

## Corporate Profile

a report by

**Sahajanand Medical Technologies, India**

Sahajanand Medical Technologies Pvt. Ltd (SMTPL) is a name associated with commercialisation of life-saving devices and medical equipment. SMTPL is the only Indian Company that is successfully dealing with both types of coronary stents – bare metallic stent, branded ‘Millennium Matrix Coronary Stent System’ and drug-eluting stent, Paclitaxel (drug)-eluting stent, branded as ‘Infinium®’. The quality management system (QMS) of the bare stent manufacturing company abides guidelines of ISO 9001-2000 and ISO 13485-2003.

#### **Bare Stent**

The CE-marked Millennium Matrix™ coronary stent is manufactured from S.S. 316L tubes by laser cutting. It is a cylinder laser cut into a serpentine mesh shape with no welding joints. The raw material S.S. 316L tubes used for the manufacturing of Millennium Matrix™ coronary stent comply with the ASTM F-138 standard.

#### **Drug Substance – Paclitaxel**

The active ingredient in Infinium™ Paclitaxel-eluting coronary stent system is Paclitaxel, a natural diterpenoid compound extracted from the bark of *Taxus brevifolia*, the western yew tree. Owing to its diverse mechanisms of action, including microtubule stabilisation, arrest of cell mitosis, retardation of cell migration and immunomodulation, it has been reported to prevent endothelial cell proliferation and migration *in vivo*. Paclitaxel is also a highly lipophilic and poorly soluble in aqueous solution, making it an excellent candidate for sustained delivery from stents and prolonged deposition in atherosclerotic vessels. The US Food and Drug Administration (FDA) has granted approval to Paclitaxel for treating ovarian (1992) and breast (1994) cancers as well as AIDS-related (1997) and lung (1998) cancers.

Paclitaxel is SMTPL’s drug of choice, because it is an extensively studied compound and its effects are well understood. Paclitaxel was selected for its multifunctional properties to address the complex process of restenosis, as it is known in preventing excessive cell proliferation.

Paclitaxel complies to USP-26 monograph and is manufactured as per current good manufacturing practice (cGMP) regulations. A certificate of analysis for the Paclitaxel drug is supplied by the manufacturer for each batch.

#### **Biodegradable Polymers**

The biodegradable polymers have been widely utilised as drug delivery systems because of their good biocompatibility, non toxicity and biodegradation characteristics. Biodegradable polymers are manufactured as per cGMP regulations and are known for usage in human implants.

#### **Brief Outline of the Manufacturing Process**

The stent is manufactured from surgical grade Stainless Steel 316L tubes. The tubes are first cut with laser machine according to the programmed design. The cut stents are electropolished for surface smoothness. These stents are transferred to a clean room where a quality check is carried out, and further proceeded to a coating room where they are coated with the drug (Paclitaxel). The coated stents are crimped on rapid exchange balloon catheters. The packed stents are sterilised with EtO. A quality check is carried out at each stage and non-conforming stents are rejected.

#### **Infinium® – Paclitaxel-eluting Coronary Stent**

The Infinium® Paclitaxel-eluting coronary stent system incorporates four polymers in different ratios. Uniform drug-polymer microspheres are produced and deposited on the stent surface in multiple layers, with each layer having unique release profile and elasticity for stent expansion.

Paclitaxel-eluting coronary stent system presents in only one model type with different length and diameter for placement in various sizes of coronary artery. The Paclitaxel stent coating has an equal concentration for all lengths and diameters. This is a constant quantity of drug per unit area of stent;

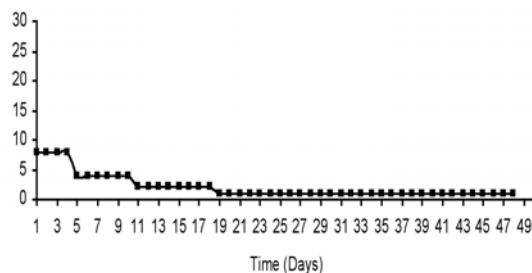
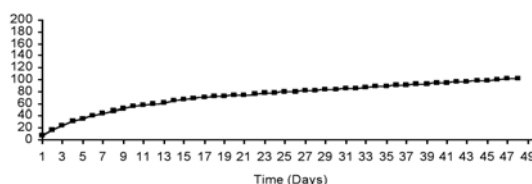


**Table 1: Designing of Layers**

Sr. No.	Stent Length (mm)	Paclitaxel content ( $\mu\text{g}$ )
1	08	51
2	11	71
3	16	102
4	19	122
5	23	147
6	29	185
7	33	211
8	34	217
9	38	243
10	39	249

**Table 2: In Vitro Release Profile of Paclitaxel from Infinnium® Coronary Stent. Total Drug (Paclitaxel) on 16mm stent: 102 $\mu\text{g}$ .**

Time (days)	Predicted Release Range ( $\mu\text{g}$ )
1 - 4	29 ~ 35
5 - 11	20 ~ 24
12 - 18	12 ~ 16
19 - 25	10 ~ 12
26 - 32	6 ~ 8
33 - 39	6 ~ 8
40 - 48	8 ~ 10
Total	91 ~ 113

**Figure 1: Release of Paclitaxel in a Controlled Manner from a Polymer Matrix Bound to the Stent****Figure 2: In Vitro Release Profile of Paclitaxel from Polymer-coated Stent**

however, as the stent length varies from 8.00mm to 39.00mm, total drug content on each stent varies from 51 $\mu\text{g}$  to 249 $\mu\text{g}$  per stent. The design and the coating pattern of all the stents is similar, hence it constitutes only one model of the stent. The summary of the stent length along with the balloon catheter used in the Infinnium® are as given in Table 1.

Combinations were finalised to develop different polymer layers with different drug releasing efficiency (see Table 2, Figure 1 and Figure 2). *In vitro* release profile and *in vivo* non-clinical pharmacokinetics conducted by the device gives excellent evidence for releasing efficiency of layers.

### Release Characteristics

The stent contains a total of three layers of coating. Only two layers contain Paclitaxel and the third layer, i.e. the outer most protective layer (third layer) contains only one type of polymer with no drug. It is meant for protection from light and moisture and also to prevent premature drug release from the underneath layers. This top protective layer is completely removed within two to three hours after implantation. In addition, the slippery nature of this coating (Lubricious hydrophilic coating) provides smooth navigation of the stent, inside the arterial system, without damage to intima.

Among the different drugs that can be used to provide beneficial effect to the injured artery (i.e. prevent thrombosis, inflammation, prevent thickening of neointimal layer, stop proliferation of smooth muscle cell, etc.), Paclitaxel has been selected because it provides the best results about the above points.

From the middle layer B about 31% of drug is released drug at a moderate rate. The base layer A has the characteristics of slow release of drug, from which about 69 % of total drug.

Programmed release pattern:

1. Middle Layer B-medium release.
2. Base Layer A- slow release.

The release of Paclitaxel from the polymer follows a profile. Initially when the stent is implanted Paclitaxel requirement is much higher to inhibit smooth muscle cell migration and proliferation which can lead to acute re-narrowing of the artery, so the B layer from the stent delivers Paclitaxel drug at about 29 $\mu\text{g}$  to 35 $\mu\text{g}$  during the first four days.

As the early effects are stabilized, the stented segment will not require such higher amount of drug to inhibit events that lead to restenosis, even though lower amount of drug should be supplied to the cells to maintain the continuous anti-proliferative and anti-inflammatory actions. This amount is supplied by the base layer A, i.e., a cumulative dose of 63 $\mu\text{g}$  to 77  $\mu\text{g}$  delivered over 37 days. ■