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Refining early stage interventional composite catheter design

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Abstract

The development paths of interventional medical devices are long and involve a significant numbers of iterative design steps. Composite interventional catheters deliver implants, facilitate the deployment of delicate therapeutic instruments, measure pressures and temperatures and can remove clots and foreign bodies. This paper summarizes the history of composite interventional catheters and the key evolutions in terms of materials and reinforcement structures. The current design practices, performance standards and general guidance available to assist composite interventional catheter design are reviewed. The environmental factors that affect the companies in which many of the leading edge interventional composite catheter designs are developed are also examined. A Predictive Modelling Framework is proposed to guide the design of composite interventional catheters to meet the key user needs. Two distinct but compatible methodologies are selected: The first method involves use of a DOE (Design of Experiments) approach to understand the influence of key variables on final catheter properties; The second involves the creation of customizable Finite Element models of the various potential catheter structures. The results of the predictive model constructed based on the DOE approach for braided composite catheters are presented and compared with experimental data. The DOE shows good alignment with experimental data in most cases. The sources of noise and error in the initial model are examined and potential improvements and learnings are discussed, with special focus on the results with poorer alignment.

Keywords: "Composite catheters; Medical device design; Design of experiments; Early stage concept development"

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1.0 Background:

In 1929 Werner Forssmann passed a lubricated ureteral catheter into his heart using a venous puncture of his left arm and is recognised as the first person to document human right heart catheterization.[1] Andre Cournard; working with Dickenson Richards of Columbia University began to systematically catheterise the right side of the heart in early 1940's.[2] The catheters they used were composed of an inner framework of fabric covered with polyvinyl chloride with comminuted tin added for radiopacity.[3] These catheters are recognised as the first composite interventional catheters used in clinical practice. Cournard, Richards and Forssmann were awarded the Nobel Prize for Medicine in 1956 for their collective contributions to cardiac catherisation.[4]

Fig 1. Pebax based braid and coil reinforced interventional composite catheters 5-10Fr range (1.7-3.3mm outer diameter). [5]

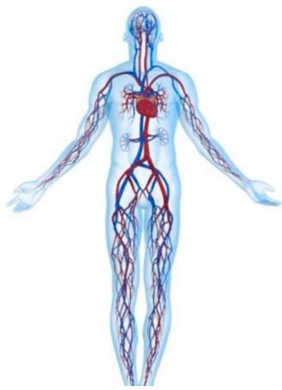

Fig 2. Human vascular system; navigated by composite catheter based interventional devices.

A patent was granted to Robert Stevens and Cordis Corporation in December 1969 for a braided catheter using steel wire.[6] This design exhibited excellent torqueability, high burst pressure and provided radiopacity through the use of bismuth subcarbonate milled into the polyurethane prior to extrusion. The tip section contained no wire which improved shape retention and softness[7]. Patents for coil reinforced sheath technology for vascular access began to appear in mid-1980's.[8] Today the majority of composite interventional catheters feature either braid, coil or a combination as the reinforcing layer. Improvements in catheter design, materials and fabrication techniques have both facilitated and enabled new therapies in the neurovascular,[9] endovascular,[10] and cardiovascular[11] interventional areas.

2.0 The current challenges of Interventional composite catheter design

Interventional catheters use the vascular system (see Fig. 2) to access a particular location for a diagnostic or therapeutic treatment. Performance requirements for composite interventional catheters used in different therapeutic areas are similar. However, the literature around catheter-based devices is written from a disease state or clinical viewpoint so this commonality in terms of catheter technology cannot be effectively examined by literature review. This lack of a meaningful body of knowledge, partially explains the tendency towards iteration based design that predominates in the development of catheter based devices. The current fragmented strategies by individual companies have been identified as unsustainable and a cause of increasing costs and timelines from bench to bedside for new medical devices.[12]

A second factor relates to the limited availability of standards. The area of intravascular catheter design has a single ISO standard (ISO 10555-1-6:2013) in terms of guidance for standard functional requirements.[13] This standard provides guidance on tensile strength testing for reinforced vascular catheters. Flexural modulus (ISO178:2010) and flow rate (ISO11070-1-2013) can both be tested against other recognized standards, but other characteristics such as torquability, torsional response, kink and pushability have no guidance in terms of ISO standards. The FDA have provided guidance specific to intravascular stents and their delivery systems.[14] This guidance is mainly in relation to balloon based systems but the flexibility, kink resistance, torque and catheter bond strength guidance can be applied to interventional composite catheter development. This lack of standard test methods compounds the issue with codification of catheter design knowledge.

A third point is that much of the early stage R&D in medical devices is dominated by individuals, usually in academic or clinical settings who are involved in the development of new technology in their respective fields. [15-17] These user innovators have been shown to produce inventions that have higher technical importance and greater impact than corporate inventions in the same area.[18] Larger, more established firms play an important part later in the development process (often through acquisition of the start-up companies).[16] It could be argued that many major medical device companies are effectively outsourcing much of their early stage R&D to start-up companies.[19] [20]

For smaller start-up companies particularly clinically focused ones, a vibrant ecosystem is required to support their needs.[21, 22] Often with catheter-based devices, the start-up's technical expertise is focused on their core differentiated technology (an implant or a unique technology in terms of the therapy or treatment delivered). These companies need to partner with specialist medtech suppliers to develop the catheter based delivery system.[23] The fragmented nature of these relationships means no strong body of knowledge on interventional composite catheter design has evolved within the medical device industry.

Due to the nature of device regulation, companies seek to have a high level of confidence that the device design concept is largely proven before entering formal design control. Much of the crucial design work happens before the design cycle formally begins (from a regulatory viewpoint). This results is a situation where a lot of concepts are effectively developed, refined and proven at a "Phase 0" or "Pre-Design Stage". Generally, limited or relatively minor changes occur once the selected concept proceeds to formal design control.

Computer simulation and modelling; finite element analysis (FEA) and computational fluid dynamics (CFD) in the area of vascular devices has been examined by Morrison.[24] FEA [25-28] has been described widely as a practice usually in relation to metal-based components. Zhang[25] is one of the few who has applied it to composite catheter design. Design of experiments (DOE) [29-31] has been employed as an early stage design tool and aid to predictive modelling within the medical device design space. In 2016 the FDA issued guidance on the reporting of computational modelling studies for medical device design.[32] Guidance from the FDA on the verification and validation in computational modelling of medical devices is expected imminently.[33] This is expected to elevate computational testing to equal consideration, which bench, animal, and human testing currently receive.

3.0 Predictive Modelling Framework:

This paper describes the development of a predictive modelling methodology for early stage catheter design as an alternative to iteration based design. This tool will allow a set of user needs to be translated into an optimal theoretical design using fixed geometric constraints. This will reduce the number of design iterations and therefore reduce the cost and time of reaching an acceptable concept design.

Fig 3 shows the information flows and conceptual blocks of the Predictive Modelling Framework. It consists of two discreet feedback loops. The lower loop is focused on determining the catheter performance requirements (i.e. Tensile Modulus, Bend Stiffness etc.). The upper loop will take these catheter performance requirements and the geometric constraints and translate them into a set of catheter design inputs (i.e. Outer material durometer, braid wire size etc.). The catheter could then be built to this specification. Testing data could then be added to the model.

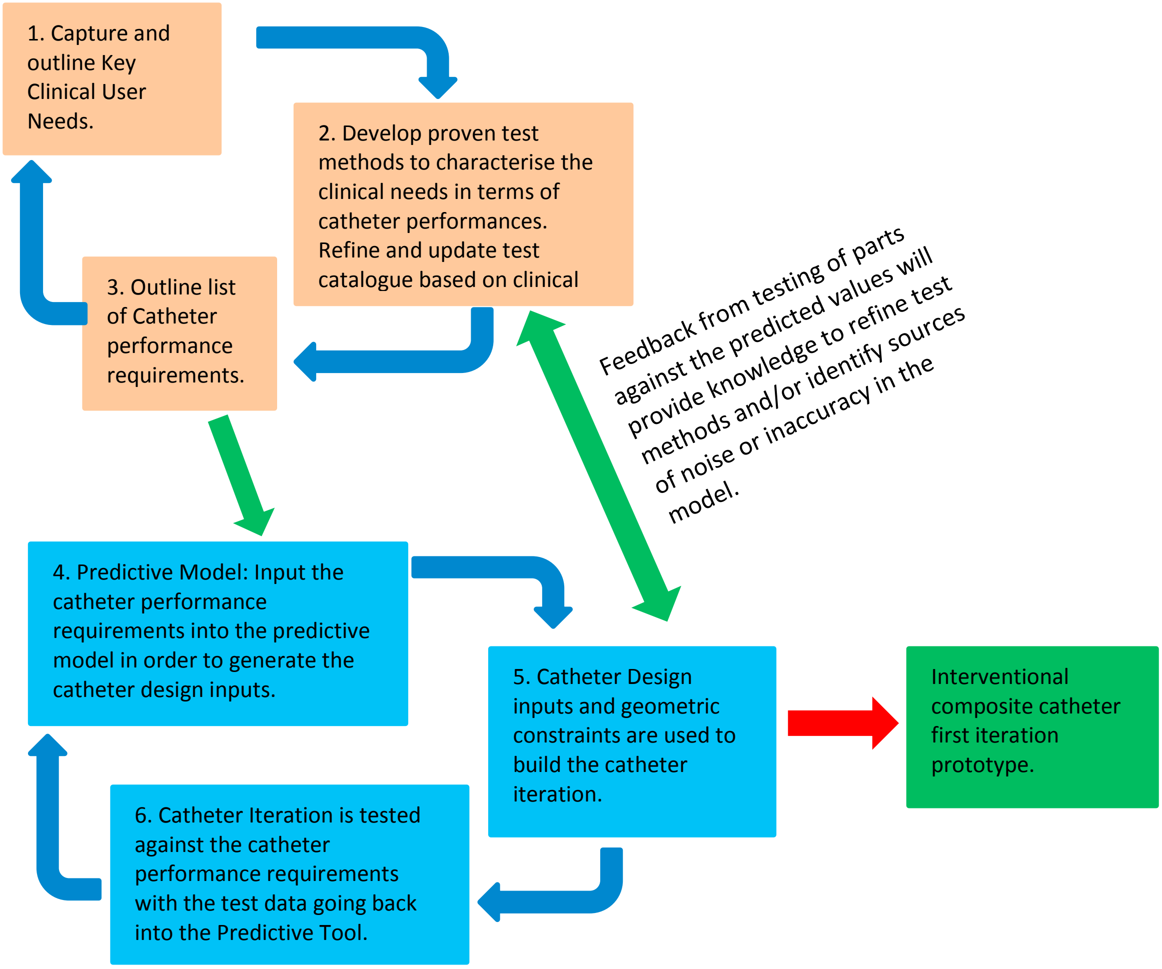

Fig 3. Information flow and discreet steps of proposed Predictive Model Framework.

4.0 Methods

This paper explores how well a preliminary predictive modelling approach based on classical design of experiments (DOE) compared to a baseline created by building and testing actual composite catheters. A second predictive modelling approach using finite element analysis (FEA) has been started and will be the subject of future work. Both the DOE and the FEA approach are being trialled based on their potential to become complementary components of a predictive modelling methodology for interventional composite catheter design.

4.1 Methods; design of experiments

JMP® Pro Version 11 software from SAS was used to design the DOE and analyse the test data. Five factors were chosen for the initial DOE to examine the braided composite catheters. These factors are shown in Table 1. The inner diameter of all catheter shafts examined was 2.30mm. A half-fractional design with 15 degrees of freedom was chosen. This allowed main effects and 2 way interactions to be examined. The liner material (PTFE), braid wire profile (flat), braid wire material of construction (304 stainless Steel) and outer material type Pebax® range (polyether-block-amide thermoplastic elastomer) were kept consistent across the initial DOE. Thin walled PTFE lined interventional composite catheters are the area of most commercial interest. The bulk of these types of catheters feature these 4 design characteristics.

Table 1 Factors selected for the initial half factorial DOE.

Factor	Description
Outer material Durometer	Grades between 74D and 25D are available within the Pebax® range. The higher the number the higher the durometer therefore the stiffer the material.
Wall Thickness	Key design characteristic for interventional composite catheters. Companies are generally trying to minimise it.
Braid Pattern	Standard & diamond patterns are used in braided catheter design. Both have same number of wire starts.
Braid Angle	The braid angle is the angle formed between a longitudinal axis (parallel to the tubing axis, which bisects the angle where the wires cross in the braid pattern) and the angle formed by the braid wire. As braid angle increases number of wire crossings per unit length reduces. Number of crossings per inch (PPI) is the control variable for angle in catheter braiding. In Table 2 Braid angle is being expressed as PPI.
Braid cross sectional area (CSA)	Different wire sizes and profiles can be used in braided catheter assembly. Often thin walled designs are attempting to maximise the braided materials cross sectional area for a specified wall thickness. This leads to use high aspect ratio rectangular cross section reinforcement shapes rather than round reinforcement shapes. In Table 2 below the CSA of 6452, 968 and 3226 microns were achieved with rectangular profiles of .051mm*.127mm, .013mm*.076mm and .025mm*.127mm respectively.

After completion of the screening DOE it was decided to add two centre point runs for the standard and the diamond braid configuration. This was done to improve the ability of the model to reflect the reality of the process. The DOE experimental design (including the midpoint runs) is shown in Table 2. The parts manufactured were tested using 7 validated test methods. The 7 test methods are listed in the first column of Table 3. Three data points were taken per run for each test.

Table 2 Braided Composite DOE Experimental Design.

Run No	Outer layer	Wall (mm)	PPI	Wire CSA (μm2)	Braid Pattern	Run No	Outer Layer	Wall (mm)	PPI	Wire CSA (μm2)	Braid Pattern
1	74D Pebax	.279	12	6452	Diamond	10	74D Pebax	.178	53	6452	Diamond
2	25D Pebax	.178	12	968	Standard	11	25D Pebax	.178	53	968	Diamond
3	25D Pebax	.178	53	6452	Standard	12	25D Pebax	.279	12	6452	Standard
4	74D Pebax	.279	53	968	Diamond	13	74D Pebax	.178	53	968	Standard
5	74D Pebax	.279	12	968	Standard	14	25D Pebax	.178	12	6452	Diamond
6	25D Pebax	.279	12	968	Diamond	15	74D Pebax	.178	12	968	Diamond
7	74D Pebax	.279	53	6452	Standard	16	25D Pebax	.279	53	968	Standard
8	74D Pebax	.178	12	6452	Standard	17	55D Pebax	.229	26	3226	Standard
9	25D Pebax	.279	53	6452	Diamond	18	55D Pebax	.229	26	3226	Diamond

5.0 Results:

The current predictive model is based on a half factorial DOE with midpoints, which ranged the five key interventional catheter design parameters described in Table 1. JMP® Pro software was used to fit a model for the data generated for each of the characteristics listed in Tables 3. The Prediction Profiler function was then used to create an adjustable model that could be configured to represent Baseline A and Baseline B. These configured versions of the profiler are shown as Fig 4 and 5 respectively. The results for both Baseline A and B are shown in Table 3.

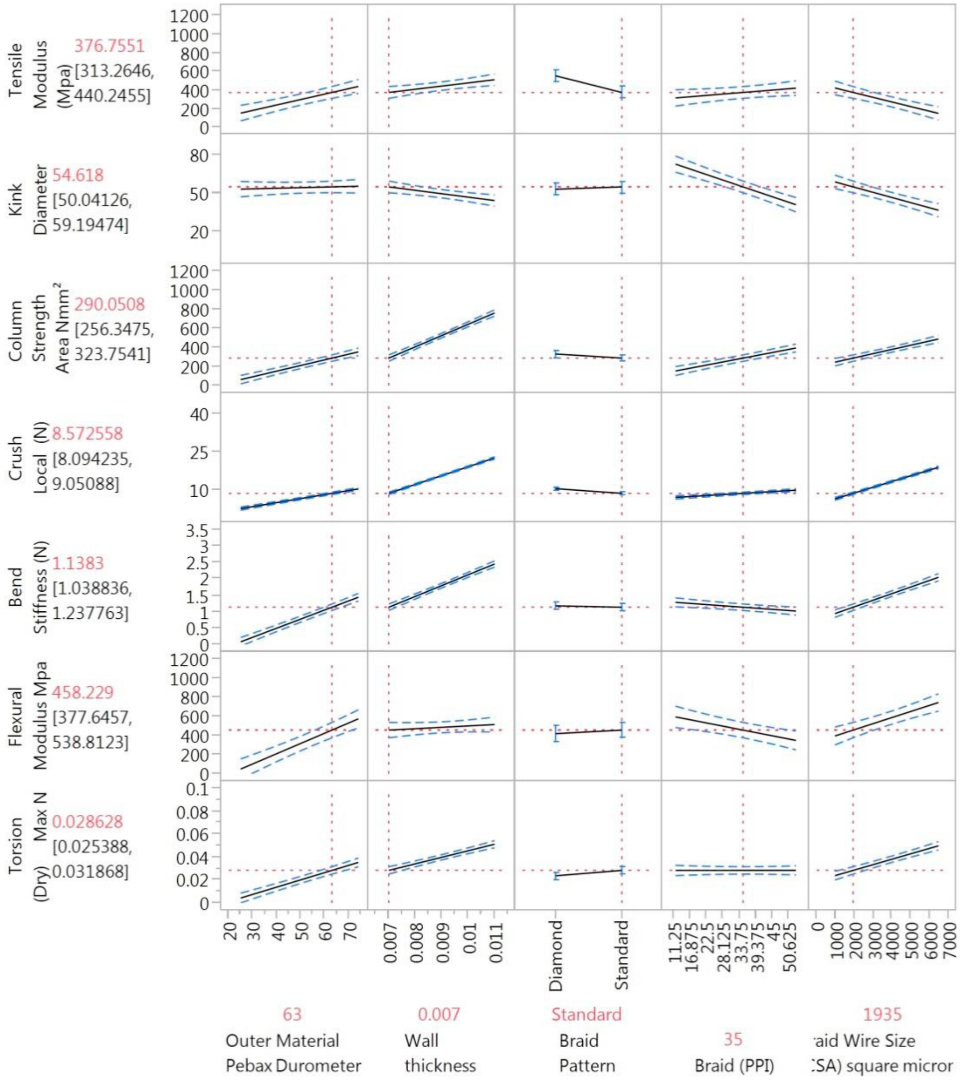

Fig 4. Prediction Profiler configured for Baseline A. Results for each of the 7 criteria shown along left hand side.

Table 3 Results for Baseline A and Baseline B design actual value versus predicted value.

	Baseline A		Baseline B	
Test Method	**Actual Value**	**Predicted Value (Percentage error)**	**Actual Value**	**Predicted Value (Percentage error)**
Tensile Modulus (MPa)	337.5	376.7 (12%)	363	404.5 (11%)
Kink Diameter (mm)	40.72	54.6 (34%)	33.27	29.4 (-12%)
Column Strength (N/mm²)	370.67	290.1 (-22%)	595.7	654.3 (10%)
Crush Resistance (N)	8.24	8.57 (4%)	16.2	20.4 (26%)
Bend Stiffness (N)	1.125	1.14 (1%)	1.89	1.85 (-2%)
Flex Modulus (MPa)	348.1	458.2 (32%)	369.4	418.3 (13%)
Torsion (N m)	0.026	0.0286 (10%)	0.0459	0.0486 (6%)

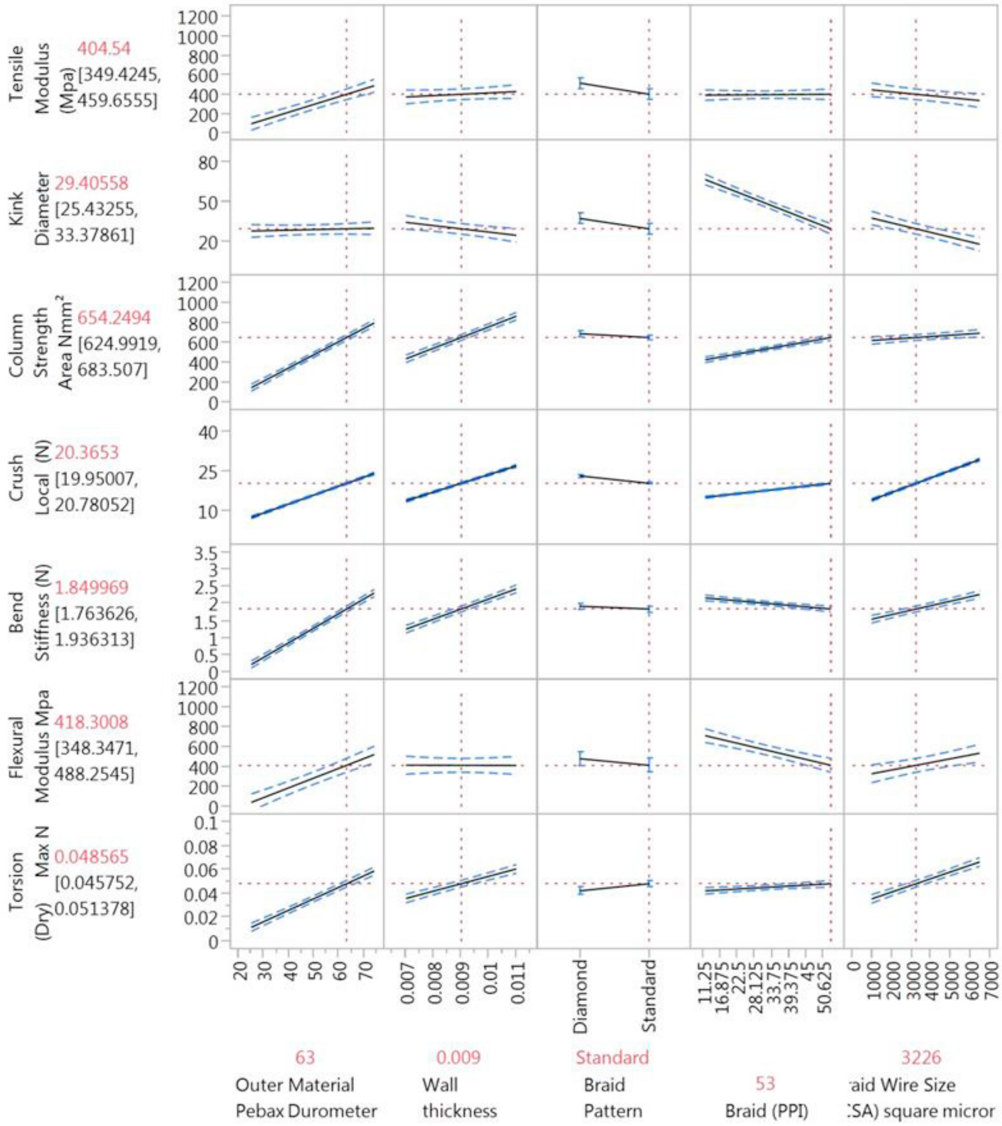

Fig 5. Prediction Profiler configured for Baseline B. Results for each of the 7 criteria shown along left hand side.

6.0 Discussion of Results:

At the concept stage of a composite catheter design, a design tool with the ability to predict a critical performance characteristic to an accuracy of +/- 20% would be of real value. This +/-20% is a practical yardstick based on AIAG guidance for measurement system analysis.[34] Review of Table 3 shows that good alignment was achieved in terms of Tensile Modulus, Bend stiffness and Torsion results. All the predicted values were within +/-12% of the tested values for both Baseline trials. Column Strength (worst case 22% variance) and Crush Resistance (worst-case 26% variance) exhibited poorer agreement. Flex Modulus (worst case 32% variance) and Kink Diameter (worst-case 34% variance) exhibited the widest range in terms of results.

The adjusted R^2 values for all five models are presented in Table 4. These are all relatively high indicating that the model fits the data relatively well. In the case of Column Strength, Crush resistance, Bend Stiffness and Torsion these values are close. A wider range exists with Tensile Modulus, Kink Diameter and Flex Modulus. The initial results demonstrate that DOE shows considerable potential as a technique for predictive modelling of interventional composite catheter performance. Reducing the sources of known error and implementing the learnings from this initial effort in future work with both braid and coil reinforced composite catheter is expected to result in better models with high prediction accuracy.

Table 4 R^2 and Adjusted R^2 Values for the data from each of the 7 tests used to construct the predictive model.

Test Method	R^2 Value	Adjusted R^2 Value	Test Method	R^2 Value	Adjusted R^2 Value
Tensile Modulus	.919	.884	Bend Stiffness	.990	.986
Kink Diameter	.950	.928	Flex Modulus	.911	.870
Column Strength	.987	.982	Torsion	.980	.971
Crush Resistance	.998	.997			

6.1 Sources of Error and learnings

A number of sources of error were identified during the catheter build and test steps. The durometer range was too wide. Assembling catheters in low durometer soft materials (2533 Pebax) is difficult. With thin walls and low profile reinforcing braid wire the soft material effect is magnified. The final manufacturing step of de-coring the low durometer catheters without stretching became difficult. In future work a higher durometer 3533 or 4033 Pebax will form the lower limit. Composite interventional catheter shafts are extremely rarely manufactured from very low durometer materials because of the pushability requirements need to track a catheter to its treatment location.

Spring braid wire was used for the smaller cross sectional area braid wires (968 and 3,226 μm^2) while the largest size (6,452 μm^2) was of the annealed form. Spring braid wire has a tensile strength of 2,250 MPa. Annealed braid wire has a tensile strength of 820 MPa. In future build spring type braid wire will be used for all builds. Finally the braided catheters featuring low PPI (12 PPI corresponding to an angle of 66° at the experimental catheter size) had issues with early failure on some tests when combined with other extreme conditions (thin wall and low durometer). In future work the lower limit will be specified with a slightly higher minimum limit (15 PPI corresponding to an angle of 61° at the experimental catheter size). Again, this change will not limit the utility of the model as catheters are generally designed with angles below 45° to optimize torque transfer characteristics.

7.0 Conclusion:

This pilot DOE approach demonstrates considerable potential as a basis for a predictive model methodology for composite interventional catheter design. The approach will need refinement in terms of test methods and to minimise the noise from catheter manufacturing techniques. It will also need to be applied to coiled constructs and applied over a broader range of catheter sizes. However the initial work demonstrates the practical viability of using a DOE generated predictive model as a tool to practically apply the conceptual predictive modelling framework outlined in Fig 3.

It is planned to run a subsequent DOE on braided composite catheters after implementing the learnings described in section 6.1. It is also planned to complete a DOE on coil reinforced composite catheters to further expand the range of the predictive model. Finally the FEA approach will be trialled and compared with the DOE results to date to assess its suitability as a component of a future integrated predictive modelling methodology for interventional composite catheter design.

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