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# Title: The Production of Solid Dosage Forms from Non-Degradable Polymers

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**Abstract:** Non-degradable polymers have an important function in medicine. Solid dosage forms for longer term implantation require to be constructed from materials that will not degrade or erode over time and also offer the utmost biocompatibility and biostability. This review details the three most important non-degradable polymers for the production of solid dosage forms – silicone elastomer, ethylene vinyl acetate and thermoplastic polyurethane. The hydrophobic, thermoset silicone elastomer is utilised in the production of a broad range of devices, from urinary catheter tubing for the prevention of biofilm to intravaginal rings used to prevent HIV transmission. Ethylene vinyl acetate, a hydrophobic thermoplastic, is the material of choice of two of the world's leading forms of contraception - Nuvaring® and Implanon®. Thermoplastic polyurethane has such a diverse range of building blocks that this one polymer can be hydrophilic or hydrophobic. Yet, in spite of this versatility, it is only now finding utility in commercialised drug delivery systems. Separately then one polymer has a unique ability that differentiates it from the others and can be applied in a specific drug delivery application; but collectively these polymers provide a rich palette of material and drug delivery options to empower formulation scientists in meeting even the most demanding of unmet clinical needs. Therefore, these polymers have had a long history in controlled release, from the very beginning even, and it is pertinent that this review examines briefly this history while also detailing the state-of-the-art academic studies and inventions exploiting these materials. The paper also outlines the different production methods required to manufacture these solid dosage forms as many of the processes are uncommon to the wider pharmaceutical industry.

**Keywords:** controlled release; hot-melt extrusion; EVA; silicone elastomer; thermoplastic polyurethane; implants.

## 1. INTRODUCTION

Over the past decade the main research focus of polymers for drug delivery has been concerned with biodegradable or bioerodible materials [1]. These polymers permit the dosage form to provide controlled release of drug, while the polymer itself is broken down and eliminated from the body. However, this behavior is sometimes counterproductive to the function of a drug delivery system. Intravaginal rings, subdermal implants and intrauterine devices, need to be constructed from polymers that will not degrade or erode over time but will maintain mechanical integrity while implanted. The focus of this review will be on the three main non-degradable polymers used in the manufacture of solid dosage forms; detailing how each possesses very different chemistries and pharmaceutical properties. Silicone elastomer is a hydrophobic thermoset rubber. Ethylene vinyl acetate (EVA) is a hydrophobic thermoplastic copolymer. The last polymer under review is thermoplastic polyurethane (TPU), a polymer with a considerable breadth of chemistry – where one grade of material is hydrophobic and another hydrophilic and water-swellable. This review will detail the chemistry, properties and history of each polymer in the laboratory, clinic and marketplace. It will also give an overview of the manufacturing steps required in the production of different solid dosage forms.

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### 1.1. Drug delivery: solid dosage forms

Solid dosage forms are defined as dosage forms which have a definite shape and volume and include tablets, capsules, implantable devices and transdermal patches. The release kinetics of a drug is dependent on the type of device, how it is formulated and manufactured as well as the physicochemical properties of the drug [2]. The majority of solid dosage forms such as tablets and capsules are designated as immediate release, where a typical specification requires that 70% of the drug content is released within a 45 minutes period during an *in vitro* dissolution test [3]. Some tablets, particularly freeze dried tablets, are termed rapidly dissolving and very rapidly dissolving formulations, and offer even faster release rates. However, for certain clinical applications, there is a preference for dosage forms, particularly tablets, that provide much slower release rates, such that release is extended or prolonged over many hours [4–6]. In these so-called extended release or sustained release dosage forms, which are the most common types of modified release drug delivery systems, the drug is released slowly at a rate governed predominantly by the design of the solid dosage form [2]. Many sustained release dosage forms are specifically designed for once-daily per-oral administration, thereby increasing patient compliance and acceptability compared with conventional multiple daily dosing regimens.

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Controlled release solid dosage forms, such as implantable devices and transdermal patches, are a further aspect of 'modified release', where the drug is released at a predictable and reproducible rate from the delivery system according to a pre-defined mathematical pattern and the release of the drug is under control of the drug delivery system [7]. Controlled release dosage forms are often designed to provide zero-order drug release, whereby a constant drug release rate allows maintenance of a near-constant plasma drug concentrations, avoiding the undesirable peaks (supra-optimal) and troughs (sub-optimal) typically seen with multiple daily dosing regimens, thus minimising toxic side effects and reducing overall dosing costs [8]. The duration of release from a controlled release dosage form can range from one day to several years, depending upon its design and clinical applications. However, the characteristic that sets it apart from sustained release systems is the kinetic control of release rate over the dosing period.

There are two types of controlled release solid dosage forms: matrix and reservoir. In matrix solid dosage forms, the drug is homogenously dispersed throughout the dosage form and results in the release rate being proportional to the drug loading and the surface area of the dosage form. The release from matrix solid dosage forms is first-order and thus decreases over time. Reservoir solid dosage forms consist of a centralised core surrounded by a drug-free membrane, which determines the rate of release. This membrane results in the release being zero-order, where the release rate remains constant over time [7,9]. Brief descriptions of the main types of solid dosage forms produced from non-degradable polymer are provided below.

### *1.1.1. Implantable devices*

Implantable drug delivery devices can provide a continuous release of drug for months or even years in some cases [10]. Depending on whether the device is a reservoir or matrix device the release can either be zero or first order. A range of implantable devices are available, such as subdermal implants, vaginal rings, intrauterine devices, ocular implants and intracerebral implants. Administration of an implantable device usually requires surgical implantation or a specialised injecting device, except in the case of vaginal rings and some ocular implants which can be self-inserted and removed [11]. Due to these devices being in constant contact with tissue for prolonged periods of time the polymers used in their construction must be biocompatible, that is, they must not cause any undesirable local or systemic effects, such as irritation at the site of implantation or result in infection.

### *1.1.2. Subdermal implants*

A subdermal (or subcutaneous) implant is a solid dosage form that is placed underneath the skin. They are one of the most readily used implants today as the subdermal region of the skin has a large number of absorption sites available and removal of the device is straightforward. Subdermal implants will deliver drug at fixed rates until the device is removed. However, one disadvantage is that insertion and removal must be performed by a trained medical professional. Fig. (**1**). is a rendering of the Nexplanon® contraceptive implant marketed by Merck (USA) that is a reservoir device constructed from EVA.

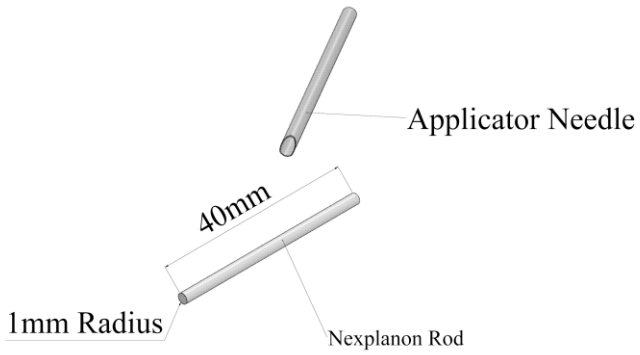


**Fig. (1).** Nexplanon® subdermal implant with representation of the applicator needle.

### *1.1.3. Intravaginal rings*

The vaginal ring is a flexible, torus-shaped drug delivery device that is capable of delivering one or more drugs to the vagina in a sustained fashion. It is inserted into the vagina for up to twelve months at a time, where it slowly releases one or more drugs to provide either a local or systemic effect. Measuring between 5 to 9.5 mm in cross-sectional diameter and between 50 to 75 mm in overall diameter, the rings have, to date, been primarily developed for the systemic delivery of contraceptive steroids and the localised and systemic delivery of steroids for hormone replacement therapy. There are two main types of vaginal rings available, the matrix and the reservoir vaginal rings. The vaginal ring overcomes many of the disadvantages associated with more traditional vaginal drug dosage forms, such as gels, tablets and pessaries, which are often messy, interfere with intercourse and are poorly retained within the vagina. However, the major advantage of a ring is the ability and versatility in providing long-term, continuous release of drug(s) at constant pre-determined rates, thereby increasing cost-effectiveness, patient compliance and therapeutic efficacy. Furthermore, the vaginal ring is user controlled and thus does not require minor surgery or a physician for vaginal placement.

### *1.1.6. Ocular implants*

Ocular (or ophthalmic) implants are solid (in some cases semi-solid) dosage forms that are implanted into the eye. They are usually anchored to the sclera or injected into the vitreous and can release drug over a period of months and even years, from both biodegradable and non-degradable polymers. Precise drug delivery to the eye using topical administration can be very difficult due to the production of tears and tear drainage, which quickly removes the drug away from the eye. Ocular implants allow the drug to be maintained at a constant level for a sustained period of time. They offer the advantages of increased ocular residence and thus prolonged delivery of drug; increased patient compliance; more accurate dosing and reduced systemic absorption. However, due to their solid nature they can cause patient discomfort and impair vision.

### *1.1.5. Intrauterine devices*

An intrauterine device (IUD) or coil is a small T-shaped contraceptive device, which is inserted into the uterus. They are a type of long-acting, reversible contraceptive and are one of the most effective methods of reversible birth control. They are usually manufactured from flexible materials so that they can resume their shape after distortion. The first generation IUDs contained no drug and thus could not be described as sustained release devices. They worked by inducing local endometrial responses. The next generation of IUDs were medicated and released either progesterone or copper for up to a year or 40 months respectively. The progesterone IUDs are reservoir devices and thus provide zero-order release. Fig. (**2**). is a rendering of the Mirena IUD as marketed by Bayer (Germany).

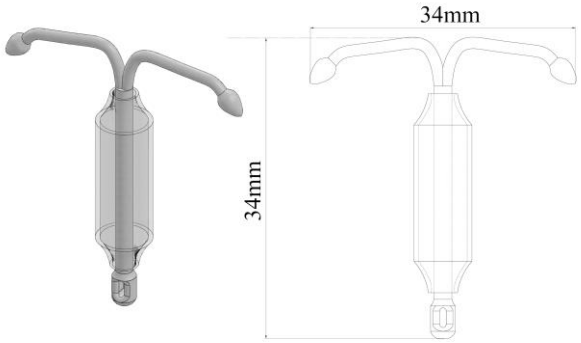


**Fig. (2).** Mirena® intrauterine device consisting of a polyethylene T-shape and drug-loaded EVA jacket.

## 2. PRODUCTION METHODS

The importance of manufacturing processes for the production of solid dosage forms which are accurate, reproducible and cost-effective cannot be undervalued. Drug release is dependent on the surface area and dimensions of the device, so the system must be mass-produced under tight tolerances to ensure both efficacy and safety. The sections below outline the main manufacturing processes to produce solid dosage forms from non-degradable polymers.

### 2.1 Hot melt extrusion

Hot melt extrusion (HME) is a process that over the last decade has been increasing in importance and utility to the pharmaceutical industry [12]. The advantages of this process over other more traditional production methods has been comprehensively discussed in the literature [13–16], with the current state-of-the-art reviewed extensively [17–20] and can be listed as thus: (i) increased solubility and bioavailability of poorly water soluble drugs; (ii) a solvent free process; (iii) a continuous process with fewer processing steps; (iv) improved content uniformity; (v) no need for good compressibility of powder blends; (vi) increased stability and (vii) flexibility in manufacture due to the number of screw geometries and die shapes available. However, HME does have a number of disadvantages, which include the inherent levels of shear and requirement of high temperatures, which are not conducive to the stability of thermolabile active ingredients [19,21]. Two of the main areas which HME has been focused on are solubility and bioavailability enhancement [21,22] and taste masking of bitter drugs[23,24].

Polymer extrusion is a long established industrial process which employs at least one reciprocating screw to convey a thermoplastic resin along a heated barrel until molten, before being forced through a die as a uniform shape. An extensive overview of the process is available in a number of publications [25–27]. Industrial applications for extrusion include shape forming of plastic resin into a wide range of profiles; chemical modifications of resin through reactive extrusion processes; blending of multiple resins; and dispersion of additives and fillers in the resin. Action of the reciprocating screw has a plasticising effect on the polymer forcing resin between the screw flight and the heated barrel wall with conveyance in the direction of rotation. Processing occurs under set conditions, such as temperature, pressure and screw speed. Polymer enters the extruder from a feed hopper that sits above the feed throat of the extruder barrel. The thermoplastic resin as granules or powder can be flood-fed to the screw (i.e. feed hopper is filled with resin) or starve-fed by sophisticated systems such as volumetric or gravimetric feeders that more accurately dose the resin, other polymers and/or additives during the extrusion process.

The extrusion process can be simply thought of as having three zones – feed, compression and metering. The feed zone conveys the resin entering the screw forward and the first heat is introduced into the material. In the compression zone, the polymer granules melt due to heat from the barrel and through the action of shear. Compression homogenises the melt and acts to drive out gases trapped within the melt. The metering zone ensures consistent melt temperature and pressure as the material exits the extruder through the die. Extruder length is described by the L/D ratio, which is the ratio of the length of the flighted screw to the outside screw diameter. In general, the L/D ratio of most industrial extruders is between 20 and 40, where the shorter the extruder the higher the output. Longer (above 40 L/D) extruders are sometimes required for niche applications, such as double venting or high-speed processing. Extruder length is usually process dependent but can also be material dependent, as some polymers do not readily melt or have high discharge pressures. Therefore, while extruder output is high on the list of commercial considerations in choosing a machine, material properties should be an overriding factor of any decision so as to ensure premium performance of the final product.

Screw design is material dependent but in general, designers aim to optimize polymer melting efficiency; control shear; homogenize polymer melt; enhance filler dispersion; reduce polymer and additive degradation; and regulate the temperature and pressure of the molten polymer exiting the die. Shear is the dominate flow behaviour along the screw. Elongational flow will only occur in mixing sections. The rheological properties of a material, particularly with respect to shear, are a critical factor in screw design. For example, highly viscous polymer resins will require deeper screw channels than less viscous materials. The design of screws is balanced between the need for as short a residence time as possible and that of delivering a uniform, highly homogenized melt from the die face.

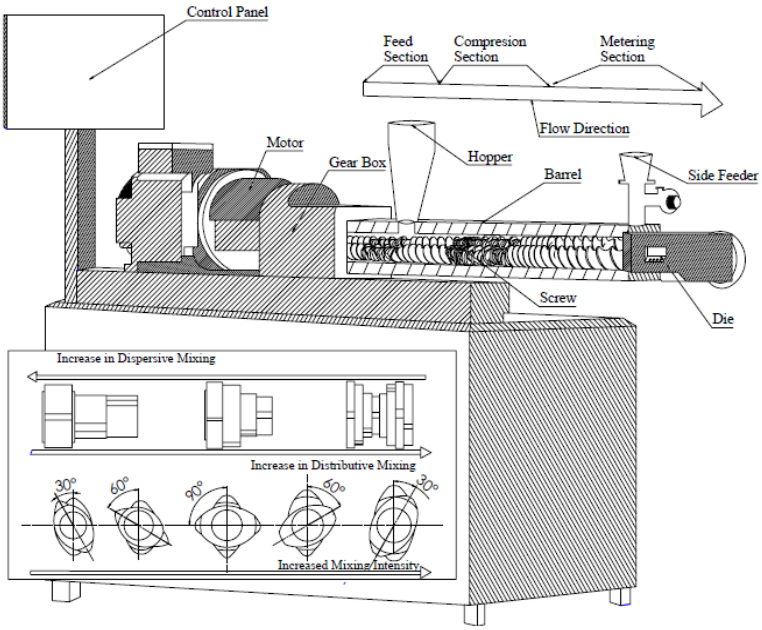


**Fig. (3).** Twin-screw extruder with visible screws in barrel and an inset detailing screw element influence over mixing.

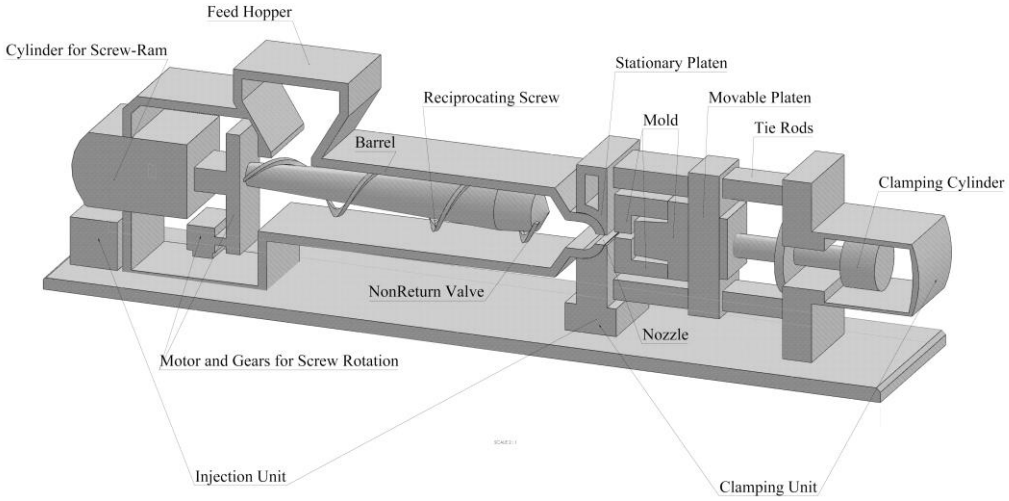


**Fig. (4).** Injection moulder for the production of thermoplastic parts.

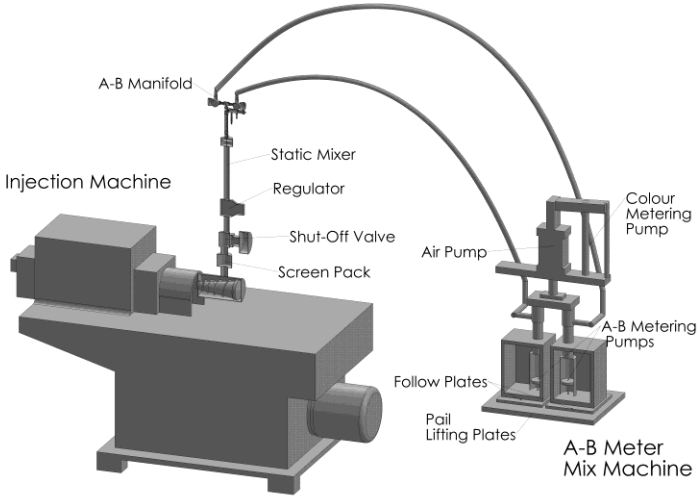


**Fig. (5).** Reaction injection moulder two-component system for the production of silicone elastomer parts**.**

### 2.2. Co-extrusion

Co-extrusion is the simultaneous extrusion of two or more materials through the same die, creating a multi-layered extrudate. The final product will combine the properties of each material into a single form. Multi-layerfilm packaging is one such example as each layer confers a particular property to the packaging material, such as barrier performance, printability or tear resistance. In this way, different materials can be combined to offer a cost-effective packaging solution for vendors to protect products during the supply chain. Other industrial examples of co-extrusion include pipes, wires, cable and tubes. Each material present in the multi-layer structure requires a separate extruder. Each of these extruders feed into a single die.

Die design is the critical parameter of co-extrusion as it ultimately controls the placement and thickness of each layer. Manifold dies are necessary for co-extrusion and they channel polymer melt from entry to exit. Both single and multiple manifold dies are available. Single manifold dies combine with a feed-block to form the multi-layered extrudate. It is the feed-block which streams the incoming polymer melts that are fed from each extruder. This multi-layer stream is then fed directly into the die for shape-forming. Multi-manifold dies consist of a die with a channel for each incoming polymer melt stream. Each manifold evenly distributes the polymer melt layer prior to them being combined inside the die. A more uniform distribution of layers is achievable in multi-manifold dies compared to single. The multi-manifold is also the more expensive of the two options. Annular dies are used in the production of multi-layer tubing instead of manifold dies. Multiple layers are combined in spiral mandrel dies in a cylindrical, conical or radial configuration. The incoming polymer melts are divided into separate streams by means of a star-like-spiral channel mandrel or an arm-like spiral channel mandrel.

In spite of all the design sophistication of modern dies, it is of fundamental importance that the materials being co-extruded have similar rheological behaviour. Mismatched materials will lead to flow instability that will disrupt the formation of distinct layers on exit from the die. If layers do not adhere to each other, tie resins are often employed to prevent delamination. EVA is often used as a tie layer as it is naturally tacky and is cheaper than more sophisticated tie resins offered by companies such as DuPont (USA) and Mitsui Chemicals (Japan).

### 2.3. Twin-screw compounding

Twin-screw compounding is an extrusion process that consists of two intermeshing, co-rotating (or counter-rotating) screws in a heated barrel. In-depth reviews of the process are available [28,29]. Fig. (**3**). is a rendering of a twin-screw extruder that highlights the main features. Twin-screw compounding is capable of a high degree of physical mixing of molten polymer and additives when compared to single screw extrusion. Screw design governs interpenetration of the screws providing precise control over both shear and dispersive (or distributive) mixing. In addition to the three main zones, twin screw extrusion can consist of a broad range of specialized screw elements. Even the most complex formulations and heat sensitive additives (with the appropriate polymer choice) can be readily processed due to absolute control over the extrusion process offered by this type of screw design. The twin-screw extruder is a self-cleaning system as the two intermeshed screws will wipe clean the surface of the corresponding element on the adjacent screw as well as the barrel surface on rotation. Such self-wiping behaviour eliminates dead spots and reduces residence time via efficient mixing. Additives (or fillers) can be added to the feed throat of the twin-screw extruder (starve-feed only) or anywhere along the barrel using a side feeder that forces powdered additive into the melt. Side feeders can have a plunger-style action or be of a screw design. Liquid additives are introduced to the melt using a liquid pump and liquid injection system.

Pharmaceutical grade twin-screw compounding extruders are based on existing industrial machine designs, but are reengineered to meet the stringent cGMP standards for the production of drug delivery systems. Extruders come completely covered in stainless steel and equipped with leak-proof couplings. All contact surfaces are composed of medical grade steel so as not to be reactive, additive or absorptive. The oils and lubricants used for machine function are fully FDA-conformant. Process analytical technology (PAT) is built into the operating systems of the newer generation machines offering the ability to analyse and control the HME operation through online monitoring [18,30,31]. Another intrinsic feature of these machines is aimed specifically at meeting stringent cleaning protocols inherent to cGMP processes. In addition, pharmaceutical grade extruders have enhanced ease of disassembly and limited dead spots, allowing for both efficient cleaning and maintenance. Leading vendors of pharmaceutical grade twin-screws, such as Coperion (Germany), Leistritz (Germany) and Dr Collin (Germany), offer extruders in the size range of 16mm up to 70mm. These companies provide smaller-scale extruders that permit low volume production that minimizes batch size, so as to limit the amount of required active ingredients, which is ideal for expensive compounds or experimental drugs of limited quantities.

### 2.4. Injection moulding

Injection moulding is a forming process were molten polymer is forced at high pressure into a mould. Fig. (**4**). is a rendering of an injection moulding machine. The interested reader can readily find comprehensive publications on this topic [32–34]. Many of our everyday items are manufactured through this process as it offers a range of possible designs, from small to large and from simple to intricate. Injection moulding machines come in various sizes and functions. Tonnage is the main machine descriptor used within the industry and denotes the maximum tonnage a machine has to inject molten material into a mould. Effectively, the larger the part the more tonnage required. However, thin walled parts or parts with intricate fine features may also require larger tonnage regardless of the material volume. Machines are available in the horizontal axis for continuous cycling or in the vertical axis for overmoulding. Multi-shot moulding is the latest technological development and permits the injection of multiple materials into a single mould.

The injection moulding process shares many of the same features of single screw extrusion. Resin granules enter the

screw from a feed hopper and are conveyed along a heated barrel. However, instead of being forced through a die the melt collects at the end of the screw at a set volume known as the shot. A plunging motion by the screw forces the molten shot out through a nozzle into a mould at a set injection pressure and speed. The mould consists of two halves and will open once the molten polymer has cooled sufficiently to be ejected. The moulding cycle then begins again. Injection pressure, packing pressure and mould cooling are all important parameters of the moulding cycle.

Although screw design is an important consideration for this process, it is mould tool design that is the critical parameter, as it ultimately governs the ability of the engineers to produce consistent parts. There are many considerations for every mould tool design. The core design brief is governed by the structure and proposed function of the part, but to achieve this, consideration must be made to the flow characteristics of the molten polymer entering the mould. For example, how the molten polymer enters then flows around the mould is vitally important, since points of stress will be frozen-in as the part cools and therefore, it is important that these are identified and eliminated at the design stage. Modern computer aided design software is the cornerstone of mould tool design and mould flow simulation enables the engineer to test the validity of designs before the expensive machining of the tool commences.

Injection moulded parts exhibit a three-region multilayer skin-core morphology. These regions are (i) the gate region, (ii) the fully-developed-flow region and (iii) the end region. The differences in the various regions are related to the thermal and shear history during the injection moulding process. The shear rate experienced by the melt at the end region is much lower than the shear rate experienced at the fully-developed-flow region. As the polymer melt travels from the gate region through the fully-developed-flow region to the end region, it becomes cooler and more viscous. This in itself would have an important effect upon shear and the formation of the various layers and crystalline development. The crystalline structure and distribution of crystallinity is therefore strongly dependent on the position from the gate. The numbers of layers can vary within each region; for example the gate region where the melt enters the mould has a complex eight layer structure. The fully-developed-flow region which makes up the majority of the injection moulded part has a five layer structure and the end region has a three layer structure.

### 2.5. Thermoset processing

Not all polymeric drug delivery systems are made from thermoplastic resins. Thermosets are polymers when once formed will remain in a permanent solid state and cannot be reshaped. In very simple terms, it is easiest to think of thermoset injection moulding as the reverse of thermoplastic injection moulding i.e. liquid polymer raw material is injected from a cold injection system into a heated mould (> 100ºC) to be formed into a solid part. This forming is a curing process involving two or more component parts reacting together to form a cross-linked polymer. The majority of liquid silicone rubber systems consist of two component systems but other systems are available that contain separate polysiloxane polymer, crosslinker and catalyst components.

Reaction injection moulding systems are required for the processing of thermosets. Fig. (5). is a rendering of a reaction injection moulder containing pumping system for a two component silicone elastomer. These systems consist of a liquid dispensing unit, a metering pump, a static mixer, an injection unit and a heated mould. Each component is usually contained within a pail or drum that will fit directly into the cabinet of the liquid dispensing unit. Each pail is an industry standard and therefore piston plates will fit perfectly into the pail and form a seal thus avoiding the necessity of handling the liquid silicone. The pumping mechanism rams the piston plate down inside the pail thus forcing the liquid polymer into the pipelines. A metering device delivers both components to the mixing section at the correct ratio, usually 1:1, but can be up to 10:1 depending on the polymer system. Static mixers are the most common form of mixing device. Static mixers can be constructed from stainless steel or from inert polymers for disposal between batches. Dosing of API, pigment and/or filler takes place at this section, along with screening for gels or prematurely cured material.

Premixed liquid polymer then enters the injection unit for shot dosing to the mould. The unit is of a similar construct to the injection unit of the thermoplastic injection moulding machine – a flighted screw inside a barrel. The barrel is water cooled to prevent premature curing. The screw does not have compression zones but aims instead to provide a constant stream of liquid polymer. A shut-off valve in the nozzle prevents backflow of liquid polymer during injection. Like the barrel, the nozzle of these injection units need to be cooled with chilled water during processing. The mould is heated to temperatures in excess of 100ºC but do not usually exceed 200ºC. The higher the temperature the faster the curing rate and therefore the shorter the cycle time but too excessive temperature will lead to premature curing and an unfilled mould.

Analogous to thermoplastic injection moulding, the outer skin of the part will cure first, followed by curing through the layers after injection. Each cured layer will act as a heat insulator and therefore mould temperature must be sufficient to prevent non-curing of the core. Parts will usually undergo post-mould curing in an oven to ensure complete curing. Mould design is the most critical parameter for reaction injection moulding. Design engineers aim to control hot-spots; provide uniform heat; optimize gate placement and reduce under-cuts. In-mould cold runner systems are increasingly employed to limit premature curing and reduce the heat transfer to the nozzle. Reaction injection moulding machines are the same build as vendors' thermoplastic machines but with a different injection unit and a software interface that can control the pumping. Machines are available that can be readily interchanged between the two processes.

In addition to the reaction injection moulding, silicone extrusion systems are also available. Silicone extrusion is of high-consistency rubber (HCR), which is a gum-like material that comes in two component parts. Mixed HCR silicone is created via a two-roll mill that is then cut into homogeneous polymer strips and fed into the extruder by a roller feeder.

Silicone extrusion consists of a single flighted screw with an L/D ratio of 10:1 to 12:1. The flight depth is deep but becomes shallower further down the barrel as the screw compression increases. Double flights are sometimes a feature of these screws to permit a consistent high output. A number of methods are available to cure the extrudate but it is important to note that curing temperatures are in excess of those used during moulding as the extrudate must shape-form within seconds of exiting the extruder. The extrudate commonly passes through an air-circulating heated chamber at temperatures that can top 700°C. Curing time is dependent on both cross-diameter of the extrudate and the oven temperature. Alternative curing systems include molten salt baths and pressurized steam ovens. Post-extrusion curing is also readily utilised to complete curing reactions and to remove any volatiles.

## 3. SILICONE ELASTOMER

The first polysiloxane polymer was synthesized by Frederick Kipping in 1901 [35]. He coined the term 'silicone' in the mistaken belief that the silicon atom was attached to the oxygen by a double bond. Silicone elastomer was forthcoming in 1945 as part of a wartime effort by Dow Corning (established 1943) to find a suitable replacement for Far East derived natural rubber. The first *in vivo* medical application for silicone elastomer was as tubing for urethra replacement [36]. The potential as a drug delivery material was first posited in 1964, when researchers at the Naval Medical Research Institute described the implantation of a drug loaded polysiloxane capsules into dogs [37]. Since that time silicone elastomers have found wide spread use in a diverse number of medical applications including prosthetic implants, drug delivery systems and catheter tubing [38,39]. Silicone elastomers have an almost ideal mix of properties for such purposes, having excellent biocompatibility, no toxic or mutagenic effects and a shore hardness that is non-abrasive to tissue. The sections below will outline the chemistry and physical properties of polysiloxane polymers and elastomers, describing the history of drug delivery of the material in the literature and as commercial products.

### 3.1. Chemical structure and properties

Silicone elastomers have found wide spread use in medical applications by offering biocompatibility, sterilisability and high degrees of strength and toughness [40–42]. The silicone polymer is an alternating chain of silicon and oxygen atoms. This molecular backbone is described as siloxane and silicone polymers are more correctly known as polysiloxanes. Polysiloxane chemistry is based on the type and position of organic groups (methyl, vinyl or phenyl) along the molecular backbone. By far the most utilised polysiloxane in medicine is the polydimethylsiloxane (PDMS) which as the name suggests consists of two methyl groups attached to the silicon atom along the full length of the linear polymer chain. Fig. (**6**). is the chemical structure of PDMS. PDMS chains are trimethyl terminated. Polysiloxane polymers remain in the liquid form even at very high molecular weights and have typical viscosities that range from 10 to 100,000 mPas. The chemical structure and properties make PDMS an ideal material for medical devices and long-term implants. The methyl groups which run along the whole of the polymer chain act to shield the siloxane backbone. This shielding effect provides PDMS with a very hydrophobic character that has limited intermolecular interactions, thus bestowing a chemical (or biological) stability ideal for long-term implantation. The siloxane backbone is a construct of strong polar bonds that is of low rigidity. These features are ideal properties for an implantable drug delivery system as they permit both sterilization (resistance to thermoxidative attack) and drug diffusion (permeability).

The elastomeric form of silicone is derived from the ability to crosslink polysiloxane chains. Typically, there are two crosslinking mechanisms – addition or condensation – which are dependent on the polysiloxane and the desired elastomeric form. The crosslink is a silicon based oligomer that joins polysiloxane chains one to another to form a three-dimensional network that has a solid physical form. The physical properties of the elastomer are strongly dependent on polysiloxane polymer, crosslinker and crosslink density [43]. Elastomer hardness increases with crosslink density. Silica based fillers, such as diatomaceous earth, are often added to silicone elastomers to improve overall mechanical strength.

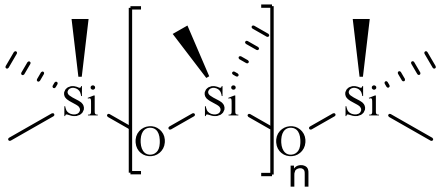


**Fig. (6).** Chemical structure of PDMS.

Addition curing of PDMS proceeds via a hydrosilylation reaction in the presence of a platinum-based catalyst where silicon hydride is the crosslinking agent. Non-medical PDMS can also undergo free radical crosslinking initiated by hydrogen peroxide. During the hydrosilylation reaction chain-to-chain crosslinking involves the addition of a silicon-hydrogen oligomer connection between carbons on respective methyl side-groups. At room temperature, the reaction will proceed but in practical terms most silicone elastomer systems will require elevated temperatures (>100ºC). Momentive (USA) have developed a UV curable silicone elastomer system, where a photosensitive platinum catalyst upon exposure to UV light, initiates the hydrosilylation reaction so that no thermal curing is required [44]. Condensation curing requires different polysiloxane polymers, oligomer crosslinkers and metal catalysts. For example, hydroxy-terminated PDMS is crosslinked by tetra-alkyloxysilane in the presence of a stannous octoate catalyst. Unlike addition based curing, this type of curing reaction will lead to the formation of a condensation alcohol by-product. This by-product will diffuse to the surface and is removed prior to implantation. However, there is potential to exploit these condensation alcohols for their lubricious properties in catheter tubing [45–47].

### 3.2. Drug delivery: silicone elastomers

Drug diffusion in the solid elastomer is achieved due to the low rigidity of the polymer chains permitting very high permeability of drug compounds, especially small molecule lipophilic actives. Polysiloxanes even in the polymeric liquid

form have found numerous pharmaceutical applications. PDMS (referred to as dimethicone) is an active ingredient and excipient in skin creams and lotions, transdermal patches and in anti-flatulent medication [48]. For skin treatment, the polymer provides activity against acne [49,50] and ulceration [51–53]. PDMS is used in antacid and/or anti-flatulent medications as it has well established anti-foaming properties due to the polymer's ability to disrupt the air/liquid interface [54,55]. Non-toxic PDMS does not upset gastric pH and the polymer chains are too large to be absorbed by the GI tract.

### *3.2.1. Drug delivery - catheters*

Silicone elastomers have been used for many years in a large range of drug delivery systems in matrix devices, reservoir devices and drug loaded coatings [39,42,48]. One of the largest medical applications for the polymer is as catheter tubing. A urethral catheter is tubing that is a convenient means of emptying the bladder of incapacitated patients undergoing care after major surgery or trauma. A vascular catheter is tubing that is inserted into a patient's vein for intravenous (IV) drug administration. Insertion may be in a vein of the arm (short-term care) or a central vein in the chest for longer term administration of therapeutics or nutrients. Catheters are also used in the construction of shunts that drain excess cerebrospinal fluid away from the brain. Fig. (**7**). is a rendering of a shunt catheter. Biofilm formation on catheter tubing is major area of concern for clinicians as it can lead to a serious infection in what is already a vulnerable person. Biofilm formation and mechanisms of infection have been extensively reviewed [56–61]. Urethral catheterization for longer than a week will lead to a urinary tract infection in half of all adult patients [62]. Blood stream infections are a complication associated with vascular catheterization, particularly those of methicillin-resistant Staphylococcus aureus (MRSA) [63].

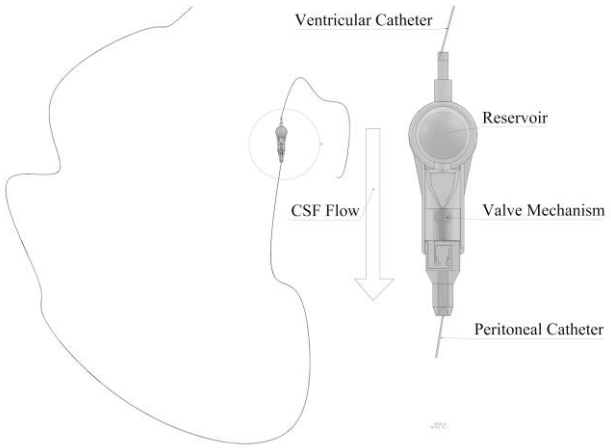


**Fig. (7).** Shunt catheter with details of the valve mechanism.

Silicone elastomer tubing is not immune to biofilm formation [64–69]. Preventative strategies have included surface coatings and treatments [70–77], ethanol lock therapy [78–82] and silver based technologies [83–87]. There are known challenges with each of these methods of mitigation. Although many and varied, surface coatings can have a limited lifespan regardless of active ingredient as they may be washed away by body fluids during long-term catheter placement. Ethanol lock therapy has questionable efficacy and safety [88,89]. Concerns have been expressed over both efficacy of silver based catheters [90–98] and the general safety of implanted silver based technology [99–103].

The first investigative work into antimicrobial impregnated silicone catheters started in the mid-Seventies with incorporation of gentamicin in shunt catheters by Bayston *et al.* [104,105]. His original approach was to mix the drug compounds into the component polysiloxane polymers prior to curing but then opted for a solvent impregnation approach so as to permit appropriate antimicrobial choice by the clinician [106]. The solvent impregnation approach comprises dissolving drug in chloroform at a low concentration. The commercial product (catheter or shunt) is then fully immersed in the solution for a set time. The device is removed, dried in an oven and thoroughly rinsed. Antimicrobials that have successfully been impregnated into silicone elastomer via this method are rifampicin [107–112], sodium fusidate [106], diethanolamine fusidate [106,107], trimethoprim [107,110], spiramycin [107], clindamycin HCl [106–109,111], triclosan [110,112] and sparfloxacin [112]. Low drug concentrations (<1%) of these systems provides for efficacy [113–120] but does not impede mechanical performance and reduces systemic delivery of the drugs [109]. The most potent antimicrobial activity was observed for drug combinations [107]. The combination approach prevents issues of resistance [108].

The solvent impregnation method has the potential to be adapted for other catheter systems as the impregnated drugs can be adjusted to suit different antibacterial requirements. Bayston *et al.* have already undertaken preclinical assessment of the suitability of this approach for applications in continuous ambulatory peritoneal dialysis silicone catheters [110]. Antimicrobial impregnated silicone elastomer catheter patents have been described on a few occasions. The Procter & Gamble Company filed a patent in 1979 for an antimicrobial silicone catheter with active ingredients consisting of one or more free n-alkane monocarboxylic acid compounds or salts [121]. The active ingredients were premixed into the silicone elastomer prior to curing. Colorado Biomedical, Inc. filed a patent in 1987 based on Bayston's impregnation approach for antimicrobial catheters [122]. In 1995, Baylor College of Medicine, filed a patent describing another method to impregnate catheters [123]. A heated methanol based solution in which catheters could be dipped contained an alkalinizing agent (sodium hydroxide), minocycline and rifampicin (patent contains an extensive list of antibiotics) and a penetrating agent (butyl acetate).

### *3.2.2. Drug delivery – intravaginal rings*

The first intravaginal ring was developed in the late Sixties and was constructed from silicone elastomer [124,125]. The purpose of the ring was for the systemic delivery of medroxyprogesterone acetate as a form of contraception. From these early, but successful short trials, there followed extensive investigation of the silicone elastomer vaginal ring concept involving preclinical and clinical testing of different contraceptive hormones [126–

149]. The contraceptive hormones investigated during these intervening years were chlormadinone acetate [126,128], 3H-progesterone [127], progesterone [128,138,148,149], R-2323 [130,132], d,l-norgestrel [131,133–135], estradiol [135,137,140–142,144,146], R-2010 [136], levonorgestrel [137,140,143–145,147], norethisterone [138], oestrone [139], ST-1435 [142,144] and etonogestrel [146]. The patent landscape is peppered with filings for silicone elastomer contraceptive rings from 1973 onwards. Roseman's patent relates to a two-layered ring where the core layer is non-medicated and the sheath layer was medicated for implantation in "a living mammalian body, for example man and valuable warm blooded animals such as dogs, sheep, cattle and horses" [150]. The patent does not describe a particular therapeutic application but *in vitro* and *in vivo* tests described medroxyprogesterone acetate as the active ingredient. Schering AG patent described a vaginal ring where the main body was also non-medicated but instead medicated strips ran around the internal diameter and the periphery of the ring [151]. These medicated rims contained non-ionic, lipophilic drugs and no single therapeutic application is specified but instead the patent makes a list of progestins, estrogens, neuroleptics and antibiotics.

The Population Council ring was the first reservoir silicone elastomer vaginal ring [152]. The ring was constructed from three layers – a middle non-medicated core, a medicated sandwich layer and then a non-medicated sheath. The medicated layer was specified to contain estradiol and levonorgestrel, dl-norgestrel or norethindrone. The method of manufacture involved three production steps. The inner core was molded and then dip coated in a suitable solution that contained silicone and the active ingredients. After curing the two layered ring was dipped in a non-medicated solution. The Population Council further developed a vaginal ring that had up to three hollow channels into which medicated inserts could be placed [153]. Fig. (**8**). is a rendering of the Population Council insert-core vaginal ring.

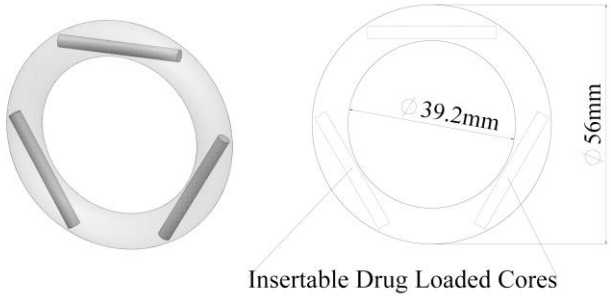


**Fig. (8).** Population Council insert-core vaginal ring.

A reservoir intravaginal ring was filed by Aktiebolaget Leo to treat menopausal women [154]. The core was fully medicated with 17β-estradiol and the ring manufactured in a step-wise fashion. A Dow Corning patent describes the production of a reservoir ring via co-extrusion [155]. The two ends were joined by a layer of uncured silicone. They did not specify a therapeutic application but instead list hormones, antibiotics, antiseptics and histamines. Leiras Oy developed a ring system that constituted a non-medicated main body support over which a medicated sheath could be slid over [156]. Enhance Pharmaceuticals described a co-injection moulding method for the production of reservoir rings [157]. Their approach also included a means of manufacturing a ring with a core of different segments. Galen Pharmaceuticals developed two reservoir rings, one as hormone replacement therapy (HRT) for menopausal women [158] and the other as testosterone therapy for premenopausal women [159]. International Partnership in Microbicides describe a platinum-catalysed silicone elastomer ring that incorporated a microbicide (dapivirine) [160]. It is a matrix ring designed to deliver between 1 and 3 mg of the drug in the initial 24 hour period of release.

Building on the clinical development and commercialisation of hormone–releasing silicone elastomer rings, research interest turned to the utility of such rings for other areas of medical intervention. Malcolm (The Queen's University of Belfast, UK) has been the prime mover in the development of silicone elastomer intravaginal rings for the delivery of microbicides [161–170]. The CAPRISA trial of 1% tenofovir vaginal gel demonstrated the importance of adherence to the dosing regimen in preventing HIV transmission [171] and therefore, underlined the need for vaginal ring based solutions. Overall the tenofovir gel reduced the incidence of HIV infection by approximately 39%. However, the reduction rate was 54% for those who adhered to the dosing regimen more than 80% of the time; a 38% reduction rate was seen for those with between 50 and 80% adherence, while those with less than 50% adherence had a 28% reduction rate. Acceptability studies have demonstrated a greater preference and adherence to vaginal rings compared to gels [172,173].

The first microbicide releasing ring contained a non-ionic surfactant (nonoxynol-9) as an active ingredient [165], but development of this ring stopped when the compound was shown to be an irritant to the vaginal mucosal after frequent application thus increasing the risk of HIV transmission [174–178]. Attention then was drawn to finding a safe and potent microbicidal compound. By far the most investigated and the furthest along the development pipeline for release from a silicone elastomer ring is a compound known as dapivirine. The drug is a non-nucleoside reverse-transcriptase inhibitor developed by Janssen (USA) [179]. The drug is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine has also the ideal physiochemical properties for delivery from a silicone elastomer ring – a small, hydrophobic molecule [167–170,180].

A matrix silicone elastomer ring containing 25 mg dapivirine is currently in two Phase III trials [181–183]. Fig. (**9**). is a rendering of the 25mg dapivirine silicone elastomer ring. The dapivirine ring has been through eight clinical trials, establishing acceptability, safety and tolerance [181]. Pharmacokinetic studies have demonstrated sustained delivery of high levels of dapivirine for up to one month of usage. The results of these two simultaneous studies should be available early 2016 and are expected to provide sufficient evidence to secure regulatory approvals and licensure. More than 4,500 women from across eastern and southern Africa have been enrolled in the studies. Both studies deliberately follow a similar protocol - double-blind,

randomized controlled trial of enrolled HIV-uninfected women, between the ages 18 – 45 years. Participants replaced the ring monthly for a minimum of one year. Running both studies concurrently will shorten the approval process and if successful start meeting the needs of at-risk women as soon as possible. ASPIRE (MTN-020) is led by the NIH funded Microbicide Trials Network and The Ring Study (IPM-027) is led by the developers of the dapivirine ring the International Partnership for Microbicides. These studies will also determine safety, acceptability, adherence, HIV-1 drug resistance mutations (if virus acquired) and steady state drug concentrations.

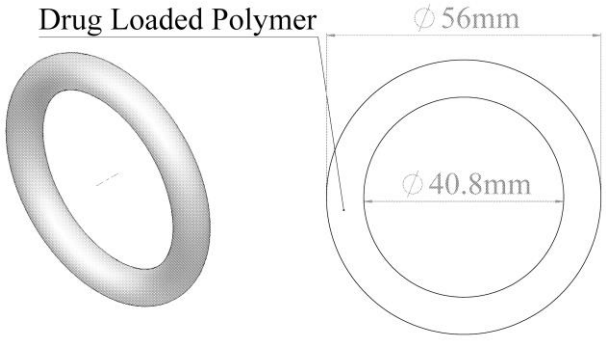


**Fig. (9).** Matrix silicone elastomer ring containing 25mg dapivirine.

Recently, vaginal rings that can release multiple drugs have gained considerable interest to the research community. Silicone elastomer rings have a long history in the simultaneous release of multiple hormones from a single device [135,137,140,142,146]. The renewed interest in this release strategy centres around two concepts - combination microbicide products and multipurpose prevention technologies (MPT). Antiretroviral combinations are commonplace in the treatment of HIV infection [184] and it is believed a similar approach could work as a preventive measure particularly if each drug has different mechanisms of action [185]. Simultaneously release of two or more microbicide compounds would offer: i) increased targeting of emerging resistant HIV mutations; ii) lower clinical concentrations for efficacy due to additive or synergistic effects; and iii) targeting of the HIV virus replication cycle at multiple stages. A silicone elastomer ring has been developed by IPM that contains dapivirine (NNRTI) and 100mg maraviroc (an entry inhibitor) [186]. A Phase 1 clinical trial of this ring (IPM 026/MTN 013) was completed in 2014 [187]. The results showed that although the ring was safe and well tolerated, the maraviroc did not release at sufficient quantities from the ring. Further work is continuing to improve the release of maraviroc. Another combination silicone elastomer ring being developed by the Malcolm *et al*. releases dapivirine (100mg) and a protease inhibitor darunavir (300mg) [188,189]. A pharmacokinetic study involving macaques revealed both drugs showed very similar tissue concentrations.

Silicone elastomer rings are also being developed as MPT strategies. IPM and the Malcolm group have been jointly developing next generation dapivirine rings that will both prolong release of the drug [170,190] and will also include contraceptive hormones thus creating a multi-purpose prevention technology [190–193]. Extending duration of a single ring would greatly reduce treatment cost per patient. Prolonged release of dapivirine can be achieved if the ring is of sheath-core construct (reservoir). Another benefit of the sheath-core construct is that contraceptive hormones could be included in the core. These drugs require the zero-order release afforded by this system to provide levels that are both safe and effective. Dapivirine has been combined with the hormones nesterone, ethinylestradiol, etonogestrel and levonorgestrel in the core [192–194]. Catalyst inhibition was observed in platinum catalysed silicone rings for ethinylestradiol and etonogestrel These binary drug systems also displayed eutectic behaviour [193]. Levonorgestrel showed the most potential to be further developed into a MPT ring in combination with dapivirine [191,195].

Another silicone elastomer based device that has the potential to be a MPT is the SILCS contraceptive diaphragm. This device has been under development by the PATH (USA) since 1994 as an one-size-fits-most cervical-barrier and has since entered the marketplace [196–204]. The device is now marketed as the Caya® Diaphragm [205]. Similar in format to a reservoir vaginal ring device, SILCS contains a specially designed shape-forming thermoplastic spring core, which is over-molded with silicone elastomer to form the barrier sheath. There is potential to incorporate a microbicide directly in the thermoplastic core [206]. A modified SILCS device comprising an injection-molded thermoplastic core, loaded with up to 20% dapivirine and over-molded with the standard silicone elastomer material, has been shown to provide constant *in vitro* daily release rates during continuous testing over six months [207]. SILCS diaphragm could also be inserted in tandem with a microbicidal gel formulation [208–210]. Fig. (**10**). is a rendering of the SILCS diaphragm showing the thermoplastic spring-core prior to overmoulding.

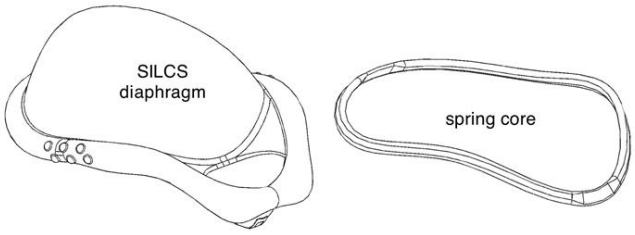


**Fig. (10).** SILCS diaphragm and embedded spring-core.

Pre-clinical studies are ongoing for other microbicide compounds released from silicone elastomer rings, including maraviroc [186,211], CMPD167 [211,212], MC1220 [213] and UC781 [214]. Partial protection was demonstrated against multiple RT-SHIV162P3 vaginal challenge of rhesus macaques fitted with a silicone elastomer vaginal ring releasing MC1220 [213]. Malcolm *et al.* have also investigated the potential of silicone elastomer rings as a platform for peptide and protein release [215–217]. A rod-insert ring is effectively a silicone ring with holes for the placement of rod formulations containing hydrophilic or large molecule peptide and protein actives that could not be released effectively from a silicone elastomer matrix. Rod formulations for this system can be lyophilized polymer gel

rods or directly compressed tablets. The ring body also has the potential to be loaded with drug. Freeze-dried aqueous gel formulations could potentially contain peptide and protein microbicides. Slow reconstitution of the gel by vaginal fluid leads to sustained release of these large molecule compounds.

### *3.2.3. Drug delivery – subdermal implants*

Silicone elastomer subdermal implants have been primarily for the release of hormones in both humans and animals. The Population Council (1966) was the first to develop the concept of a subdermal implant as a means of long-term but reversible contraception [218] and was a logical iteration of the device posited by Folkman and Long [37,219]. In a landmark study, Dziuk and Cook assessed the *in vitro* and *in vivo* diffusion of steroid hormones from silicone elastomer capsules [220]. A saline solution containing the silastic capsules would become saturated with melengestrol acetate within a 24 hour period. The same implants were shown to suppress the estrus cycle of ewes. Building from this, the organisation developed a contraceptive implant for women. The device consisted of six 34mm long capsules containing crystalline levonorgestrel (36mg) cores encapsulated in silastic tubing and sealed at both ends with silicone adhesive [221]. The capsules were then inserted subcutaneously in the inside upper arm providing a consistent 30µg daily dose of levonorgestrel for up to five years. This device was marketed as Norplant®.

The Population Council developed a second generation rod device that replaced the crystalline levonorgestrel cores with continuous solid dispersion (75mg) cores encapsulated in a dimethylsiloxane/ methylvinylsiloxane copolymer [222–227]. The new device required only two rods for insertion providing contraceptive protection for up to five years. The silicone elastomer copolymer used in the construction of the device was first described in a patent by Schering AG [228]. This second generation device is marketed as Jadelle®. Silicone elastomer rod implants have been shown to have the potential to be developed as a pre-exposure prophylaxis strategy [229]. Implants were shown to provide for the controlled, sustained, zero-order release of the potent prodrug tenofovir alafenamide in beagle dogs for over 40 days at levels over 30 times higher than those associated with HIV-1 PrEP efficacy in humans.

Implants are inserted into cattle to release hormones for growth promotion in calves for the beef industry [230]. The hormones released will increase production of muscle tissue and reduce overall body fat – providing for a leaner cut of meat and improved feed efficiency. Both estrogenic and androgenic implants are available for use at different stages of the animal's life [231]. Estrogenic implants can contain estradiol, progesterone or zeranol [232]. Androgenic implants often contain trenbolate acetate or testosterone propionate. The first silicone elastomer growth-promoting implant dates from 1980 and was filed by Eli Lilly [233]. It was a solid, cylindrical construction (variously sized) that could release different doses of estradiol. A patent by Sumitomo Pharmaceuticals Company, Limited describes a silicone elastomer matrix implant that released a high molecular weight growth promoter such as growth hormone, growth hormone releasing factors and somatomedin [234]. The implant would also release low molecular weight actives in the presence of albumin. In 1989, Hoffmann-La Roche, Inc. filed a patent for a reservoir rod implant that could deliver steroid hormones for either growth promotion or estrus cycle control [235].

## 3.3. Commercially available resins and products

NuSil (USA) produces specific grades of silicone elastomer for both medical implantation and drug delivery. Grades include liquids silicone rubbers, high consistency rubbers and low consistency elastomers. Bluestar Silicones (France) have Silbione® grades for drug delivery, medical implantation and catheter tubing. The company's pharmaceutical grade dimethicones and simethicones trade under the name Bluesil Oils 47. Dow Corning (USA) lists their medical device grade resins under different product codes depending on the chemistry of the material. Catheter grades are under the Silastic® trade name. Wacker (Germany) SILPURAN® grades are silicone rubbers used for tubes in the pharmaceutical and medical industries. SILFAR® simethicones and dimethicones are for pharmaceutical applications, including antiflatulent medication. Shih-Etsu Silicones (Japan) supply USP Class VI compliant and ISO 10993 standard tubing and moulding grade resins. Applied Silicone (USA) are a company which specialise in implantable grade silicone materials.

The following is a brief overview of some of the silicone elastomer based products currently in the marketplace. Bactiseal®, the invention of Bayston, is marketed by DePuy Synthes (USA) and contains rifampicin and clindamycin HCl. Silverline® Catheters (Spiegelberg GmbH, Germany) incorporate less than 1% silver nanoparticles and insoluble silver salt. There are three commercial silicone elastomer vaginal rings currently available - Estring®, Femring® and Progering®. Estring® is a ring for hormone replacement therapy that is designed to be worn for 90days. It is reservoir device, containing 2mg estradiol in the core providing a daily dose of 7.5µg and is marketed by Pfizer (USA). Femring® is manufactured from condensation cured silicone elastomer and is marketed by Actavis (Ireland) for hormone replacement therapy. Femring is available in two estradiol acetate dosing regimens 50µg/d (12.4mg) and 100µg/d (24.8mg). The ring is intended for three month placement. Progering® is marketed in regions of South America as a contraceptive for lactating women by Laboratorios Silesia SA (Chile). The ring releases progesterone (2g) at a daily dose of 10mg per day. The ring is worn continually for 90 days before replacement.

Two implants are on the market for the purposes of long-term (5 years) contraception. They are similar in construct and dosing - two silicone rods each containing 75mg levonorgestrel each. Jadelle® is marketed by Bayer Plc (Germany) and Sino-Implant II (Shanghai Dahua Pharmaceutical Co Ltd, China) is marketed in various Asian countries as Zarin, Femplant, Trust, Simplant and under other trade names. Compudose® (Elanco Animal Health, USA) is a silicone elastomer subdermal implant containing micronised estradiol (25.7mg) and oxytetracycline (0.5 mg) in a medicated core. This animal growth promoting implant is effective for at least 200 days. The implant is not removed prior to slaughter. Silicone elastomer is also utilised in the

production of three commercial transdermal patches. Transiderm Nitro 5 Patch (Novartis, Ireland) releases a daily dose of 5mg glyceryl trinitrate in the treatment of stable angina from $10cm^2$ patch. The same company markets an HRT transdermal patch (Vivelle-Dot®) that releases estradiol in five available strengths (25-100μg/d). Durogesic® (Janssen, USA) is a patch for the treatment of chronic pain that provides a daily dose of 0.288-24mg fentanyl (opioid analgesic).

## 4. ETHYLENE VINYL ACETATE

The invention history of ethylene vinyl acetate is rather unclear, as there are limited descriptions in the literature. The first patents these authors could find that describe the polymerization of vinyl acetate were a series filed by Shawinigan Chemicals Ltd (Canada) for material compositions in the production of gramophone records [236–240]. Following these patents, there were those filed by DuPont [241] and Celanese [242], who were the first companies to commercialise EVA resin and are still the leading suppliers of EVA resin worldwide. Industrial applications of the copolymer include cling film, soles, hot melt adhesives, toys, tubing, cable coating and bottle teats. The sections below will outline the chemistry and physical properties of EVA copolymers describing the history of drug delivery of the material in the literature and as commercial products.

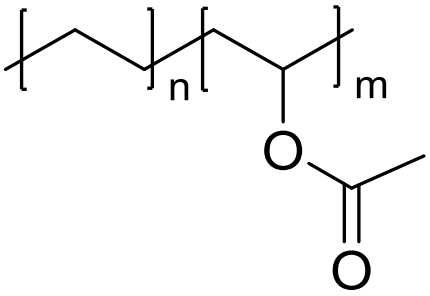


**Fig. (11).** Chemical structure of EVA copolymer.

### 4.1. Chemical Structure and Properties

EVA is a copolymer of ethylene monomer and vinyl acetate (VA) monomer, produce by free radical polymerization under high pressure conditions in either autoclave or tubular reactors. Fig. (**11**). is the chemical structure of the EVA copolymer. EVAs are commercially available with between 5 and 50% VA content. Due to the reactivity ratio between VA and ethylene being close to 1, the VA monomers are randomly distributed along the ethylene back bone. The VA content and its distribution along the back bone will influence the various physical properties of the EVA such as its melting point, crystallinity and hydrophobicity. The crystallinity of EVA will influence its mechanical properties such as flexibility and hardness, while its hydrophobicity will influence the solubility and thus diffusivity of small and large molecules through the EVA as well as its compatibility with other polymers. The higher the VA content the higher the inherent tackiness of the material; with adhesion to both polar and non-polar substrates possible. Changing the ethylene:VA ratio will influence the permeability of the polymer, thus tailoring the release kinetics of the various dosage forms.

### 4.2. Drug delivery: EVA copolymers

EVA copolymers have a long history of use within the pharmaceutical industry and academia. Drug release from EVA is diffusion controlled and can either be zero or first order depending on the design of the dosage form. EVA has been investigated for the controlled release of insulin from subcutaneous implants as well as the manufacture of intravaginal rings for either contraception or the prevention of HIV. EVA has also been investigated for the fabrication of ocular implants, as a rate controlling membrane on transdermal patches and for solid oral dosage forms.

#### *4.2.1. Drug delivery – subdermal implants*

EVA was investigated as a potential polymer for use in implantable devices for the delivery of insulin to treat diabetes. In 1976, a landmark paper published by Langer and Folkman demonstrated that out of the numerous polymer systems studied for their biocompatibility and sustained release of proteins, only two, EVA and hydroxyethylmethacrylate were shown to be biocompatible [243]. Pellets manufactured from EVA created no significant inflammation after implantation, while *in vitro* release data showed a small initial 'burst', it was slower overall and persisted significantly longer, compared to the hydroxyethylmethacrylate, making it more suited to the in vivo delivery of proteins. In order to try and reduce the initial burst, researchers coated the protein-loaded pellets with pure polymer, which was relatively successful.

The potential for EVA to be used *in vivo*, for the sustained delivery of proteins, encouraged further research into its release kinetics to improve the release profile for proteins. However, one major problem encountered was the uneven distribution of the protein within the pellets, which resulted poor reproducibility of the early studies. This was a result of the protein settling during the casting and drying stage of the pellets and at room temperature insoluble protein would migrate resulting in significant variation in protein-loading from pellet to pellet. To improve the homogeneity of the protein within the pellets Rhine developed a low temperature casting procedure, which resulted in more reproducible protein release profiles [244].

Once the issue of protein uniformity within the pellets was alleviated, researchers then set out to understand how large proteins could penetrate through and almost impenetrable polymer matrix. Using microscopy on EVA films Bawa *et al* demonstrated that upon casting the EVA films with no protein were essentially nonporous, while those with protein had a network of interconnecting pores [245], which allow for the diffusion of the large protein molecules through the EVA matrix. Drug release from EVA devices has two phases: the first is what is known as the 'burst', where drug on the surface is initially released. The second, slower and more sustained phase of release is due to the drug diffusing through the interconnecting porous network within the EVA matrix.

Creque *et al*. subcutaneously implanted insulin-loaded EVA pellets into diabetic rats. Within the first 24 hours glucose levels fell from 374-412 mg/dl to 87-127 mg/dl and

remained stable for 26 days, when it began to rise quite rapidly [246]. Furthermore, characterisation of the insulin released from the EVA pellets determined that it was 100% biologically active. However, approximately only 35% of the insulin was released *in vivo*. Researcher found that by using a more soluble form of insulin and by increasing the insulin loading it was possible to improve the in efficient release in vivo and to extend the duration of release [247]. Furthermore, by changing the method for producing the insulin-loaded EVA pellets and by using insulin with a larger particle size, it was possible to achieve a more porous EVA matrix which allowed for more of the insulin to be released [248]. However, this resulted in the insulin being released too quickly, so the pellets were coated with pure EVA to slow the release of insulin. This resulted in an implant which provided a slow release of insulin, while allowing more of the insulin to be released, resulting in increased efficiency. An *in vivo* study of the modified EVA pellets in diabetic rats demonstrated stable glucose levels for 45 days, with the insulin continuing to be released for up to 105 days, resulting in lower glucose levels in the test group compared to the untreated control group.

### *4.2.2. Drug delivery - intravaginal rings*

Intravaginal rings have a long history in contraception [249] and hormone replacement therapy [250,251]. Recently they have also been investigated for the delivery of microbicides [194] to prevent HIV transmission and for the localised treatment of cervical cancer [252]. Silicone elastomer rings had previously dominated the marketplace with the products Estring®, Femring® and Progering® used in hormone replacement therapy due the materials properties as outlined above. However, there are a number of drawbacks with this material, such as the use of high cure and post-cure temperatures, cost of manufacture, the requirement of higher initial drug loadings and higher residual drug content after release as well as recycling issues researchers are investigating the use of EVA vaginal rings for hormone replacement therapy. Due to their smaller internal diameter and size EVA rings require a lower initial drug loading to achieve similar release rates compared to silicone rings and are more efficient as they tend to leave a lower residual drug content after release. Furthermore, EVA can be reprocessed while silicone elastomers need to be incinerated.

The first EVA ring patents were filed in the mid-Nineties [253,254]. The reservoir based rings could have be one solid core or have multiple segments. These patents include that for the Nuvaring® product. Fig. (**12**). is a rendering of the Nuvaring® vaginal ring. The ring was designed for a core to contain a mixture of a progestin (etonogestrel) and estrogen (ethinylestradiol). The General Hospital Corporation filed a patent in 2008 describing a segmented EVA ring that could contain multiple steroidal compounds (progesterone and estradiol) in separate segments [255]. Columbia Laboratories have recently required the licence for this technology [256]. Helbling *et al*. manufactured a progesterone-loaded EVA ring via HME that had an *in vitro* release rate similar to the silicone elastomer Progering® [257]. The same group demonstrated that the release rate of progesterone from an EVA intravaginal ring could be controlled by a number of formulation strategies. They were able to optimize the ring so that it had a similar *in vitro* release profile to Progering® [258]. Merck Sharp & Dohme B.V. describe the invention of a three layer EVA ring containing a medicated core and intermediate layers surrounded by a non-medicated sheath [259]. Either medicated layer could contain nomegestrol acetate or estradiol.

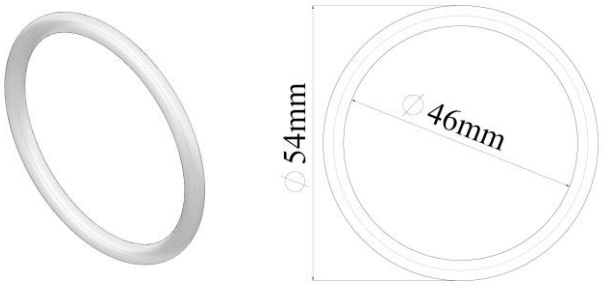


**Fig. (12).** Nuvaring® vaginal ring containing etonogestrel and ethinylestradiol.

EVA vaginal rings have been investigated for the delivery of HIV microbicides for the prevention of HIV infection. McConville *et al*. describe the development of a UC781 releasing EVA vaginal ring [260]. UC781, a highly selective and potent HIV microbicide, was mixed with EVA and compounded using HME. The extrudate was pelletized and the pellets subsequently fed into an injection moulder to produce the vaginal rings. The *in vitro* release of UC781 into simulated vaginal fluid from the EVA rings was significantly greater than that from silicone elastomer rings. The authors concluded that this was due to the EVA rings being manufactured at temperatures above the melting point of UC781 and thus it was in its amorphous form, while the silicone elastomer rings were cured at temperatures below the melting point of UC781, so the drug remained crystalline. UC781 is hydrophobic and has limited solubility in the aqueous based simulated vaginal fluid and thus its release from vaginal rings would be limited. However, by melting the UC781 and holding it in its amorphous form the authors were able to increase the release of UC781 from the EVA vaginal ring. However, Clark *et al*. compared the pharmacokinetics of UC781 in rabbits following vaginal administration of ring segments manufactured from silicone elastomer, polyurethane or EVA and demonstrated that all of the ring segments had similar *in vivo* UC8781 release rates regardless of the polymer used [214]. Loxley *et al*. described the development of an EVA vaginal ring that provided simultaneous release of both UC781 and the contraceptive levonorgestrel [261].

Uganokar *et al*. developed a novel EVA vaginal ring that was capable of releasing four drugs, MIV-150 for the prevention of HIV infection, zinc acetate for the prevention of both HIV and HSV infection, carrageenan for the prevention of HPV and HSV infection as well as levonorgestrel for unintended pregnancy at independent release rate [262]. The ring was comprised of an EVA body, which contained the drugs MIV-150 and levonorgestrel and a compressed core containing the drugs zinc acetate and carrageenan. The EVA ring body contained pores to allow the release of both zinc acetate and carrageenan from the core. MIV-150 and levonorgestrel were released from the EVA ring body via diffusion; while the zinc acetate and

carrageenan were released by diffusion via the pores on the ring body. All of the drugs released *in vitro* were active against HIV, HSV and HPV as demonstrated using cell based assays. *In vivo* all of drugs continued to be released for the full 28 days of the macaque study. Levonorgestrel serum levels were at similar levels associated with local contraceptive effects. These rings have the potential to be used as a multipurpose prevention technology, for the prevention of both HIV and HSV infection as well as unwanted pregnancies using a single drug delivery platform.

EVA vaginal rings have been investigated for the localised delivery of chemotherapeutic drugs for the treatment of cervical cancer. Keskar *et al*. incorporated cisplatin into an EVA vaginal ring and demonstrated that the release rate could be controlled by the cisplatin loading and that the rings were effective against both HPV positive and negative cervical cancers *in vitro* [252]. Boyd *et al*. formulated disulfiram, an anti-alcoholism drug which has shown to be effective against a range of cancers, into an EVA vaginal ring [263]. In this study, both EVA and silicone elastomers were investigated as matrix materials. However, disulfiram inhibited the curing process of the silicone elastomer and thus EVA was selected. The EVA rings provided diffusion controlled release of disulfiram for 14 days at levels well in excess of its $IC_{50}$ for HeLa cervical cancer cells.

### *4.2.3. Drug delivery - ocular*

EVA has been investigated for the ocular delivery of a range of drugs to treat a number of indications. 12 mg of 5-fluorouracil (5-FU) was formulated into 4mm diameter EVA disc, which provided *in vitro* release for up to weeks [264]. Subsequent subconjunctival implantation of the discs in rabbits provided release of 1mg/day for 10 days. The same study also demonstrated reduced intraocular pressure for 3 months in monkeys, although 5-FU was only released for two weeks. These same implants were evaluated in four patients undergoing high-risk trabeculectomy and in three of the four patients the intraocular pressure remained low, with a stable visual field and there were no significant side effects reported [265]. Dexamethasone loaded PVA/EVA implants were investigated for the prevention of proliferative vitroretinopathy (PVR) and released 1.5mg/h of dexamethasone for over three 3 months when implanted into the vitreous tissue of rabbits [266]. PVA/EVA implants containing 5mg of dexamethasone were implanted in rabbit eyes and significantly reduced ocular inflammation for over three months [267]. PVA/EVA implants containing cyclosporin A were able to maintain a concentration of 500ng/mL for more than six months after intravitreal implantation in both rabbit and monkey eyes [268]. A PVA/EVA episcleral implant containing betamethasone provided zero-order release kinetics both *in vitro* and *in vivo* after implantation on the sclera in rabbit eyes [269]. Betamethasone concentrations in the retina-choroid were maintained at levels above that required for suppressing inflammatory reactions for more than 4 weeks.

Ocusert® was a reservoir ocular implant with a core consisting of pilocarpine and alginic acid, which was surrounded by an EVA membrane to control the release of pilocarpine into the eye [270–272]. It was the first rate-controlled drug delivery device where the strength is reported on the label by the rate of drug delivery *in vivo* rather than by the amount of drug it contained. Ocusert® was capable of providing a predictable, time-independent constant concentration of pilocarpine in ocular tissue, which greatly improved the selectivity of pilocarpine and significantly reduced its side effects of miosis and myopia, while reducing intraocular pressure in glaucoma patients. Ocusert® was available in two doses, Pilo-20 that delivered the drug at a rate of 20µg/h for 7 days and Pilo-40 that delivered at a rate of 40µg/h for seven days. The Pilo-40 contained the same amount of pilocarpine as the Pilo-20, but the membrane of the Pilo-40 contained di(2-ethylhexyl) phthalate, which increased the rate of diffusion of pilocarpine across the EVA membrane, thus increasing the release rate.

### *4.2.4. Drug delivery - oral*

The gastrointestinal tract can be an extremely harsh environment for drugs due to enzymatic degradation and the wide range of pH, i.e. 2 in the stomach to close to neutral in the colon. For this reason, formulation scientists employ polymers to encapsulate and protect the drug in this harsh environment; while these materials also provide controlled release. EVA has potential to be such a material for oral drug delivery, particularly in the controlled delivery of potent, water soluble drugs, with relatively short biological half-life and good thermal stability. Almeida *et al*. demonstrated that metoprolol tartrate release from hot melt extruded EVA oral tablets was dependent on the vinyl acetate content of the EVA polymer, drug loading and extrusion temperature [273]. Almeida *et al*. also evaluated the influence of the swelling agent polyethylene oxide (PEO) on the release of metoprolol tartrate from hot melt extruded EVA matrices [274]. They demonstrated that metoprolol tartrate release was diffusion controlled as well as being dependent on the VA and PEO content, the PEO molecular weight, porosity of the EVA matrix and the size and distribution of the pores. Diltiazem HCL loaded EVA microparticles manufactured via the phase separation technique demonstrated zero-order release kinetics [275]. Drug release was increased by increasing the initial drug loading, varying the VA content of the EVA, increasing the porosity and reducing the size of the microparticles. Oral administration of the microparticles in animals demonstrated no significant difference in $AUC_{0\text{-}10}$ and $C_{max}$ between the microparticle formulation and the marketed control Cardizem®.

Tallury *et al*. investigated the influence of surfactants and drug loading on drug release from nystatin-loaded EVA oral films for the treatment of fungal infections in the oral cavity [276]. They produced the films using the solvent casting method. EVA, nystatin and surfactants were dissolved in dichloromethane and the films were cast by pouring the solution into a mould and evaporating off the dichloromethane to leave the EVA films. The release of nystatin increased with the addition of surfactants as well as an increase in both the surfactant and drug loading. Tallury *et al*. also investigated the release of an anti-fungal, acyclovir, and an anti-microbial drug chlorhexidine diacetate (CDA) from EVA oral films [277]. The films were manufactured using the solvent casting methods as mentioned previously. The release rate of acyclovir was

higher than that of chlorhexidine diacetate and increasing the VA content increased the release rate for both drugs, while coating the films reduced the release rate for both drugs. The use of delivery devices that that can release a combination of drugs may prove more effective in treating persistent oral infections in immunocompromised patients.

#### *4.2.5. Drug delivery - intracerebral*

Yang *et al.* produced 1,3-bis(2-chloroethyl)-l-nitrosourea loaded EVA discs using the solvent cast method for the treatment of localized brain tumors [278]. The EVA discs were subsequently implanted both intracranially and into the peritoneum of rats. The study demonstrated that the intracranial implants resulted in significantly higher drug levels in the brain compared to the peritoneum implants. Furthermore, drug was detectable in the brain tissue for up to 9 days from the intracranial implant and only 12 hours for the peritoneum implant. This study demonstrated that delivery from an intracranial implant maybe more efficacious in treating localized brain tumors.

### 4.3. Commercially available resins and products

Celanese (USA) is the leading supplier of medical grade EVA copolymer resins in the world. The VitalDose® grade of resins are all implantable grades and are tailored for controlled release applications. The company states that the material is being utilised in the development of a variety of pharmaceutical products via different routes of administration, including transdermal, subdermal, intravaginal, ocular, buccal, sublingual and rectal [279]. Neither, DuPont (USA) or Arkema (France) offer pharmaceutical grade EVA copolymer resins.

NuvaRing® (Merck, USA) is an intravaginal ring product that is used as a contraceptive and is manufactured by compounding etonogestrel and ethinylestradiol with EVA using HME and the extrudate subsequently cut to length and formed into a vaginal ring. It releases a daily dose of 120µg and 15µg of etonogestrel and ethinylestradiol respectively into the vaginal epithelium, thus avoiding the daily fluctuations in serum levels which are associated with oral contraceptives. Each ring is put in place for three weeks followed by a ring free week. A user acceptability study conducted in both North America and Europe demonstrated that 81% of 1,950 women preferred the ring compared to oral contraceptives, which had 66% preference rate before the study [280]. Furthermore, 85% of women and 71% of their partners stated that they never felt the ring during intercourse [280]. A clinical study demonstrated that the ring is highly effective, safe and well tolerated offering a robust inhibition of ovulation [281]. Implanon® (Merck, USA) is a contraceptive implant containing Etonogestrel and manufactured by HME. Like with NuvaRing®, etonogestrel is compounded into EVA via HME and the extrudate cut into rods that is 4cm long and 2mm in diameter [282].

Vitrasert® is an EVA based ocular implant that releases ganciclovir for the treatment of cytomegalovirus retinitis marketed by Auritec Pharmaceuticals (USA). It consists of a compressed ganciclovir tablet coated with polyvinyl alcohol and EVA to control release. Vitrasert® has the advantages of convenience, lack of systemic toxicity and reduced costs. The Vitrasert® implant was compared to intravenous administration of ganciclovir in a randomised control trial in 188 patients with AIDS and newly diagnosed CMV retinitis [283]. The Vitrasert® implant increased the median time to progression from 120 days for intravenous administration to 210 days. Thus Vitrasert® was approved by the International AIDS society for the treatment of CMV retinitis in AIDS patients [284].

## 5.0 THERMOPLASTIC POLYURETHANE

Thermoplastic polyurethane (TPU) has the most versatile chemistry of the three polymers described in this review. Otto Bayer first synthesised polyurethane in 1937 and it has since been harnessed to make a wide array of products. Polyurethanes can be both thermosetting and thermoplastic and both play extremely important roles across a number of industries. Thermoset resins can be soft foams, rigid foams, hard coatings or the matrix materials in composites. TPU can be hard and strong, finding use as automotive interiors, rigid gaskets and toothbrush bristle, or it can soft and rubbery employed in the manufacture of flexible tubing, seals and toothbrush grips. TPUs can be hydrophobic or hydrophilic. Polyurethanes can be engineered to have chemical linkages that are biodegradable, so that the material can be broken down *in vivo* and expelled by the body. TPUs are used in the fabrication of medical implants such as cardiac pace makers and vascular grafts. Some TPUs are toxic in biological environments but others are biocompatible even when implanted in excess of five years. The sections below will outline the chemistry and physical properties of TPU describing the history of drug delivery of the material in the literature and as commercial products.

### 5.1. Chemical Structure and Properties

Polyurethane chemistry, although extensive, is well understood in the literature and has been the topic of in-depth publications [285–287]. Polyurethane synthesis occurs via a polyaddition reaction between a diisocyanate and a polyol. Other chemical compounds may also be involved in the synthesis of commercial grades, including chain extenders, catalysts and additives. TPUs are linear block copolymers that consist of alternating blocks of polymer chain segments. The hard segment is composed of the dissocyanate and a chain extender. The soft segment consists of the polyol. These two thermodynamically immiscible segments remain in separate phases within the TPU matrix with the hard segments acting as physical crosslinks between respective soft segments. Separate hard segments form hydrogen bonds and will cluster into ordered domains. The soft segments remain in a disordered amorphous state. Careful design of phase domains will control the bulk properties of the TPU. Hard segments provide TPUs with plastic properties including strength and toughness. The soft segments instill elastomeric properties, including flexibility and elasticity. The composition of polyurethane elastomers can be varied to produce hard and stiff to soft and rubbery materials. The bulk properties of the TPU can be further altered by varying the constituent diisocyanate, polyols and chain extenders in the respective segments.

Diisocyanates have either an aromatic or aliphatic form. The main aromatic functional groups are toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), p-

phenylene diisocyanate (PPDI) and naphthalene diisocyanate (NDI). The aliphatic diisocyanates are hexamethylene diisocyanate (HDI), hydrogenated MDI (HMDI) and isophorone diisocyanate (IPDI). Fig. (**13**). is the chemical structure of a typical polyurethane. Aromatic diisocyanates tend to produce TPUs that have better mechanical properties and are more thermally stable; while the aliphatic forms produce more UV stable resins. Aromatic based TPUs will undergo UV initiated oxidative degradation that will discolour the material and give a loss in mechanical performance. Since this reaction occurs at the aromatic ring, aliphatic based TPUs will not discolour or lose mechanical performance when exposed to sunlight. Aromatic TPUs find the most widespread use in industry as they are ideal for applications requiring flexibility, strength and toughness. Aliphatic based TPUs are best suited to aesthetic products that require good light stability and optical clarity.

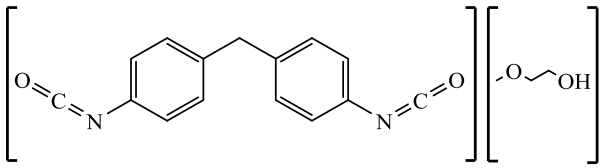

**Fig. (13).** Typical polyurethane chemical structure containing an isocyanate (MDI) and a diol (ethylene glycol).

Polyols are long-chain diols and are sometimes referred to as macroglycols. Polyol molecular weight has a significant effect on TPU processability and mechanical properties. Phase separation of the segments increases with increasing polyol molecular weight which provides for better elastomeric performance. Increasing TPU molecular weight will increase the melting point and decrease processability. Polyurethane polyols can be grouped into polyether, polyester, polycaprolactone, polycarbonate and acrylic, although acrylic is not suitable in the production of TPUs. Each polyol offers different property characteristics for TPUs and they will influence thermo-oxidative degradation.

Polyester based TPUs have very good resistance to oils and chemicals, but are vulnerable to hydrolytic degradation as the aliphatic ester bonds are susceptible to hydrolysis. Polyether based TPUs are more hydrolytically stable and offer low temperature flexibility. Polyester based TPUs have better mechanical performance. Polycaprolactone based TPUs have a similar mechanical performance to polyester-based TPUs, especially at low temperatures, and a relatively high resistance to hydrolysis, although not as high as polyether based TPUs. Polycarbonate based TPUs exhibit high tensile modulus but low elasticity. Not all TPUs are suitable for implantation. Polyester based TPUs are hydrolytically unstable and will breakdown *in vivo*. Polyether based TPUs will undergo oxidative degradation and must be stabilized with copolymers such as silicone. Polycarbonate based TPUs are the most suitable for long-term implantation as they do not undergo hydrolytic or oxidative degradation.

### 5.2. Drug delivery: thermoplastic polyurethanes

Thermoplastic polyurethane, as befits its versatile chemistry, can provide zero-order, Fickian-diffusion-driven or hybrid drug release profiles. Drug release is dependent on the bulk properties of the polymer, namely crystallinity, steric hindrance and hydrophilicity. TPU crystallinity increases with increasing hard segment. Softer grades of the polymer are virtually amorphous but increasing the ordered hard segments leads to a more semi-crystalline material. Crystallinity hinders the diffusion of drug in all thermoplastic materials, therefore softer TPUs in general will promote Fickian-diffusion. The spatial structure of the hard segments will further influence the diffusion pathway of drug molecules, since higher content and the closer packing of hard segments will significantly impede diffusion of molecules. Since diffusion from TPU matrix systems is Fickian driven, the release rate will also be governed by polymer permeability, drug solubility, drug particle size and drug loading. The last factor controlling drug release is the hydrophilic nature of the polymer. The hydrophilic nature of TPU can be controlled through polyol selection. The more hydrophilic the TPU, the more water will ingress into the material which will lead to swelling of the polymer. Water swelling can both speed-up and slow-down drug diffusion, since the phenomenon simultaneously increases the free volume and lengthens the diffusion pathway. Water-swelling can also switch release kinetics from Fickian diffusion to zero-order or provide for a mixture of the two. The majority of pharmaceutical applications of thermoplastic polyurethane have been focused on two drug delivery systems – catheter tubing and intravaginal rings.

#### *5.2.1. Drug delivery - catheters*

Polyurethane catheter tubing dates back to the late 1970s [288]. TPU catheters are as prone to biofilm formation as silicone catheters and therefore require similar eradication strategies. The first approach to overcome this issue was to complex TPU with different compounds, such as iodine, that are shown to be active against biofilm at different stages along the formation pathway [289,290]. The first drug eluting TPU catheter patent was filed in 1988 with TPU listed alongside silicone elastomer as a material of manufacture for a catheter loaded with a silver salt and a biguanide as an anti-infective strategy [291]. The following year Becton, Dickinson And Company filed a patent for a drug-eluting catheter produced from an extruded TPU tubing containing chlorhexidine as the active agent [292]. Columbia University filed a patent for hydrophilic TPU tubing coated with hydrophilic polyurethane containing a synergistic combination of triclosan and chlorhexidine or hydrophilic TPU tubing coated with hydrophobic polyurethane containing silver sulfadiazine [293].

There have been a number of key publications from academia in TPU based catheters, almost all of which are in the relation to the prevention of biofilm formation. In addition to the substantial investigation of different functional coatings [58,294–296], there has been the development of antifouling polymers, especially polyethylene glycol, which can be grafted to TPU surfaces [297–301]. Antifouling polymers express a number of characteristics which inhibit biofilm formation – they are hydrophilic and water-swellable; they have excellent surface wettability; they are hydrogen receptors and they are electrically neutral. Francolini *et al.* have developed TPUs for the construction of catheters or as a coating for implants

that have intrinsic antifouling properties that inhibit the biofilm formation [302]. Their approach is to maximise both bulk hydrophilicity and surface wettability. Their TPU containing a poly-l-lactide soft segment and a MDI-dihydroxymethyl-propionic acid hard segment was shown to completely inhibit *Staphylococcus epidermidis* adhesion after 24 hour exposure.

A number of drug-eluting catheters are also being developed. Mandru *et al.* have described the release of nystatin and rifampicin from TPUs with two different urethane group concentrations [303–305]. Release of drug increased as the urethane concentration decreased in two different TPU systems. The systems were able to release drug at much higher levels than the minimum inhibitory concentration for fungi and Gram-positive bacteria respectively. A number of publications have described the development of experimental drug loaded polyurethane based coatings that are suitable for catheters and longer-term implants [306–313]. Ma *et al*. have taken a different approach to biofilm infections, moving beyond traditional antibiotic therapy in an effort to overcome antibiotic resistance [314]. They describe the controlled release of two novel chelated gallium or zinc complexes. These agents act to prevent soluble iron uptake of most bacteria. These agents are released from polyether based polyurethanes via an incorporated polyethylene glycol pore-forming agent for period of up to 90 days. *In vitro* testing of film samples exhibited ≥ 90% reduction of both Gram-positive and Gram-negative bacteria. An *in vivo Pseudomonas aeruginosa* challenge study in mice showed the film possessed a strong ability to protect against bacterial infection.

### *5.2.2. Drug delivery – intravaginal*

Intravaginal drug delivery from polyurethane drug delivery systems dates back to 1968, when polyurethane is mentioned as a suitable material for the manufacture of a vaginal ring for the delivery of a range of actives, including medication, hormones and vitamins [315]. In 1977, Ortho Pharmaceutical Corporation patented a non-medicated contraceptive diaphragm made from polyurethane that could be polyester or polyether based [316]. Leading on from this, the Southern Research Institute filed a patent in 1986 for a disposable, spermicide-releasing contraceptive diaphragm [317]. The device was constructed from a blend of a thermoplastic polymer (polyurethane), a water-soluble polymer (polyethylene glycol) and a spermicide (nonoxynol-9). The preferred polyurethane was polyether based but polyester based TPUs were also listed.

Kirschbaum's patent describes water-swellable polyurethane as the outer layer of a tubular insertion that contains a medicated liquid reservoir [318]. The polyurethane both acted as means of gripping the walls of the vagina and as a porous sheath for controlled release of a drug locally or systemically. The 1995 patent describing the 17β-oestradiol eluting intravaginal ring by Galen Pharmaceuticals also listed polyurethane in addition to silicone elastomer as a material of construction [158]. The Population Council took a similar patent strategy for their insertable core ring [153]. A patent filed by The General Hospital Corporation describes a segmented ring for the release of multiple drugs that is preferably constructed from EVA but has polyurethane listed as a suitable alternative [255]. Merck Sharp & Dohme B.V. patent also lists polyurethane as a suitable alternative material to EVA in the construction of a multilayer vaginal ring [259].

Ferring B.V. filed a patent in 2007 for a hydrophilic (water-swellable) polyurethane intravaginal ring for the release of proteins, benzodiazepines, anti-migraine agents and anti-infective agents [319]. This is the first filing of a patent to expressly describe polyurethane as the preferred material for the construction of a vaginal ring. The patent filed by the University of Utah Research Foundation in 2008 describes a polyether based TPU matrix ring capable of zero-order release [320]. The University filed a patent in 2011 for a reservoir ring with a sheath of either water-swellable or non-water swellable polyurethane [321]. Dsm Ip Assets B.V. filed a patent in 2011 for a TPU intravaginal ring constructed from water-swellable polyurethane with surface modifying agents for the release of preferably two or more drugs of different physiochemical properties [322]. Chemo Research, S.L. patent describes the invention of a reservoir ring that consists of a water-swellable TPU core and an EVA sheath. The medicated core can potentially be loaded with any active pharmaceutical compound but the patent describes the testing of a ring loaded with ethinylestradiol and levonorgestrel [323]. The main inventive step of the patent is to limit the physical changes of water-swellable polyurethanes but still provide zero-order release. The EVA layer regulates drug release even though the polyurethane still swells, therefore providing better control of the release of water-soluble drugs and structural integrity.

Academic research in polyurethane based intravaginal rings has mostly been focused on HIV prevention with the work of Kiser (Northwestern University, USA) leading the field. TPU has been a particularly useful material for the release of potent hydrophilic microbicides, such as tenofovir, that cannot be effectively delivered from silicone elastomer or EVA. After establishing in principle that TPU could deliver effective quantities of a lead microbicide [324], Kiser has shown the potential of this material to deliver a broad range of microbicide candidates, including tenofovir [325–330], tenofovir disoproxil fumarate [331–335], dapivirine [324,325,336], UC781 [214,337], IQP-0528 [338], IQP-0532 [338] and SAMT-10 [339]. A key focus for the group has been on the development of multi-segmented rings that are capable of the simultaneous delivery of multiple drugs of different physiochemical properties at independent release rates.

In the first iteration, the drug loaded TPU was solvent cast prior to hot-melt extrusion into 4.5mm rods [325]. The separate sections of non-water swellable and water-swellable TPU were simply welded together to form an oval-shaped ring. Dapivirine (a hydrophobic drug) and tenofovir (a hydrophilic drug) displayed much different release profiles from the two different TPUs. The non-swelling TPU displayed Fickian diffusion behaviour in releasing 20% of available dapivirine in 30 days while the water-swellable TPU released 70% of available drug in 30 days. This difference is related to the ingress of water pushing apart the polymer chains providing for a less hindered diffusion pathway. Tenofovir did not release from the non-swellable TPU at all; while the drug released readily from the water-

swellable TPU with the amount released dependent on drug loading. Release was non-linear, particularly for the lower loadings due to the effect of drug depletion. At higher loadings linearity of release increased as release was not solely reliant on Fickian diffusion but was instead anomalous transport driven.

The next iteration of the multi-segmented TPU ring added reservoir segments. In one instance of this ring, TPU tubing was filled with a paste containing tenofovir [328]. The second reservoir segment was produced via co-extrusion and was loaded with the contraceptive hormone levonorgestrel. The ring is a multi-purpose prevention technology. This ring had similar mechanical performance to the contraceptive vaginal ring Nuvaring®, indicating that it would likely be well tolerated *in vivo*. *In vitro* release testing revealed time-independent release rates for both drugs and that flux could be tuned via sheath thickness, segment length and loading. The desired release rates were optimized to achieve a clinically effective target of approximately 10 mg/d tenofovir and 10 or 20 µg/d levonorgestrel. *In vivo* release rates in sheep were within range of these targets even after 90 days.

A scaled down TPU tubular ring was shown to completely protect pigtailed macaques from multiple vaginal simian-HIV challenges [332–334]. The ring produced from polyether based TPU tubes was filled with a paste containing the prodrug tenofovir disoproxil fumarate. Strategies were employed in an attempt to overcome the lag issues associated with reservoir devices. NaCl was added to the paste formulation as an osmotic excipient to attract vaginal fluid into the core to solubilize the drug and rapidly establish a concentration gradient of soluble and diffusible drug to drive release. Also, to further limit lag the rings were exposed to elevated temperature post manufacture to drive drug into the tube walls. Pharmacokinetic studies revealed that monthly sustainable protective levels of the drug were achieved in both vaginal fluid and tissue, and that that the ring was safe and well tolerated. Six macaques treated with the drug eluting vaginal ring remained unaffected after months of repeated weekly vaginal (TCID50) challenges with simian-HIV. Eleven out of twelve of the control macaques became infected after a median of four exposures to infection. The next phase is for the tenofovir disoproxil fumarate vaginal ring to enter the clinic. A Phase 1 Safety and Pharmacokinetic trial has already been completed and both placebo and TDF-loaded rings were well tolerated. Tenofovir levels exceeded the clinical correlate of protection previously established for a gel product [171,172]. Fig. (**14**). Is a rendering of the segmented TPU vaginal ring going forward into the clinic. An intravaginal ring may well overcome issues of adherence laid bare by the CAPRISA trial. Nevertheless, there may well be some issues in relation to consistent use of ring products [340].

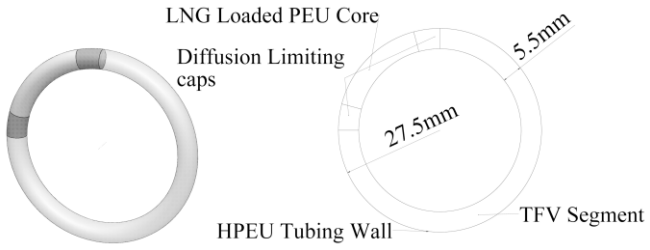


**Fig. (14).** Segmented TPU vaginal ring developed by the Kiser group at the University of Utah.

### *5.2.3. Drug delivery - other implants*

Other TPU based implantable devices have been patented or are being actively investigated in academia. Alza Corporation had the first patent (1972) for a capsule-like implant that could be swallowed and provide for the prolonged release of drug [341]. A later patent by the company in 1975 mentions a semi-permeable implant that could also be swallowed and remain in the patient for an extended period for delivery of a pre-programmed regimen [342]. Polyurethane was described as a potential material in the manufacture of a non-biodegradable wall of the device. Ethicon, Inc. patent from 1975 describes the employment of polyurethane antimicrobial coating for sutures [343]. Minnesota Mining and Manufacturing Company patented an implant that can be delivered via ballistic means into livestock for the release of a wide variety of potential actives [344]. Polyurethane was one of the materials mentioned as a forming material for the device's microporous membrane.

There have been a number of patents that specify specific TPU chemistries as part of the invention. An 1984 patent by the Research Corporation describes a transdermal or transmucosal device constructed from a poly(ether urethane)-PDMS block copolymer for the zero-order release of lipophilic drugs for prolonged periods of time [345]. The device was especially suitable for the release of phenytoin, primidone and dapsone. A special type polyether based TPU was used to construct a reservoir rod implant for the zero-order release of histrelin, risperidone, dexamethasone, naltrexone, metolazone, clonidine, or selegiline was described in patent filed by Endo Pharmaceuticals Solutions Inc [346]. A patent by Ferring BV describes the invention of a linear, amphiphilic TPU for melt-processing into a controlled release implant, such as a ring, patch or buccal insert [347]. The polymer is obtained by reacting together polyethylene glycol or polypropylene glycol; a block copolymer (PEG-PPG-PEG or PPG-PEG-PPG); a diol or a diisocyanate. The active compound could be a pharmaceutically active agent for human or animal use.

Ghent University have investigated the suitability of TPU as a matrix polymer for oral dosage forms [348,349]. The tablets were produced in two steps via hot-melt extrusion compounding and injection moulding. The tablets produced were solid dispersions of drugs in the matrix as processing occurred below the melting point of the drugs. They were able to achieve very high drug content in the tablets. Release of metoprolol tartrate was controlled over a 24 hour period and in the case of diprophylline could only be achieved in combination with glycol 4000 or Tween 80. No burst release and no changes in the physical size of the tablets were observed. A Simulator of the Human Intestinal Microbial Ecosystem (SHIME) was used to demonstrate that this TPU material did not affect the GI ecosystem. The studies are very encouraging as TPU has the potential to offer unique characteristics in the formulation of oral solid dosage forms.

### 5.3. Commercially available resins and products

The two leading suppliers of implant grade TPU are Lubrizol (USA) and DSM Biomedical (USA). Lubrizol's Pathway™ grades are aimed specifically at pharmaceutical applications. The grades are entirely customisable, designed to match the exact need of the customer and are manufactured in compliance with the IPEC-PQG and USP/NF good manufacturing practice guidelines for pharmaceutical excipients. The grades are aliphatic polyether based but can be tailored to be either hydrophobic or hydrophilic. The hydrophilic grades can be formulated to absorb anywhere between 20% to 1,000% water by weight. The company's Tecophilic™ and Pellethane® grades are also utilised in the production of transdermal patches. DSM Biomedical provide a wider range of pharmaceutical grade TPUs. PurSil® grades are thermoplastic silicone-polyether polyurethane based and benefits from having the combined properties of silicone and polyurethane. The addition of the silicone component provides for a TPU with increased biocompatibility and biostability. CarboSil® is a grade of TPU combining the biocompatibility of silicone with the mechanical robustness of polycarbonate based polyurethanes. Bionate® is thermoplastic polycarbonate polyurethane that has been used in the construction of longer term implants for nearly two decades. BioSpan® is a segmented polyether polyurethane aimed particularly at applications requiring flexibility over an extended period of time.

## 6.0 CONCLUSION

Non-degradable polymers have a long and distinguished history in drug delivery. The properties of these materials have served a specific purpose, permitting the development of life-enhancing therapies that would not have otherwise been possible. The advancement of non-degradable polymers and methods of manufacturing solid dosage forms will allow for the development and production of drug delivery devices that will release their active(s) in response to stimuli such as glucose levels or changes in temperature and pH. These dosage forms could be long-term implantable devices that will only release drug when required by the patient i.e. when glucose levels dip or local temperatures increase due to infection. This will bring in the third generation of drug delivery which is personalized medicine, defined as "the customisation of healthcare to an individual patient". The potential of non-degradable polymers in these areas of drug delivery has not been fully realised. The development of new, 'smarter' non-degradable polymers that can be implanted and release drug for much longer periods will allow for the continuous and cost effective treatment of chronic diseases such as diabetes, hypertension, cardiovascular disease and even cancer. These devices would have the potential to be tailored to the patients' needs and remain in place for years, significantly improving their quality of life.

## CONFLICT OF INTEREST

The authors have no conflict of interest and do not receive funding from any of the companies mentioned in this review.

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