Release Liner Selection for Drug Delivery and Medical Device Design

Sponsored by: Saint-Gobain Specialty Films

Introduction & Applications

Release liners are a critical component in the overall development and performance of medical products such as transdermal drug delivery systems, medical devices, advanced wound care dressings and other pharmaceutical packaging products. Release liners must be selected to provide consistent release performance and inertness in the end-use application while meeting increasingly stringent performance and regulatory criteria in regards to quality, cleanliness and purity. Careful evaluation and analysis is required to assure the proper release liner is selected for the drug or medical product under development.

Figure 1 - Transdermal drug delivery patches are packaged and protected using medical release liners. (Source: Saint-Gobain Specialty Films)

Considering the many factors involved, evaluation of several candidate release liners fit for function is a recommended key step in the medical liner selection process.

Adhesive formulations can vary widely containing tackifiers, wetting aids, viscosity modifiers, fillers and other additives, which can impact release performance. The drug loaded into the adhesive adds another layer of complexity and unknowns until the compatibility of pharmaceutical ingredients with the release liner materials is determined. Considering the many factors involved, evaluation of several candidate release liners fit for function is a recommended key step in the medical liner selection process.

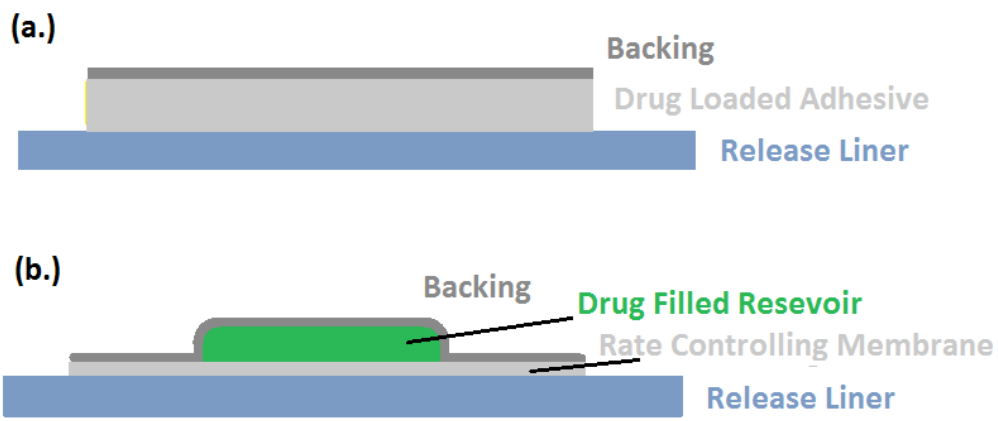

Figure 2 - Schematic views of liners holding (a) a drug-loaded adhesive product, and (b) drug-filled reservoir. (Source: IEEE Globalspec)

Release liners provide several functions in medical device manufacturing and pharmaceutical packaging. They package and protect a wide range of products (Table 1). Liners are also process carriers enabling easier handling, converting and assembly without the adhesive medical products sticking together.

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NORFILM™ Performance Coated Solutions

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IEEE

Medical/ Pharmaceutical Applications	Product Examples
Diagnostic & Point of Care	• Diagnostic Test Strips (Blood Glucose, Cholesterol, Urinary Tract Infections) • Point of Care / Diagnostic Devices
Drug Delivery & Pharmaceutical Packaging	• Transdermal Drug Delivery System (TDDS) - Drug Loaded Monolithic Matrix - Resevoir with Rate Controlling Membrane - Transdermal / Medicinal Patch • Transmucosal Drug Delivery System (TMDS) - Buccal Mucosal System - Oral Thin Films (OTF) / Oral Strips • Pharmaceutical Packaging Tapes
Fixation, Surgical & Wound Care	• Advanced Wound Dressing (Extended Wear, Burn Treatment, MVTR, etc.) • Catheter Placement • Incise / Opthalmic Incise Films • IV Holders • Medical Fixation Tapes • Ostomy Pouches / Components • Surgical & Isolation Drapery
Medical Sensors & Electrodes	• Disposable electrodes • ECG, EKG, and TENS Pads / Electrodes • Grounding Pads • Oxygen sensors
OTC / Consumer Healthcare	• Cosmetic Patches (Face strips, acne pads, etc.) • Eye patches • First Aid Bandages & Tape • Hygiene products (Diapers, sanitary napkins, incontinence pads) • OTC Therapeutic Patches
Process Carrier Liner	• Enables handling, conversion, and assembly of pharmaceutical and medical products

Table 1 - Release liner applications in drug delivery, medical devices and pharmaceutical packaging products.
(Source: IEEE Globalspec)

Medical Liner Construction & Manufacturing

Figure 3 - Advanced, high-precision web coating equipment manufactures medical release liners under cleanroom conditions. (Source: Saint-Gobain Specialty Films)

Release liners consist of a release coating on a plastic film, paper or cloth substrate (Figure 4). Medical release liners typically utilize plastic film substrates. Medical release liners are manufactured on high-speed roll-to-roll or web coating machines under cleanroom environments to precise coating weights. After deposition onto the substrate, the release liner coating is dried or set using heat or UV light.

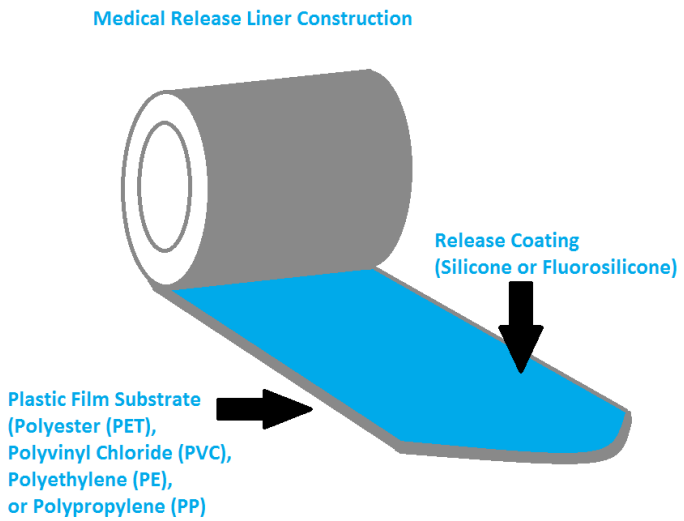

Figure 4- Sketch of medical release liner construction (Source: IEEE Globalspec)

Plastic films and substrates used in medical release liners are typically polyester (PET), polyvinyl chloride (PVC), polyethylene (PE), polypropylene (PP) and various fabrics. The liner substrate should have sufficient mechanical properties (tensile strength, elongation percentage and tear resistance) to avoid breaks during handling and converting processes. The film should cut cleanly during slitting, die-cutting and other converting steps. Polyester and polyethylene substrates

tend to have higher tear resistance. In addition, polyester and polyethylene carrier films are available in wider gauge ranges (92 to 1400 and 100 to 2300 gauge, respectively) compared to polystyrene and polyvinyl chloride films (~800 to 1000 gauge). The release liner substrate must have enough rigidity so patients or healthcare professionals can easily peel off the liner. Polyester tends to have better die-cutting and kiss-cutting performance compared to PVC, PP and PE. Certain applications require consideration of additional properties such as thermoformability and optical transmission or clarity. For instance, optical clarity of the release could be required to properly position a medicine-laden dressing over a wound or allow monitoring for allergenic response. In some designs, a reservoir well needs to be created by thermoforming the substrate material. Polystyrene and polyvinyl chloride films are thermoformable. Polyester substrates have excellent smoothness and optical clarity. Table 2 summarizes the application suitability, thicknesses and key properties of various films used in NORFILM™ medical grade release liners.

NORFILM™ Medical Grade Silicone Release Liners*

Film	Gauge	Applications	Key Properties
Polyester (PET)	92-1400	Pharmaceutical, Toiletries, Health & Beauty Transdermal, Hydrogels, Wound Care, EKG, Hygiene	High Tensile and Tear Resistance Excellent Smoothness High Clarity Gauge Control Temperature Resistance Recyclable Back Side Printable Mechanically Stable Spliceable
Polystyrene (PS)	750-1000	Hydrogels, Wound Care, EKG Piggyback	Thermoformable Good Stiffness Back Side Printable
Polyvinyl Chloride (PVC)	800-1000	Transdermal, Hydrogels, EKG	Thermoformable
Polyethylene (PE)	100-2300	One/Two Side, Transfer Wound Care, Hygiene	Tear Resistance Conformable High Yield

*Represent typical performance properties and should not be used for specification purposes

Table 2 - NORFILM™ medical release liner film types, liner gauge availability and their key properties for drug delivery, medical device and pharmaceutical packaging applications. (Source: Saint-Gobain Specialty Films).

Another important component in a release liner is the release coating, which provides the nonstick or release characteristics. Silicone and fluorosilicone are the mainstay release coatings for medical release liners. Release liners must have consistent coating thickness levels to avoid silicone skip (too thin) and over-coating of silicone (too thick). Coating thickness inconsistencies can cause dispensing, patch/device movement and converting problems. The medical release liner must avoid pre-dispensing and retain the medical device or drug delivery product until manually peeled off.

Both UV-cured and thermal-cured release coatings are available. An ideal release coating should be slow to degrade, have a high degree of chemical stability and long shelf-life while maintaining consistent release properties over the lifetime of the medical product. UV-cured release coatings have a shelf-life and warranty of 12 months, while thermal-cured coatings have a shorter six-month shelf life and warranty. Both UV- and thermal-release coatings can produce optical clarity release liners. Release coatings can be solvent-based, water-based and solvent-free or 100 percent solid.

The release properties of a release liner can be adjusted from easy to moderate to tight. An easy release liner can be removed by low peel force. A tight release requires a higher peel force value to remove the adhesive medical product. Numeric release or peel force values are given in force per length (g/in, cN/m or N/m), determined by measuring peel force at a controlled peel rate (in/min, cm/min). Medical release liners are available with peel release levels ranging from 5 to 200 g/in. A differential release liner has release coatings on each side with different levels of release, which can be useful in a few more complex multilayer medical product constructions. Single-coated release liners are used in most medical applications such as transdermal drug delivery patches, wound care dressings, surgical tape and electrodes. An easy release would be recommended in applications with a soft silicone gel adhesive or delicate drug-loaded adhesive to avoid damage to the gel or adhesive.

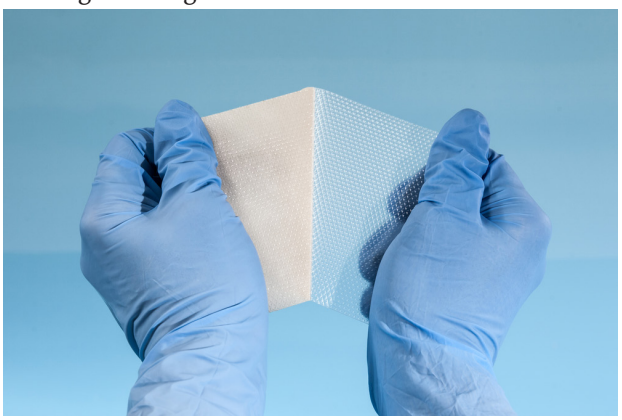

Figure 5 - Release level and liner film should be selected to enable the end user to easily remove the release liner. (Source: Saint-Gobain Specialty Films)

Since adhesives are viscoelastic materials, the stripping or peel rate can impact the effective release force. The release profile plots the release force for a series of peel rates. A flat release profile is usually desirable because the release force will be consistent with varying manufacturing processes or end-use peel forces. Adhesive used, peel speeds, temperature, time at temperature (Keil aging) and surface roughness can alter release properties. Every manufacturer has its own unique test methods and release-level designations, so it is advisable to stick with the same supplier throughout your selection process.

The adhesive should not be retained or transfer to the release coating, and the release coating should not transfer to the adhesive. Transfer could reduce the stickiness of the adhesive or impair drug delivery; the release coating

must keep the adhesive tacky. In most applications, the release liner is discarded. Some medical applications may require reuse, repositioning or reapplication such as sensors or TENS electrodes, so an adhesive-coated medical device may need to be peeled on and off the release liner.

Different release coatings are available depending on specific medical adhesives or drug-loaded adhesives. Silicone release coatings can be used with acrylic (polyacrylate), polyisobutane (PIB) and polyisoprene (synthetic rubber) adhesives. Silicone and soft silicone gel adhesives are increasingly used in medical device and wound dressing applications because they can provide a gentler action and less trauma on delicate skin or injured tissue. Silicone adhesives require a fluorosilicone release coating.

Medical Release Liner Coating	Compatible Adhesive
Silicone (Polysiloxane)	Acrylic (Polyacrylate) Polyisobutane (PIB) Polyisoprene (Synthetic Rubber)
Fluorosilicone	Acrylic (Polyacrylate) Polyisobutane (PIB) Polyisoprene (Synthetic Rubber) Silicone PSA

Table 3 - Suitability of silicone and fluorosilicone release coatings for several adhesives commonly used in medical applications. (Source: IEEE Globalspec)

Drug Master File (DMF) and Compliance Factors

While a medical liner with the proper characteristics (film type, thickness, release level, etc.) can provide operational and technical success of a product, ensuring regulatory success is more complex and a medical product cannot go to market without regulatory approval and compliance. Release liners used in a medical product must meet food and drug contact regulations and standards (FDA CFR 177.160, USP, Ph.Eu., EDQM, etc.). Regulations restrict the purity or levels of contaminants such as monomer, metal, and solvent residuals to ppm concentrations (USP 467, Table 4). The release liner must also be devoid of animal-based raw materials, according to BSE/TSE requirements. The release liner should be able to go through EtO, UV or thermal sterilization regimes to meet microbial limits without any property degradations. The release coating must not transfer, leach out additives or contaminate the drug-loaded adhesive, medicine in a reservoir, or monolithic matrix. The release liner must also prevent any leakage of medicine from a drug reservoir, and it must not extract or react with any of the medicine in a reservoir or within a monolithic matrix. Medical liners can also have additional compliance restrictions such as allergen-free, latex-free, REACH, phthalate-free and melamine-free.

Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

Table 4 - UPS 467 Class 2 residual solvents ppm levels. (Source: Table 2 in USP 467)

A medical packaging product can have permitted status or a broader approval status. FDA approval indicates that the raw materials have actually been tested for compliance. Permitted materials have just been reviewed and deemed not to have any harmful effects for specific FDA categories. Medical release liners should have an FDA DMF (Type III Packaging) status for incorporation in a medical device or pharmaceutical packaging. A Drug Master File (DMF) contains documentation on the raw materials, formulation, processing, testing and analysis demonstrating that the medical release liner meets all of the FDA regulations and standards required. The Drug Master File contains proprietary information and remains confidential between the liner OEM and the FDA. Manufacturers incorporating a release liner

into a medical product reference the liner DMF in their drug application to the FDA or notified body. The release liner OEM will provide the medical product manufacturer with a Letter of Authorization to reference the DMF numbered product in the drug application.

In addition, medical release liner manufacturers frequently undergo comprehensive audits of their facilities and quality management systems to assure their processes are compliant. Release liners are considered an inactive packaging product by the FDA, so a full GMP manufacturing is not required. However, medical release liners are manufactured in cleanrooms devoid of pest and microbial contamination sources.

Recommendations and Next Steps

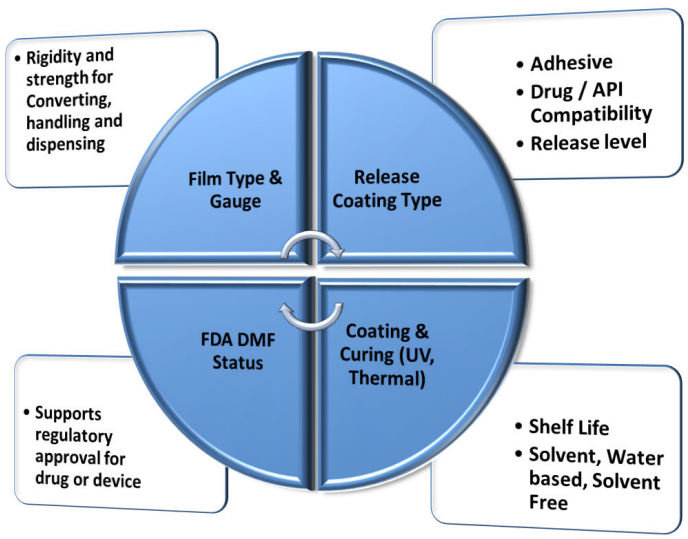

Figure 6 - Factors for medical release liner selection. (Source: IEEE Globalspec).

Selecting a medical release liner involves multiple considerations. The release liner must have strength to hold up to converting, handling and assembly during medical device manufacturing. The proper rigidity allows the release liner to be peeled off the pressure-sensitive adhesive easily. The specific release coating type depends on the adhesives and medicine as well as the desired release level. All medical release liners should have FDA DMF status. Utilizing a release liner without DMF status can hinder or derail the regulatory approval process for your medical product. Proper medical liner selection begins with sampling and testing of several release liner samples in product assemblies using the actual adhesive or drug-loaded adhesive formulations.

After considering the multitude of complexities in the design, approval and implementation of products using a medical liner, identifying a strong, experienced release liner OEM such as Saint-Gobain to work with early in the development process helps to maximize performance, reduce costs and troubleshoot problems.

Recommended steps for selecting a medical release liner include:

- Review adhesive or drug-loaded adhesive formulations with release liner supplier,
- Select FDA-approved medical liners with DMF status,
- Screen a wide swath of release liners before narrowing down candidate liners,
- Evaluate and test UV-silicone release systems first, since these liners have a longer shelf-life,
- Have patience – the approval process for new drugs and medical devices is a long process (3 to 5 years).

A well-respected, established and reliable release liner with a broad offering and custom engineering capability can quickly respond and provide a solution to your medical liner implementation issues that can occur during product development. Once a medical release liner system is found that reliably delivers the performance required for your application, it is important to minimize product variability and maintain product quality by selecting a single release liner OEM such as Saint-Gobain.

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Saint-Gobain Performance Plastics' group of businesses gather solutions to save energy, provide protection, improve comfort and sustain the environment for a variety of markets.