1630 cm^{-1}. Symmetric aromatic ring stretching vibration (C=C) observed at 1602 cm^{-1}. Stretching vibration of aromatic ring between 1600 and 1400 cm^{1}. (C-O-C) and benzonate trans (-CH) vibration at 1281 cm^{-1}, 1033 cm^{-1}, and 959 cm^{-1}. The development of urethane linkage is demonstrated by the C-N stretching and N-H deformation vibration represented by the band around 1530 cm−1 [56]. The FTIR spectra of the drug and polymers showed no change in the positions of the characteristic bands, supporting the compatibility between the drug and polymers [37]. Figure 4 represents the FTIR spectra.

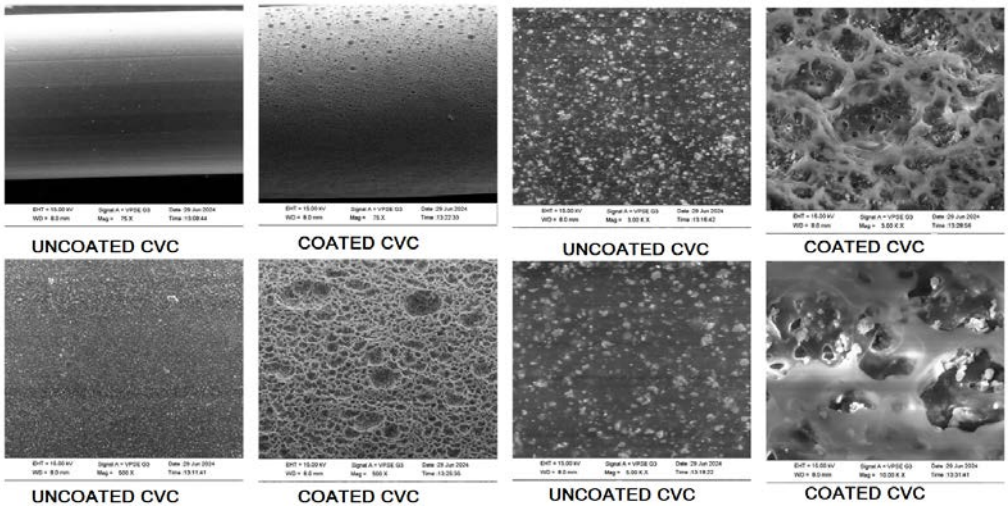

Figure 3: Scanning electron microscope images of uncoated catheter surface and catheters coated with drug, PVP & PU as base coat and top coat.

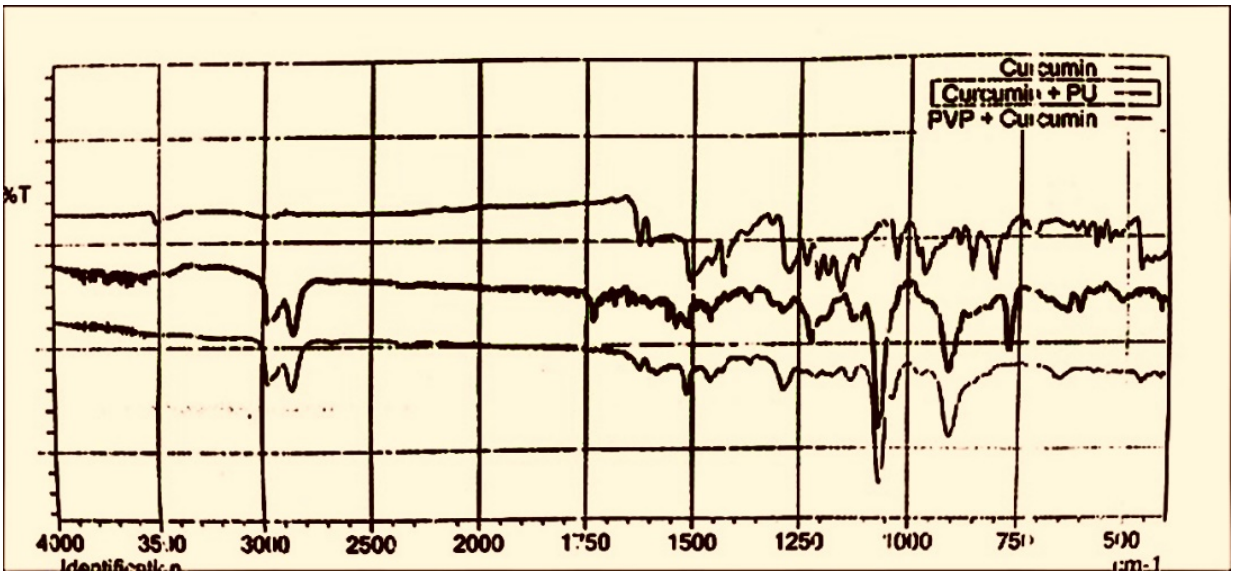

Figure 4: FTIR spectra of Curcumin, Curcumin mixed with PU, and Curcumin mixed with PVP

By Differential Scanning Calorimetry and Thermo Gravimetric Analysis

The TGA curve of curcumin indicates single-stage decomposition, whereas the uncoated catheters, polymer mixture, and coated catheters exhibit a multi-stage degradation without any intermediates. There was no chemical reaction between the drug and the additives, as evidenced by the absence of distinct degradation zones between the polyurethane with and without additives [57]. There is no significant shift in degradation temperature compared to the pure drug, suggesting no interaction between the drug and other formulation ingredients. The thermograms are given in Figure 5.

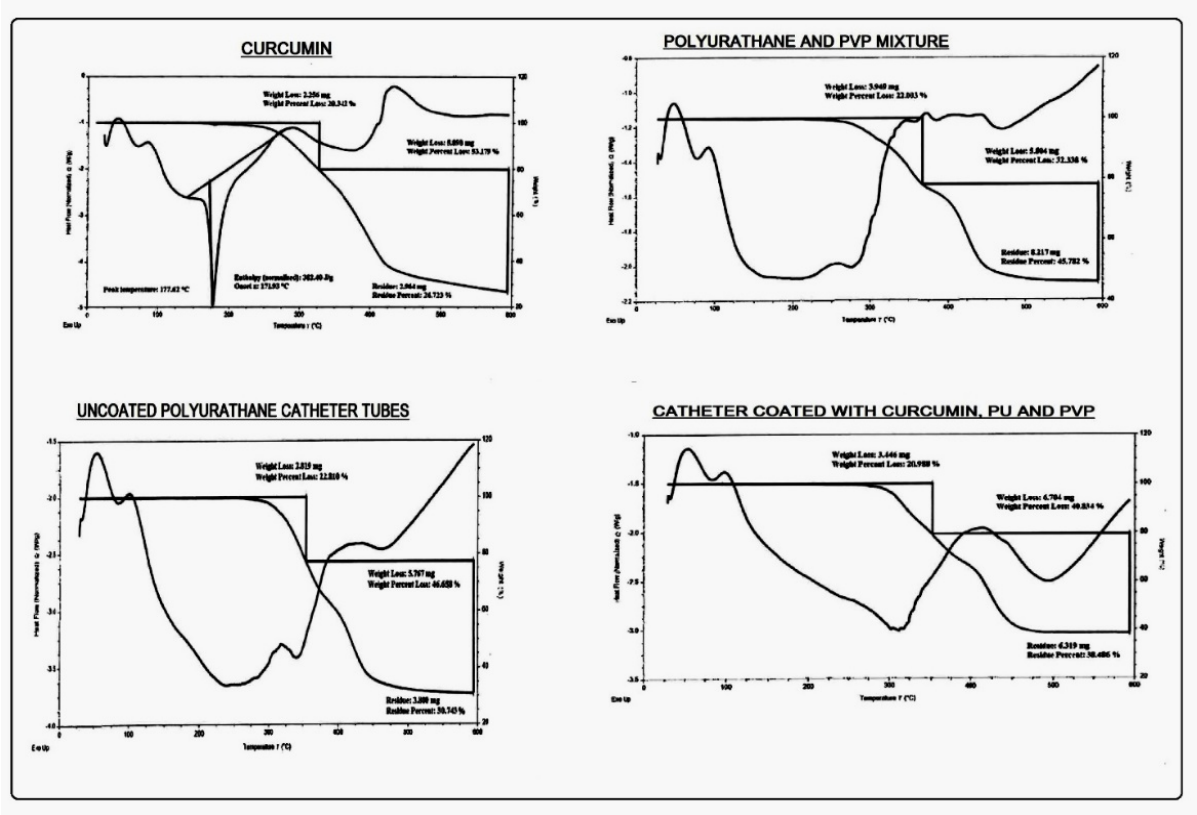

Figure 5: The DSC-TGA thermograms of Curcumin, PU & PVP, uncoated PU catheter and catheter coated with Curcumin, PU & PVP

EVALUATION OF COATED CATHETERS

The dip coating technique was found to be successful, as the coated catheter surface was devoid of defects, and the catheters showed uniform coating [34]. SEM analysis confirmed the successful coating with a smooth and uniform surface. The uniformity of coating depends on the various variables like concentration of coating solution, uniformity in the dispersion of polymers in coating solution, dipping and withdrawal speed of the catheter from the coating solution, contact time of the catheter in the coating solution, intermittent stirring of the coating solution, drying procedure, and drying temperature [58]. As the concentration of polymers increased, the viscosity of the solution also increased, leading to the formation of a thick layer, more drug loading onto the catheter surface, and vice versa. At concentrations above 35% of PU, a highly viscous solution was formed, and a uniform coating could not be achieved. The chances of creating a rough surface were higher when the polymers were not dispersed uniformly.

The dipping and withdrawal speeds of the coating machine were found to be crucial parameters in achieving uniform coating and optimum drug loading. A slower dipping speed results in the formation of a thick layer, whereas a higher dipping speed leads to the formation of a thin layer. A slower withdrawal speed results in the formation of a thin layer, whereas a higher withdrawal speed leads to the formation of a thicker layer [58-60]. By maintaining the optimum dipping and withdrawal speeds, a uniform surface and optimal drug loading can be achieved on the catheter surface. As the contact time of the catheter inside the coating solution was longer, a thicker coating and more drug loading were observed [58]. When the catheter was withdrawn immediately after reaching the bottom, a uniform coating surface with the desired drug loading was obtained. Keeping the coating solution uniformly dispersed throughout the coating procedure was crucial [58]. When the solution was not stirred intermittently, the dispersed particles settled to the bottom and formed a thick, more viscous solution. This, in turn, led to the formation of a thick layer at the bottom end of the catheter. Once the catheters are coated, the drying procedure and temperature play a crucial role in maintaining a uniform coated surface. When the coated catheters were dried immediately after coating in a hot air oven at 45°C, followed by natural drying, the entrapped air bubbles escaped to the surface of the coating, forming a non-uniform granular air bubble surface on the catheter. The ideal procedure for drying the coated catheters involved natural drying for 24 to 36 hours, depending on the polymer concentration used, followed by drying in a hot air oven at 40°C for 20 minutes, and then allowing the catheters to dry naturally for an additional 6 hours. The higher the concentration of polymer, the longer the natural drying time, and vice versa [58, 61]. The exact drying procedure is followed after the application of the top coat of PVP. The thickness of the coated catheters was within the ISO limits. The thickness depends on the concentration of the polymer solution, dipping, withdrawal speed, and contact time [58]. The tensile strength of the coated catheters, measured using a universal testing machine, was within the ISO limits. The thickness of the catheter increased after coating. This significant difference in thickness influences the tensile properties of the material [62]. The coating procedure examined in this work, however, had no impact on the structural integrity or mechanical characteristics of the coated catheter. Higher tensile strength and elongation can result from a smoother surface coating than from a rougher one [63]. The results of the representative samples, measured using the universal testing machine, are presented in Table 4.

Table 4: Results of Tensile strength of the coated formulations as per ISO.

	SAMPLES									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
A	70 N	68 N	60 N	48 N	64 N	39 N	30 N	62 N	44 N	32 N
B	56 N	71 N	UN CUT	36 N	29 N	49 N	64 N	39 N	51 N	42 N
C	UN CUT	61 N	56 N	43 N	34 N	47 N	33 N	70 N	61 N	38 N
D	64 N	57 N	62 N	60 N	63 N	41 N	29 N	33 N	24 N	76 N
E	63 N	70 N	68 N	54 N	29 N	68 N	60 N	36 N	28 N	25 N

Radio opacity of the catheter with X-ray

The coated catheters, when tested using an X-ray machine, showed radioopacity due to the presence of 20% barium sulfate in the Pellathane grade PU, which facilitates ease of insertion during implantation. The X-ray image of the coated catheter is given in Figure 6.

Radiopaque catheters enable healthcare professionals to guide the catheter during procedures, preventing unintentional damage or harm to vessels and ensuring the catheter is positioned correctly [46, 64].

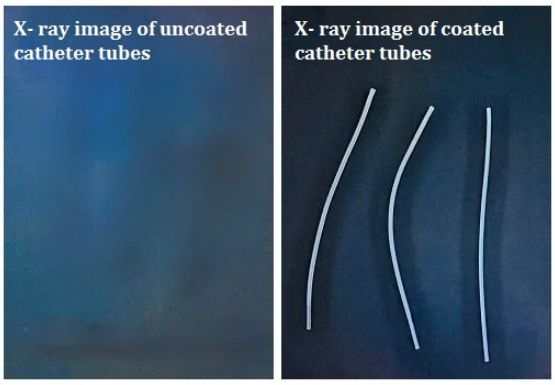

Figure 6: X-ray image of uncoated and coated catheter for distinguishing the radio opacity after coating

In-vitro drug release studies

In-vitro drug release was performed till 90% of the drug is released from all the formulations. All the formulations showed an initial burst release [A-17.71%, B-14.71%, C-14.05%, D-11.51% & E-9.40%] at the end of 24 hours. In all the formulations, the drug release after the initial burst release declined, reached a steady state, and declined as time elapsed. The burst release was attributed to the greater water solubility of PVP used in the top coat [65,66], as well as to the diffusion of some amount of drug from the base coat of polyurethane. The cumulative percentage drug release of the coated CVC is shown in Figure 7.

The formulation A with 10% of the PU showed sustained release of 93.47% of the drug up to 7 days, formulation B, C, D & E with 15%, 17.5%, 20% & 25% of PU showed 92.33% of the drug up to 10 days, 92.02% of the drug up to 11 days, 96.12% of the drug up to 15 days and 94.17% of the drug up to 21 days respectively. The formulation represents a monolithic system where the Polyurethane matrix was used to disperse the drug [67]. Pellethane™ 2363-80AE polyurethane is a category of non-swelling thermoplastic polymer designed to withstand a variety of conditions, including certain solvents and fluids, without experiencing appreciable swelling or distortion while retaining its structural integrity and physical characteristics. This non-swelling property influences the prolonged release of the drug [67]. The sustained release of the drug is attributed to the concentration of the polymer used in the base coat. As the concentration of the polymer in the base coat increases, more drug loading on the catheter surface and a more sustained release are observed. The sustained release is due to the slow diffusion of the drug from the PU reservoir [68]. This slow release of the drug, in turn, will help the catheter to exhibit surface antimicrobial action for the entire duration of implantation. Above a concentration of 35% PU, a uniform coating could not be achieved. With formulation E, which contains 25% PU, optimal drug release was achieved over the optimal duration.

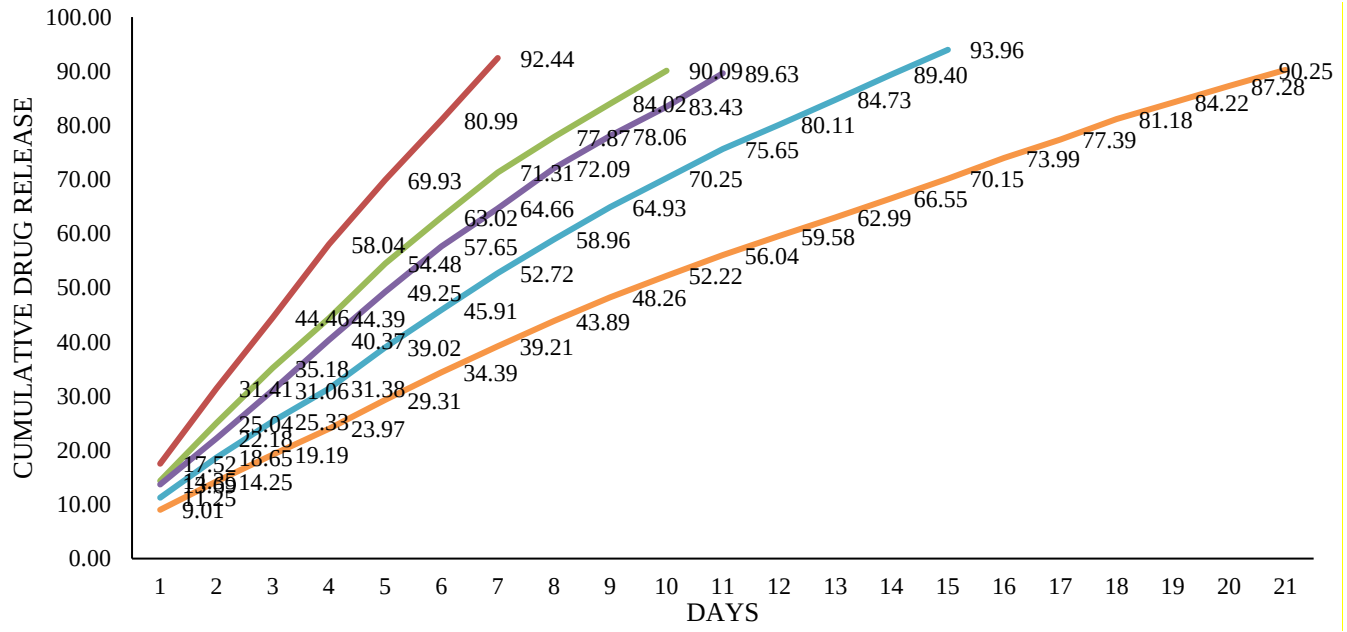

Figure 7: In vitro drug release of coated catheter in Phosphate buffer with Tween 20 showing release of almost 90% of drugs up to 21 days

Statistical analysis

Based on R^2 values in zero-order release kinetics, the formulation follows zero-order kinetics. In the Higuchi and Korsmeyer pepas model, the R^2 values are 0.9674 to 0.9909, which is nearer to 1, indicating mainly the diffusion process [69]. The results are shown in Figure 8. Kinetic data fit for the Korsmeyer-Peppas model. The n value for the coated catheters with PU concentrations of 10%, 15%, 17.5%, 20%, and 25% was 0.334, 0.389, 0.341, 0.4051 & 0.2892, respectively, which is <0.5. Based on the "n" values given in Table 5, the formulations show quasi-Fickian release [70]. Quasi-Fickian release is a diffusion-controlled process that describes the release of a material from a matrix using a combination of diffusion and other processes [71]

Table 5: Details of the release kinetics of formulations fitted in to zero order, first order, Higuchi and Korsmeyer peppas models.

TYPE OF RELEASE KINETICS	10%	15%	17.50%	20%	25%
	R^2	R^2	R^2	R^2	R^2
Zero Order	0.9909	0.9721	0.9752	0.9754	0.9674
First Order	0.9484	0.9804	0.9388	0.9208	0.912
Higuchi Model	0.921	0.936	0.9307	0.9252	0.9315
Korsmeyer Peppas Model	0.926	0.8921	0.8988	0.8854	0.8666
n Value	0.334	0.389	0.341	0.4051	0.2892

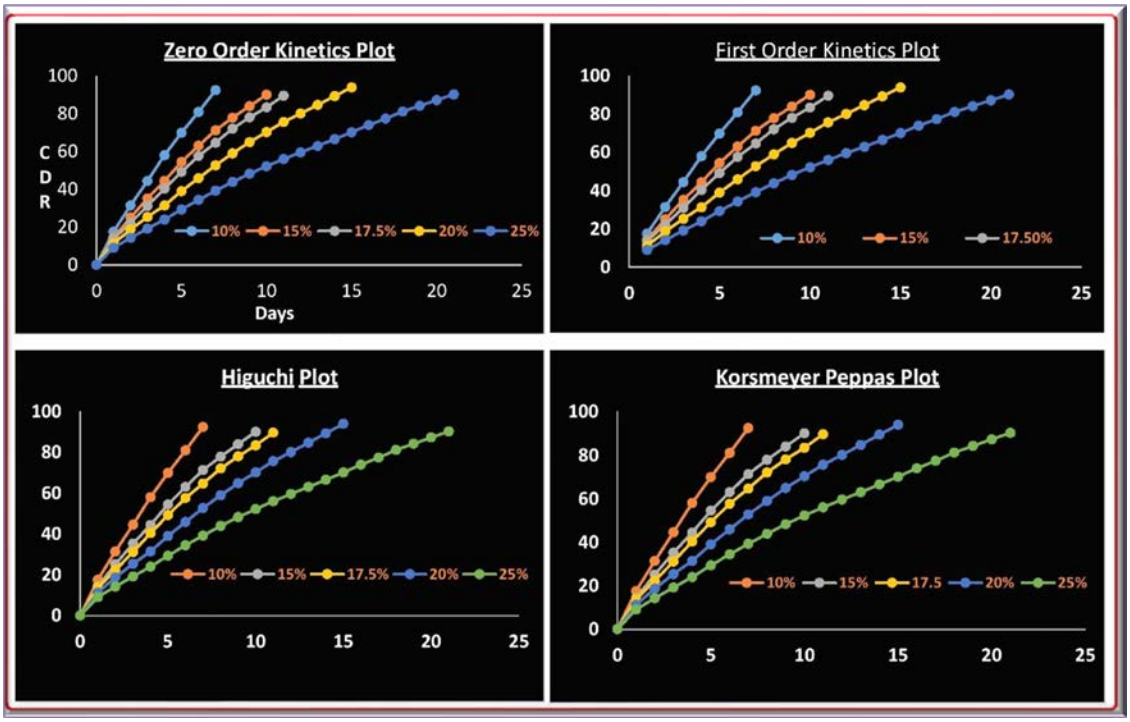

Figure 8: Kinetics of drug release fitted into zero order, first order, Higuchi, and Korsmeyer-Peppas models

CONCLUSION

CRBSI developed due to the usage of uncoated CVC carries a high chance of developing sepsis and subsequent death when compared to any other category of medical devices. The current study has demonstrated the development of antimicrobial Curcumin-coated CVC through an advanced and cost-effective dual-coating technique over PU catheters. The dual coating consists of a base coat comprising a drug and PU, and a top coat comprising a drug and PVP. This coating technique demonstrated that all physical variables and the final results of the coated CVC comply with ISO norms. Uniform distribution of the drug and polymer was indicated by surface analysis. The coating is firmly attached to the catheter when coated using this technology. The variables impacting the drug loading and

uniform coating were optimized. All the formulations showed an initial burst release within 24 hours, which could prevent the initial lodging of microorganisms on the surface of the CVC and is a prime requirement when the catheter is implanted. The sustained release of the optimized coated catheter for 21 days may help prevent the formation of biofilm and thus prevent subsequent CRBSI for the duration of implantation.

The positive results obtained in this study suggest that curcumin-coated catheters have the potential to reduce CRBSI, which in turn can lead to reduced costs associated with prolonged hospital stays, frequent catheter replacement, vessel damage during catheterization, subsequent sepsis, and a lower mortality rate. The CVC falls under category B of the ISO 10993 standards for exposure. i.e., prolonged exposure (likely to exceed 24 hours and less than 30 days) [72]. Hence, to overcome the limitations of this study, further attempts should be made to modify the coating technique to provide sustained drug release for at least 30 days after implantation, as per the ISO guidelines. Building on the encouraging results from the present study, future studies exploring ex vivo antimicrobial activity against standard and established catheter-related bloodstream infection-causing microbes, as well as biocompatibility, cytotoxicity, biofilm inhibition, biofilm eradication, and accelerated stability studies, are in progress.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Nissara Ahammed took the lead in conducting the laboratory studies, recording observations, and contributed to drafting the manuscript. Revathi Sundaramoorthi and Venkatesh Dinnekere Puttegowda analyzed and interpreted the design of experiment data related to work, performed the statistical analysis, and reviewed the articles and research work. Umashankar Chikkanna helped with the conceptualization and bibliography. All authors provided critical feedback and contributed to shaping the research, analysis, and manuscript.

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