**Hot-melt co-extrusion: requirements, challenges and opportunities for pharmaceutical applications**

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**Abstract**

**Objectives**

Co-extrusion implies the simultaneous hot-melt extrusion of two or more materials through the same die, creating a multi-layered extrudate. It is an innovative continuous production technology that offers numerous advantages over traditional pharmaceutical processing techniques. This review provides an overview of the co-extrusion equipment, material requirements and medical and pharmaceutical applications.

**Key findings**

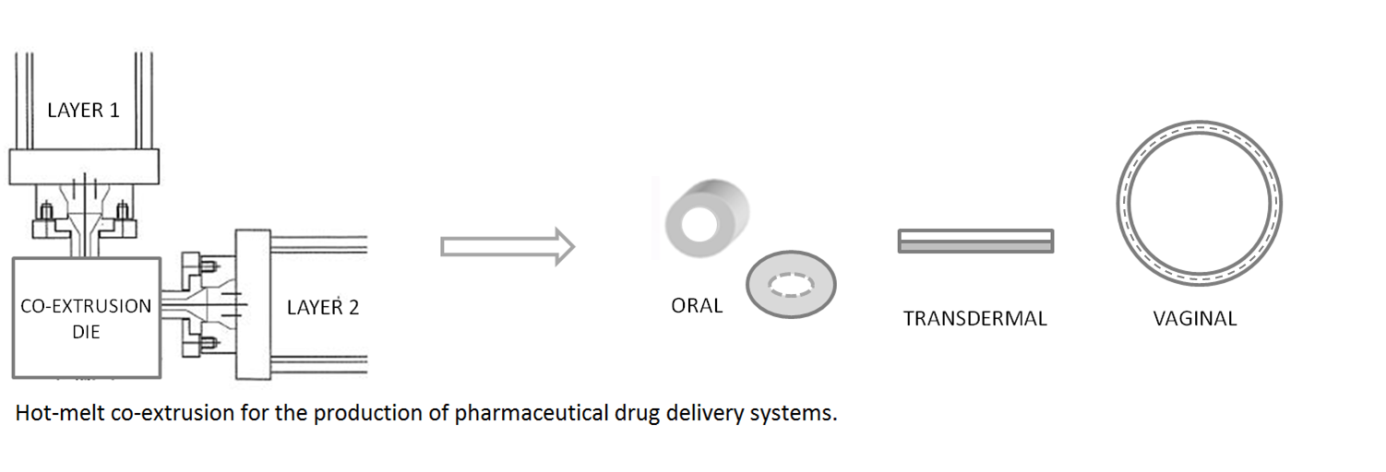
The co-extrusion equipment needed for pharmaceutical production has been summarized. Because the geometrical design of the die dictates the shape of the final product, different die types have been discussed. As one of the major challenges at the moment is shaping the final product in a continuous way, an overview of downstream solutions for processing co-extrudates into drug products is provided. Layer adhesion, extrusion temperature and viscosity matching are pointed out as most important requirements for material selection. Examples of medical and pharmaceutical applications are presented and some recent findings considering the production of oral drug delivery systems have been summarized.

**Summary**

Co-extrusion provides great potential for the continuous production of fixed-dose combination products which are gaining importance in pharmaceutical industry. There are still some barriers to the implementation of co-extrusion in the pharmaceutical industry. The optimization of downstream processing remains a point of attention.

**KEY WORDS**: Co-extrusion, hot-melt extrusion, fixed-dose combination products, co-extrusion equipment, oral drug delivery systems, pharmaceutical applications

***Graphical Abstract***



1. **Introduction**

Co-extrusion is defined as the simultaneous hot-melt extrusion of two or more materials through the same die, creating a multi-layered extrudate [[1](#_ENREF_1)]. The technique allows to combine the desirable properties of multiple materials into a single structure with enhanced performance characteristics. The simultaneous extrusion of graphite and presswood for making pencils was already patented in the 19th century. Since 1940 hot-melt co-extrusion was utilized predominantly in the plastic industry and to a lesser extent in the food industry. Co-extrusion of plastics started with the production of pipes, wires and cables. The first major plastic co-extrusion was the production of the multilayer garden hose (patented in 1947). Another early example of plastic co-extrusion is the multilayer drinking straw, that came on the market in 1963 [[2](#_ENREF_2)]. Plastic co-extrusion has a lot of applications in the packaging industry which can be divided into barrier and non-barrier applications. The incorporation of a barrier layer is used to control transmission of oxygen, carbon dioxide or moisture [[3-5](#_ENREF_3)]. Non-barrier applications include improved appearance (coloration, opacity), improved sealing characteristics, stiffness/strength adjustment and printability. Around 1984 co-extrusion became popular in the food industry to produce snacks with different colors, textures or flavors. The outer material is usually starch- or cereal-based, while the filling can be cereal-, fat-, sugar- or water-based. In comparison to plastic co-extrusion, the use of food products has additional challenges. Due to many transformations (starch gelatinization, protein coagulation, formation of amylase-lipid complexes, non-enzymatic browning [[6](#_ENREF_6)]) occurring during co-extrusion-cooking, large rheological changes are observed, which complicates the process. Moreover the shelf life of co-extruded food is often limited, because of migration of moisture or oil from the filling to the outer material [[7](#_ENREF_7)].

Due to the advantages of hot-melt co-extrusion over conventional solid dosage form manufacturing techniques, the pharmaceutical industry became interested in this innovative technology. Besides the continuity of the process its major advantages are fewer processing steps, no use of organic solvents/water and the possibility of improving drug solubility or sustaining drug release [[8-11](#_ENREF_8)]. Additional benefits of this technique include its versatility, increased throughput and reduced costs. By producing multilayer products with a reduced amount of expensive polymers and increased amount of inexpensive polymers a cost-efficient process can be achieved without sacrificing performance, e.g. by placing pigment only in appearance layers and/or by using recycled material in an inner layer [[12](#_ENREF_12)]. The technology does have a price however. Besides the investment in equipment (additional extruders) and the need for additional floor space for the extruders, there is often need for an experienced line operator (taken into account the increased levels of process complexity). In some cases the additional process costs may offset the material cost savings.

Up until now co-extrusion has been barely applied in the pharmaceutical industry. The only two coextruded dosage forms available on the market are Nuvaring®, a contraceptive vaginal ring, and Implanon®, a contraceptive implant [[13](#_ENREF_13)]. So far, there are no co-extruded dosage forms for oral use on the market and only a few papers on this topic have been published during the last decade [[1](#_ENREF_1), [14-16](#_ENREF_14)].

1. **Process and Equipment**

Co-extrusion implies extruding two or more materials through a single die. The materials for each of the layers (API, polymer, plasticizer and/or other additives) are premixed or separately fed into an extruder. In each heated extruder barrel the material is softened, mixed and finally extruded through the die, where the different melt streams are combined into the final co-extrudate. The co-extrudate is then shaped, cooled and further processed. Throughout the entire process several important process parameters need to be controlled. Process analytical technology (PAT) can be used for in-line control of the product quality.

The co-extrusion equipment that was traditionally designed for the plastics industry needed to be adapted to meet regulatory requirements for pharmaceutical use. All product contact parts need to be GMP-compliant so as not to be reactive, additive or absorptive. Pharmaceutical design also includes perfect cleanability, process reproducibility proven by stringent documentation and the use of FDA approved materials. Another challenge is the miniaturization of pharmaceutical extrusion equipment, in particular for the development of formulations with new chemical entities [[17](#_ENREF_17)]. While there is no need for a special co-extrusion design of the upstream equipment (feeders and extruders), the specific requirements for die and downstream equipment with regard to co-extrusion will be discussed. All equipment of a co-extrusion line need to fit together and the extruders have to be positioned in a way that they can easily be connected at the die. Therefore the overall design of the co-extrusion line, fit to the dimensions of the production facility, is important.

* 1. *Feeders*

In co-extrusion the material mix of each layer is fed separately into the barrel of an extruder. Materials for each specific layer can be either premixed in a fixed ratio or individually metered into the extruder. Feeding in a constant and accurate way is a challenging but very important aspect in pharmaceutical extrusion processes. Feeding is either starve-fed, where the rate is set by the feeders, or flood-fed where the extruder screw speed determines the output.

Powders are mainly fed into the extruder using screw feeders which can be optimized by choosing the type of screws according to the powder characteristics. For powders with poor flow properties co-rotating twin screw feeders can be used instead of single screw feeders. An improved hopper design and discharging aids can also be build into the feeders to avoid bridging or other feeding problems. Feeders are controlled in a gravimetric or volumetric way. The controller of a volumetric feeder imposes a constant rotation speed, which can result in high mass-flow fluctuations, whereas a gravimetric or loss-in-weight feeder monitors the weight fluctuation per time interval and modifies the rotation speed to keep the mass-flow rate constant. It is obvious that loss-in-weight feeders are typically preferred in pharmaceutical GMP installations.

Besides the equipment for powder feeding, different types of pumps are available for liquid feeding. When using a gear pump and a simple straight-end nozzle it was shown by Raman mapping that the liquid component is not always uniformly distributed in the extrudate. Adaptations in the nozzle, thereby increasing the pressure at the liquid feeder and reducing the dead volume at the nozzle proved to be a solution for a wet granulation process [[17](#_ENREF_17)]. Further investigation for the hot-melt extrusion process is needed.

* 1. *Extruders*

Extrusion processes can be categorized as either ram or screw extrusion. In ram extrusion high pressures are applied to displace a ram in order to push the heated material through a die. Screw extrusion uses one (single screw) or two (twin screw) screws to transport the material. Screw extruders are preferred over ram extruders since they provide more shear and intense mixing, resulting in a better homogeneity and temperature uniformity. The single screw extruder is the most widely used extrusion system in the plastics industry, while twin screw extruders (TSE) are preferred for pharmaceutical applications because of their high kneading and dispersing capacities, short residence time and -in case of intermeshing machines- for their self-wiping sanitary screw profile [[18](#_ENREF_18)]. TSE’s are starve-fed, which means the feeders set the rate, screw speed is independent. The screws of a twin screw extruder can be either co-rotating or counter-rotating [[19](#_ENREF_19)]. In pharmaceutical industry the intermeshing co-rotation mode is preferred, since it provides intensive mixing and ensures almost complete emptying of the extruder, minimizing loss of highly valuable product. These extruders operate by a first in - first out principle and minimize the non-motion, thus preventing localized overheating of materials within the extruder. These advantages point out that this type of extruders is the best option for pharmaceutical co-extrusion.

The three basic functional screw element types are classified as forwarding, mixing and zoning. Forwarding elements are usually flighted. They convey material away from the feed opening towards the die. Mixing elements can be dispersive or distributive. In distributive mixing individual domains are unchanged, in dispersive mixing morphological units are broken down by shear and elongation. Mixing elements may have a balance of both properties. Furthermore mixing elements can be forwarding, neutral or reversing, the latter changing the direction of material flow by pushing the material backward. Zoning elements can be used to separate unit operations [[20](#_ENREF_20)].

Based on design and function of the screws an extruder is typically divided into three sections along its length. In the feeding section the material will be transferred from the hopper to the barrel. Once the material enters the compression section it will begin to soften or melt. The temperature of this section is normally set at 30-60°C above the glass transition temperature of amorphous polymers or the melting point of a semi-crystalline polymer [[21](#_ENREF_21)]. This can be used as a rule of thumb although exceptions have been described [[22](#_ENREF_22), [23](#_ENREF_23)]. Of course intermolecular interactions also determine plasticizing or anti-plasticizing effects. In this section the mixing elements can now perform their dispersive and/or distributive mixing operation. The molten material finally enters the metering section, where the pulsating flow is reduced to ensure a uniform delivery rate through the die cavity. The output rate of the extrudate is highly dependent on the channel depth and the length of this metering section. Especially in co-extrusion it is important to make sure that the design of the screws is ensuring a stable throughput. Sometimes a melt pump is used to reduce the pressure and throughput instability, called melt pulsation [[24](#_ENREF_24)]. Apart from this technological solution, melt pulsation can also be prevented by constructional screw and barrel adaptations such as changing the length, diameter and pitch of the screws [[25](#_ENREF_25)]. Mounting intensive mixing elements results in a significant improvement of the homogenization of the processed material. In combination with using special densification elements at the end of the screw melt pulsation can effectively be eliminated.

* 1. *Dies*

Before exiting the extruder the melt is pumped through a die, which is mounted at the end of the barrel, and is hereby exposed to high pressure. The geometrical design of the die will dictate the shape of the final product [[21](#_ENREF_21)]. In co-extrusion the die design is crucial for shaping the co-extrudates with the desired characteristics. A lot of different designs are possible, but for every design the rheological behavior and temperature distribution of both melts needs to be modeled accurately. Another important aspect of co-extrusion is the contact surface between the materials, dictated by the shape of the co-extrudate, and the contact time of the materials in the die, which is illustrated by the difference between single- and multi- manifold dies.

Two basic die types used in flat-die co-extrusion systems are multi-manifold dies and single-manifold dies (Fig. 1). Multi-manifold dies exhibit individual manifolds for each layer and each manifold is designed to distribute its polymer layer uniformly before combining with other layers. In most cases the layers are combined inside rather than outside the die in order to prolong the thermal contact period and thus improve the interfacial adhesion between the layers. Since in a multi-manifold die the different layers are quite established prior to combination, migration is minimized and thus a very uniform distribution of layers is achievable, which is a major advantage for co-extrusion in pharmaceutical applications.

In a single-manifold die only one manifold is present. In plastics it is often combined with a feedblock. In a feedblock with single-manifold die design a multilayer composite is formed in a combining adaptor prior to delivery to a flat die. The feedblock arranges the incoming melt streams in the proper sequence and balances the velocities of the components. The multilayer composite is then compressed into a rectangle and delivered to a flat die where the composite is spread and thinned to its final form. Currently there is a trend to more co-extruded layers with micro-layer structures containing tens to hundreds layers of a thickness down to 1 micron produced by multilayer co-extrusion dies [[26](#_ENREF_26)]. One of the most important considerations in feedblock co-extrusion is layer uniformity. Layer non-uniformity can be corrected by feedblock profiling in order to shape the polymer composite prior to entering the die [[12](#_ENREF_12)].

The classification of dies is not only made by the distinction between single and multi-manifold, they can also be classified by their shape. Flat dies (Fig. 2) convert materials from the circular shape at the end of the barrel into a thin wide sheet and are thus suitable to produce films and lamination systems. These are used for packaging materials and for transdermal and dissolvable film applications. Since the material path along the centerline is shorter in comparison with the one at the edges these dies need a design that prevents the sheet from being thicker in the center than at the edges in order to achieve a uniform distribution of material across the width [[27](#_ENREF_27)]. When the polymer melt is extruded through a slit die onto highly polished cooled rolls which form and wind the finished sheet, the process is known as cast film extrusion. When the melt is extruded vertically into a tubular film and inflated by air, the process is known as blow film extrusion [[18](#_ENREF_18)].

For medical device applications (e.g. tubings) annular dies are used. Side fed dies and spiral mandrel dies (Fig. 3) are used in applications where a substrate needs to be coated or in co-extrusion. The mixing effect of the spiral distribution system provides improved product uniformity, which is very advantageous for pharmaceutical applications. For the design of a die the thickness uniformity, residence time and residence time distribution are important criteria. In a spiral mandrel type die the material is exposed to a larger residence time distribution, which can cause degradation because of the longer exposure to the processing temperature in the die [[28](#_ENREF_28)].

Two exit phenomena, “extrudate swell” and “sharkskin”, that can occur when the processed material leaves the co-extrusion die, need to be considered. These two phenomena are common in polymer processing, but need extra attention in co-extrusion as they can occur in each of the co-extruded layers.

“Extrudate swell”, also known as “die swell”, is a situation where the diameter of the extrudate increases upon exiting the die. The polymer melt is compressed when entering the die, followed by a partial recovery or “swell” back to the former shape and volume after exiting the die. It is an entropy-driven phenomenon that occurs when the individual polymer chains, due to their viscoelastic properties, recover from the deformation caused by the rotating screw inside the barrel, by relaxing and increasing their cross section. The extent of “extrudate swell” depends as well on external factors as on factors intrinsic to the polymer [[29](#_ENREF_29)].

The other exit phenomenon, “sharkskin”, is an extrudate surface defect characterized by small scale and high frequency roughness. Two possible explanations for its occurrence have been suggested. One associates this defect with a loss of adhesion at the polymer-wall interface. However several authors concluded that during flow regimes with sharkskin the polymer essentially sticks to the wall of the die. The second possible explanation claims that sharkskin results from the cracking of the fluid at the die exit, under action of the high tensile stresses which may develop in this zone [[30](#_ENREF_30)].

* 1. *Downstream processing equipment*

Currently several downstream solutions for shaping extrudates into oral dosage forms are used in pharmaceutical industry. When extrudates are milled and subsequently tabletted or filled into capsules, the process is ran in a discontinuous way. In pharmaceutical applications, and more specific in co-extrusion, one of the major challenges at the moment is shaping the final product in a continuous way. The following techniques have already been applied in hot-melt extrusion and could be used for co-extrudates too.

*Cooling and conveying*

Chill rolls are used as an intermediate process step, to cool down and control the temperature of extruded films. Two rolls with a defined slit opening, temperature and speed create a temperature gradient throughout the extrudate to cool it down in a controlled way. Highly polished rolls that apply a very well controlled cooling are advantageous to maintain product characteristics and can immediately process thin extruded sheets. If the extruded material is brittle the sheets will form flakes on an agitated conveyor belt. These flakes then need to be milled or crushed in a subsequent process step and afterwards the powder can be used for tabletting or capsule filling. Controlling the cooling rate is of major importance when the amorphous nature or crystallinity of the API has an impact on the in-vivo performance of the drug. Film thickness can be adjusted by changing the rotating speed of the chill rolls. A rod shaped co-extrudate can be conveyed using a conveyer belt and cooled in a water bath or by a cooling ring or air tunnel, before further processing.

*Pelletizing*

Using a pelletizing/cutting system co-extruded strands can be turned into small pellets (down to 0.5 mm) in a continuous way. These pellets can be milled, filled into capsules as such or further modified by spheronization [[8](#_ENREF_8)].

A traditional pelletizer consists of blades on a helical rotor. A drawback of this system is that uniform pellets with constant dimensions can only be obtained for rigid materials, as extrudates composed of soft material will yield deformed pellets. Therefore various variants of this technology have been patented. Rein patented a rotary flying knife cutting machine [[31](#_ENREF_31)]. In continuous mode a high throughput rate can be obtained, but the edges of the pellet are not straight. When cutting in a start/stop mode a lower throughput rate and straight edges can be obtained. Challenges are abrasion of the cutting blades and clogging of material, since cutting temperature needs to be above the Tg. Teflon-coated knifes can be used in the future to avoid clogging effects, while an air pressure nozzle can avoid accumulation of the pellets in the cutting zone. These improvement will tackle the current challenges and offer a widely applicable pelletizing system.

Although spheronization of pellets at elevated temperatures in a traditional spheronizer has proven to be a successful processing step [[16](#_ENREF_16), [32](#_ENREF_32)], currently die face cutters are available post-extrusion for the production of spheronized micro-pellets. The strand is cut immediately after it leaves the nozzle. Spheronization occurs as a result of die swelling. Recently a novel die has been designed to include a direct pelletization/spheronization step [[33](#_ENREF_33)]. Cutting of the hot, still molten strand has been achieved with a rapidly rotating cutter knife. The granules instantly form perfectly shaped micro pellets due to the action of surface tension and the shrinkage due to solidification. This way there is no need for a subsequent spheronization step and valuable time can be gained. The importance of a proper temperature control of the extrusion die has been shown by Radl et al.

In case of annular shaped co-extrudates a traditional type of pelletizer is less suitable, since the inner layer of the extrudate may be pushed out of the outer layer. Cutting of co-extrudates requires a punching system or a pelletizing system with a very sharp knife in order not to put too much pressure on the inner layer and to obtain pellets with constant composition and dimensions. Therefore this technique is not ideal for co-extrudates composed out of hard or brittle materials. Co-extrudates manually cut into small mini-tablets have open sides, which has an influence on the release pattern of the inner layer [[22](#_ENREF_22)].

*Calendering*

Calendering is the downstream solution were the molten co-extruded strand is forced between one or more pairs of temperature controlled rolls to produce sheets that may already contain single tablet cores. Calendering offers an optimization towards a continuous process by allowing an immediate final shaping of the extrudate by calendar rolls that contain tablet- or pill-shaped cavities. This technique is already used in the plastics or confectionary industry in order to produce monolithic shapes. In pharmaceutical applications the Meltrex® technology offers calendering as one of the possible solutions to shape the molten strand on line, immediately after leaving the extruder [[34](#_ENREF_34)]. There is always some waste material at the sides of the tablets or pills, which is a disadvantage when working with highly valuable active ingredients, but the continuous on line shaping of the product by calendering is a major advantage over pelletizing, where a subsequent process step is inevitable to obtain a final dosage form.

For co-extrusion calendering can be a very good solution since the shaping by the rolls will make sure that the outer layer is surrounding the inner core. Yet, it has to be mentioned that for drug delivery systems where the coat steers the release of the core, it is challenging to obtain a coat that completely occludes the core by means of calendering since it is difficult to produce a completely sealed outer layer in this way. Nevertheless calendering has an advantage over the manually cut pellets where both sides are open and the inner layer of the co-extrudate is exposed.

*Injection and blow molding*

During injection molding the molten plastic is injected into a cavity mold at high pressure. The material cools and solidifies in the cavity. The final product is removed from the cavity after the mold has been opened. This technique is the most reliable option to obtain final dosage forms with a unique shape, constantly and perfectly matching the specified dimensions,. It was transferred from the plastics industry and can be used in the pharmaceutical industry for the production of conventional and controlled-release dosage forms. It can be used as an economically advantageous alternative manufacturing technique or as an approach to new drug delivery systems [[35](#_ENREF_35)]. Quinten et al. demonstrated that injection molding of thermoplastic pharmaceutical formulations based on EC and PEO is a promising technique to prepare sustained release matrix tablets [[36](#_ENREF_36)]. Vaz et al. have shown that co-injection molding is a successful way of producing a double layer core/coat drug delivery device which opens a lot of perspective for processing co-extrudates [[14](#_ENREF_14)]. Compared to calendering the increased equipment cost for the two-step co-injection molding process is the major drawback. Co-injection molding is commercially used for the manufacturing of the Egalet® technology (cfr. section 4).

Co-extruded tubing can be shaped by means of blow molding, mainly used for the production of containers. The tubing is extruded into an open mold. After the mold has been closed, compressed air is blown into the open end of the tube, thus expanding the viscous material to the walls of the cavity, forming it into the desired shape of the container. When a product has specific shape or dimension requirements, molding is the best alternative as a downstream processing technique.

* 1. *Process monitoring and control*

Variables that need to be controlled throughout the entire process are feed rates of the ingredients, barrel and die temperatures, motor speed and specific parameters for the downstream equipment, e.g. extrudate diameter control by a laser gauge. Parameters that need to be monitored are actual feed rate and temperatures, screw speed, torque and die pressure.

Since the FDA introduced its PAT initiative, several process analytical technology tools for pharmaceutical hot-melt extrusion processes were evaluated. Several research groups have proven that Raman spectroscopy is a valuable tool to monitor API concentration and solid state on-line during a pharmaceutical hot-melt extrusion process and on an extruded film [[37](#_ENREF_37), [38](#_ENREF_38)]. Using on-line spectroscopic techniques, PAT can also lead to a better understanding of the HME process. Currently a lot of research on PAT in hot melt extrusion is being performed. Terahertz pulsed imaging [[39](#_ENREF_39)] seems a promising technique for analyzing the final co-extruded product in the future, since it not only characterizes the outer but also the inner layer of the co-extrudate.

1. **Materials used in hot-melt co-extrusion**

Proper material selection is critical to produce good quality co-extruded dosage forms. Co-extruded dosage forms are multilayer systems of which each layer consists of a mixture of one or more active pharmaceutical ingredients and functional excipients, such as matrix carriers, plasticizers and other processing aids (antioxidants, bulking agents, release modifying agents). Matrix carriers need to soften easily inside the barrel of the extruder and solidify quickly after exiting the die. The selection of appropriate carriers is important in the formulation and design of a hot-melt (co-)extruded dosage form. The carrier material properties often dictate the processing conditions necessary for the production of the dosage form. Generally, thermoplastic polymers exhibiting a low glass transition temperature or melting point are used. If the API does not exhibit plasticizing properties, the use of polymeric carriers may require the incorporation of a plasticizer into the formulation in order to improve the processing conditions, the stability or the physico-mechanical properties of the final product. Depending on the properties of the drug substance and the other excipients in the formulation, the drug can be present as crystals (crystalline suspension), in amorphous state (glassy suspension) or molecularly dispersed [[11](#_ENREF_11)] in the carrier (solid solution). The state of the drug in the final dosage form influences the processability and the stability of the product.

Since melt extrusion is an anhydrous process, potential drug degradation from hydrolysis is avoided. In addition, poorly compactible drugs can be incorporated into solid dosage forms. Nevertheless materials used in hot-melt (co-)extrusion must meet the same level of purity and safety as those used in traditional dosage forms, meeting the strict regulatory requirements e.g. Generally Recognized As Safe status (GRAS), Good Manufacturing Practice (GMP) and Environmental, Health and Safety (EHS) guidelines. Furthermore, in addition to acceptable physical and chemical stability, these materials must possess a certain degree of thermal stability, although this has to be put into perspective since Repka et al. showed that a thermally non-stable drug, hydrocortisone, could be successfully incorporated into hydroxypropylcellulose films by hot-melt extrusion [[40](#_ENREF_40)].

In comparison to conventional HME, development of a co-extruded formulation is more challenging as additional technical considerations have to be taken into account when selecting polymer combinations. A successful co-extrusion process requires that the polymer melts can be processed at similar temperatures because they need to flow through the co-extrusion die under the same temperature conditions. Although both melts may be extruded at different temperature conditions in each barrel, each temperature profile needs to allow the melt to exit the co-extrusion die at the set die temperature. Furthermore, melt viscosity matching and adequate adhesion between the layers are indispensable to ensure the quality of co-extruded dosage forms.

* 1. Viscosity matching

Layer non-uniformity is an often faced problem in polymer co-extrusion and can be caused by many process factors such as melt temperature non-uniformity, pressure variations and velocity mismatch. However the key for success is the adequate choice of materials in order to match the melt viscosities of the layers. Viscosity matching is not always easy as each polymer has its own viscoelastic properties and each layer is, depending on its location in the structure, exposed to different shear rates during the co-extrusion process. As polymer viscosity is dependent on shear and temperature it is logical that melt temperature uniformity is essential to control temperature-related viscosity.

Viscosity mismatch can cause encapsulation and interfacial instability. Encapsulation happens when a low-viscosity melt flows around a high-viscosity melt and encapsulates it. The polymer viscosity ratio determines the degree of encapsulation: the larger the difference in viscosity, the higher the risk for encapsulation. Viscosity mismatch can also lead to interfacial instabilities (Fig. 4 a) such as zigzag or wave patterns. If the layers are combined in a feedblock and then pass a single-manifold die there is a longer contact zone inside the die and more time for the layers to relocate and cause encapsulation or instability. Multi-manifold dies on the other hand can allow for a larger mismatch in polymer viscosities because the layers are only combined near the die exit. However, when feedblock technology is being used and known viscosity differences are present, modifications can be made to the feedblock geometry to correct for the viscosity mismatch using movable vanes and/or distribution pins [[12](#_ENREF_12)].

Viscosity of thermoplastic polymers is generally assessed via melt flow index (MFI) measurements. The melt flow index is a measure of the ease of flow of the melt of a thermoplastic polymer and is defined as the weight of the polymer extruded per time unit through a capillary of specific diameter and length in a melt flow indexer by pressure applied through dead weight under prescribed temperature conditions as specified by ASTM D1238 [[41](#_ENREF_41)]. MFI is inversely proportional to apparent melt viscosity. By performing measurements at different temperature and shear conditions, the viscosity of each polymer at specific conditions can be predicted.

Yet in case the viscosities are perfectly matched, layer rearrangement can still occur. This phenomenon is caused by secondary flows normal to the primary flow direction as a result of the viscoelastic characteristics of the polymer. The amount of layer rearrangement depends on the viscoelastic properties of the material and on the die geometry. Layer rearrangement increases with increasing viscoelastic characteristics. With respect to the die geometry, large interface deformations occur in square and to a lesser extent in rectangular dies, while they are less likely to happen in circular dies (due to the radial symmetry) [[42](#_ENREF_42), [43](#_ENREF_43)]. Accordingly, viscoelastic flow effects can be minimized by adequate selection of the polymers and die geometry.

* 1. Adhesion

A common problem for all layered products is adhesion control. Yet adequate adhesion between the layers is essential to avoid separation during downstream processing (Fig. 4 b). Adhesion is defined as the tendency of dissimilar particles or surfaces to cling to one another or as the molecular attraction that holds the surfaces of two dissimilar substances together [[44](#_ENREF_44)]. The adhesion between polymers has been widely studied over the last two decades*.*

The recent adhesion literature divides adhesion mechanisms into three main categories: mechanical interlocking, molecular bonding, and thermodynamic adhesion [[45](#_ENREF_45)]. The mechanical coupling adhesion mechanism (Fig. 5 a) is based on a “lock and key” effect: the material of one layer interlocks into the irregularities of the surface of the other layer. A second mechanism for explaining the adhesion between two surfaces in close contact is molecular bonding (Fig. 5 b). It occurs when surface atoms of two separate surfaces can interact via dipole-dipole interactions, van der Waals forces and chemical interactions (i.e. ionic, covalent and metallic bonding). Chemical bonding can also occur following the formation of new compounds at the interface, which is known as reaction bonding. The third category, thermodynamic adhesion (Fig. 5 c), implies that the thermodynamics of the polymer system will attempt to minimize the surface free energy. The advantage of the thermodynamic mechanism over the other mechanisms is that it does not require molecular interaction for good adhesion, only an equilibrium process at the interface [[46](#_ENREF_46)].

Polymer compatibility influences adhesion but is not a prerequisite for adhesion. Miscible polymers will diffuse into each other at the interface, creating an interphase, by one of the mechanisms described above, while adhesion between immiscible polymers is generally weak due to limited interdiffusion. Many polymer combinations used in co-extrusion are immiscible systems. Fairly often tie layers are used which are functionalized resins that are bond to adjacent polar and non-polar resins. There are also various process variables affecting adhesion in co-extrusion. For example, increasing the temperature and contact time usually increases adhesion since there is a longer time for the chemical reaction and chain entanglement to occur. On the other hand adhesion is decreased by high interfacial stress and shrinkage of one of the layers.

Generally, adhesion is quantified with a destructive test to evaluate the ability of an interface to resist mechanical stress. The testing methods can be divided into tensile, shear, cleavage and peel tests [[47](#_ENREF_47)]. Tensile and shear adhesion testing methods measure the load or stress required to fail a standard junction. The main advantage of these stress-based tests is that they are simple to perform and the calculation of the stress is straight forward. Therefore, this type of adhesion testing method is most widely used. Dierickx et al. tested the adhesion between the inner (core) and the outer (coat) layer of concentric co-extruded dosage forms using a tensile tester [[22](#_ENREF_22)]. Using a probe, which applied a downward force on the inner layer, the maximum force needed to separate core from coat was measured (Fig. 6). There are also a whole class of testing methods based on resistance to cleavage. These tests involve forcing a wedge at the interface, thereby creating cleavage stresses. During a peel test, a coating is pulled from its substrate. The crack propagates in a stable manner at the peel speed. The force required to continue cracking is monitored as a function of crack position and time. A drawback of the adhesion testing methods is that failure happens sudden and can occur at the interface or within one of the layers, meaning that it is not always adhesion which is measured.

* 1. Other considerations

The degree of interdiffusion of the layers should also be considered. If the two adjacent layers are miscible, drug and/or polymer of one layer can diffuse into the other layer. It is most likely to happen using a single manifold die because the melt streams have more time to interact. Migration can be studied via Raman spectral imaging (or mapping), which is a method for generating detailed chemical images based on a sample’s Raman spectrum. It involves the collection of spectral data from discrete sections of an area. The colors of a Raman map (Fig. 7) represent the abundance of a component at a certain area [[48](#_ENREF_48)].

To prevent delamination of the co-extruded structure, the shrinkage of the polymers also needs to be taken into account. Delamination occurs when the shrinkage of both layers differs too much. Considering for example a co-extruded tube consisting of two concentric layers. If the shrinkage percentage of the inner layer is more than that of the outer layer, a gap will form between the two layers. If the outer layer is brittle and shrinks more than the inner layer it might burst or in case the outer layer is stretchable, it might tighten around the inner layers and a delamination-free structure may be achieved [[49](#_ENREF_49)].

Given that carriers used in co-extruded dosage forms need to be thermoplastic and meet the regulatory requirements (GRAS, GMP and EHS) and taking into account the extra considerations (viscosity, adhesion, miscibility, shrinkage) for combination of polymers, it is obvious that polymer selection for co-extrusion is not always straightforward. There is a need for new polymers to improve the polymer variety in order to facilitate the choice of polymers in a co-extruded dosage form.

1. **Medical and Pharmaceutical Applications**

In medical applications extrusion was already used for years to produce balloon tubing and single- or multi-lumen tubing, to be used for minimally invasive diagnostic and therapeutic procedures. Now the technology has advanced to co-extrusion in order to create tubing with multiple layers of different materials or with colored stripes of the same material. Co-extruded tubing is especially useful for angioplasty, placing stents, guiding catheters and dialysis [[50](#_ENREF_50)]. For multiple-layer tubings the different materials (e.g. silicone, nylon, polyurethanes) are selected to be compatible to prevent delamination of the tubing. Chemically dissimilar materials can be extruded together using a tie layer as an intermediate layer between the core layer and the outer layer. The co-extruded multi-layer tubings show enhanced performance characteristics, since materials with different but complementing properties can be combined. A tri-layer tubing with a thin hydrophilic surface coating can e.g. provide low friction for the advancement of a guide wire or catheter through the lumen without comprising strength and stiffness. The stripes on a co-extruded tubing can be coloured, contain radiopaque materials that make the tubing visible on X-rays or ensure built in lubricity. Co-extrusion is gaining importance in tubing for medical use with more layers and much thinner walls. Therefore unprecedented levels of dimensional accuracy and flaw detection are required. As tubes get smaller, and walls and layers get thinner, medical-tubing manufacturers have to put more emphasis on gauging for quality control [[51](#_ENREF_51)].

Table 1 gives an overview of pharmaceutical products manufactured via hot-melt co-extrusion. In medical devices there is a trend to combination products where a medical device is loaded with a drug in order to deliver it at the site of action or to influence the release of the loaded drug. Some examples are drug eluting coronary stents, contraceptive implants, vaginal rings and transdermal patches. The design of advanced drug-delivery systems has moved to the forefront in pharmaceutical technology. In the design of such systems, co-extrusion and supporting downstream solutions can provide unique advantages [[52-63](#_ENREF_52)].

The commercially available drug products that are produced by means of co-extrusion are in most cases combinations of a drug with a medical device, e.g. Implanon® and Nuvaring®. Implanon® (Schering-Plough), a non-biodegradable flexible rod that contains etonogestrel, provides contraceptive efficacy during a period of 3 years [[64](#_ENREF_64)]. The rod is 4 cm in length by 2 mm in diameter and consists of a solid core of ethylene vinyl acetate with embedded etonogestrel crystals. The core is surrounded by an outer ethylene vinyl acetate membrane that controls the release rate. The ends of the rod are not covered by an outer layer to allow an initial rapid hormone burst after the implant is inserted in the arm, just under the skin [[13](#_ENREF_13)]. Nuvaring® (MSD), a contraceptive intravaginal ring releasing etonogestrel and ethinyl estradiol for 21 days, consists of a coaxial fiber, prepared by ethylene vinylacetate copolymers. The coaxial fiber consists of a core polymer - with two steroids incorporated in a molecularly dissolved state - that is enveloped with a thin polymer membrane. The outer EVA membrane regulates drug release and provides a near zero-order rate of release over a 21-day period. This polymeric reservoir system is prepared by a co-extrusion installation, consisting of two single screw extruders connected to a spinning block. The molten polymers for core and membrane are delivered to two gear pumps and subsequently combined in a spinneret, thereby forming the coaxial fiber [[65](#_ENREF_65)]. Following extrusion, the rod is cut and end-fused to create a ring [[66](#_ENREF_66)].

Some pharmaceutical products are composed out of two extruded layers, but these were not extruded simultaneously. The Egalet® technology, an erosion-based delayed-release system, consists of an impermeable shell with a plug of active drug as the core of the drug delivery system [[67](#_ENREF_67)]. The shell consists of polyethylene glycol monostearate combined with higher-molecular-weight polyethylene glycols and polyethylene oxides. During the injection molding production process the shell is formed during the first injection in the mold and afterwards the core is molded during a second injection. This manufacturing process provides a high accuracy in the dimensions of the matrix, which is very important since the drug delivery system is designed to show a continuous zero-order release, directly proportional to the area eroded [[68](#_ENREF_68)]. Mirena, a levonorgestrel-releasing intra-uterine delivery system, is mainly composed of polydimethylsiloxane. The device is produced by removing the inner part of a drug-loaded extrudate and inserting an extruded application device as final core [[69](#_ENREF_69)]. Jadelle, a non-biodegradable, flexible, subdermal levonorgestrel implant for contraception consists of two rods of dimethylsiloxane/methylvinylsiloxane copolymer. The core of each rod is a 1:1 physical mixture of silicone rubber elastomer and levonorgestrel, and is covered with a thin silicone rubber tubing. Rod and tube are cured in an oven to cross-link the drug core. After the open ends of the tubing are sealed with medical adhesive the implants are sterilized [[70](#_ENREF_70)].

Co-extrusion is gaining importance in the production of oral drug products for several reasons [[71-75](#_ENREF_71)]. First of all combination therapy is increasingly recognized as a major advantage, not only for life cycle management of drugs but also for therapeutic reasons [[76](#_ENREF_76), [77](#_ENREF_77)]. Fixed-dose combination products contain two or more active pharmaceutical ingredients in a single dosage form. Via the incorporation of different drugs in different layers, the release pattern of each drug can be optimized separately. The combination of two or more drugs with complementary modes of action improves the therapeutic effect. Moreover fixed-dose combination dosage forms will improve patient adherence [[78](#_ENREF_78)]. The production of oral drug delivery systems via co-extrusion further offers the opportunity to modulate drug release and to enable the simultaneous administration of non-compatible drugs.

So far, there are no co-extruded dosage forms for oral use on the market, but several research studies have already been done in this field. Quintavalle et al. characterized hot melt co-extruded cylindrical systems for controlled drug delivery. The sustained release profile was obtained by extruding two concentric theophylline-loaded matrices: an inner hydrophilic polyethylene glycol-based matrix combined with an outer lipophilic layer, mainly consisting of microcrystalline wax. A screening of several devices, differing in dimensions and relative proportions of inner and outer part was performed based on the in vitro drug release. The release mechanisms were studied with the use of a mathematical model [[1](#_ENREF_1), [15](#_ENREF_15)]. Iosio et al. produced pellets with two cohesive layers via co-extrusion-spheronization. An inert layer of microcrystalline cellulose, lactose and water was combined with a second layer containing a self-emulsifying system for the model drug vinpocetine. In order to evaluate the effects of formulation variables an experimental design was used. In vitro dissolution and in vivo tests demonstrated that it was possible to produce bi-layered cohesive self-emulsifying pellets by means of co-extrusion/spheronization, with good quality and an improved solubility and in vivo bioavailability of the poorly water soluble model drug. [[16](#_ENREF_16)]. A recent study by Dierickx et al. [[22](#_ENREF_22)] described the successful preparation of fixed-dose combination mini-matrices with good in vitro and in vivo characteristics via co-extrusion. A core/coat dosage form was developed, wherein the core and coat exhibited sustained and immediate release properties respectively, using a combination of polycaprolactone (core) and PEO/PEG (coat).

Recently, the same research group developed a multilayered dosage form characterized by a dual release profile of the same drug by means of co-extrusion. Co-extrudates consisted of two concentric polymer matrices: a core having a lipophilic character, and a coat with a hydrophilic character. The maximum drug load in core and coat on the extrusion temperature and the die dimensions, while adhesion between core and coat was mainly determined by the drug load and by the extrusion temperature [[79](#_ENREF_79)]. Finally, co-extrusion has also been used to successfully produce fixed-dose combination mini-tablets with metoprolol tartrate embedded in a matrix core offering a range of controlled release profiles and hydrochlorothiazide incorporated in an immediate release coat. The influence of adjusting the concentration of polyethylene oxide as a hydrophilic component or changing the drug load in the plasticized ethylcellulose matrix was studied [[80](#_ENREF_80)].

1. **Discussion and conclusion**

Today’s drug development challenges have tremendously increased. Pharmaceutical production processes need to gain efficiency while the drug substances are more difficult to process because their bioavailability is often poor. Hot-melt extrusion is the perfect answer to these challenges, supplying the possibility to formulate a drug substance as a solid dispersion in a consistent continuous process. Since combination products are gaining importance therapeutically and optimal drug delivery is a prerequisite for a new drug product, co-extrusion is a very promising drug formulation technique. Combining several drug substances, whether or not they are chemically compatible, in different matrices exhibiting specific release patterns creates the possibility to tailor the dosage forms to be utmost therapeutically effective and patient-friendly.

Barriers to the implementation of co-extrusion in the pharmaceutical industry are the significant investment initially required and the limited number of thermoplastic polymers available. The optimization of downstream processing remains a point of attention. Integration of co-extrusion with in-line injection molding may be a next generation of manufacturing technology for processing the co-extrudates.

Other future perspectives focus on improving the solubility limitations of poorly soluble drug compounds. A combination of co-extrusion with other known techniques to improve solubility is promising. Drug particle engineering using nanotechnology has gained much interest. Miller et al. demonstrated the suitability of HME as a novel and viable approach for nanoparticle engineering by overcoming particle aggregation, morphological instability and poor wettability. It was shown that HME did not alter the morphology of the drug particles and homogeneously dispersed them within the polymer carrier matrix [[81](#_ENREF_81)]. Also the use of cocrystal formation can be combined with the co-extrusion technique. Liu evaluated the in-situ formation of cocrystals by preparing solid dispersions using hot melt extrusion. This seemed an efficient method to lower the processing temperature and thus to minimize the thermal degradation for heat-sensitive drugs [[82](#_ENREF_82)].

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**FIGURES**

**Figure 1:** Schematic representation of a multi-manifold die and a single-manifold die.

**Figure 2:** Example of a flat die.

**Figure 3:** Thermo Fisher Scientific® co-extrusion spiral mandrel die with cylindrical core and annular coat. (Reprinted with permission of Thermo Fisher Scientific®)

**Figure 4:** Typical co-extrusion problems: a) Interfacial instability; b) poor adhesion.

**Figure 5:** Adhesion mechanisms: a) mechanical interlocking; b) molecular bonding; c) thermodynamic adhesion.

**Figure 6:** Tensile test for co-extruded mini-tablets.

**Figure 7:** Raman map of the core/coat intersection of a co-extruded dosage form representing the abundance of the drug incorporated in the core (red color) and the absence of this drug in the coat.

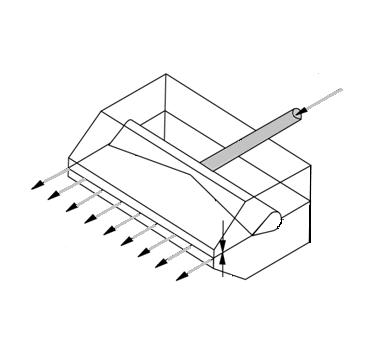
**TABLES**

**Table 1:** Overview and composition of pharmaceutical products manufactured via hot-melt co-extrusion.

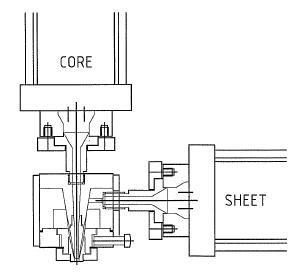
**Fig. 1** Schematic representation of a multi-manifold die and a single-manifold die.



**Fig.2** Example of a flat die.



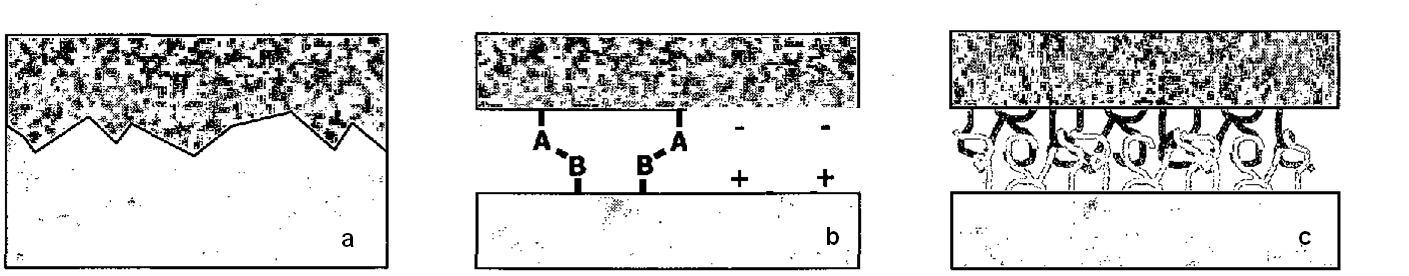
**Fig. 3** Thermo Fisher Scientific® co-extrusion spiral mandrel die with cylindrical core and annular coat. (Reprinted with permission of Thermo Fisher Scientific®)



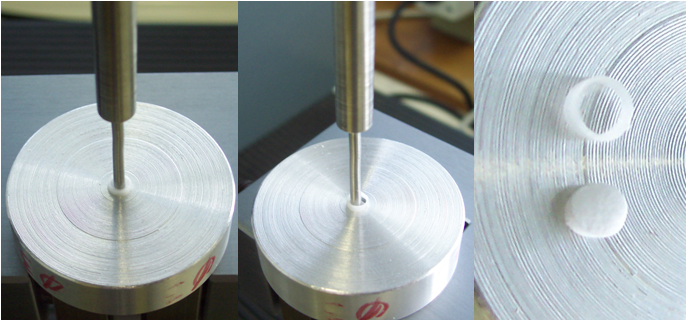
**Fig. 4** Typical co-extrusion problems: a) Interfacial instability; b) poor adhesion.



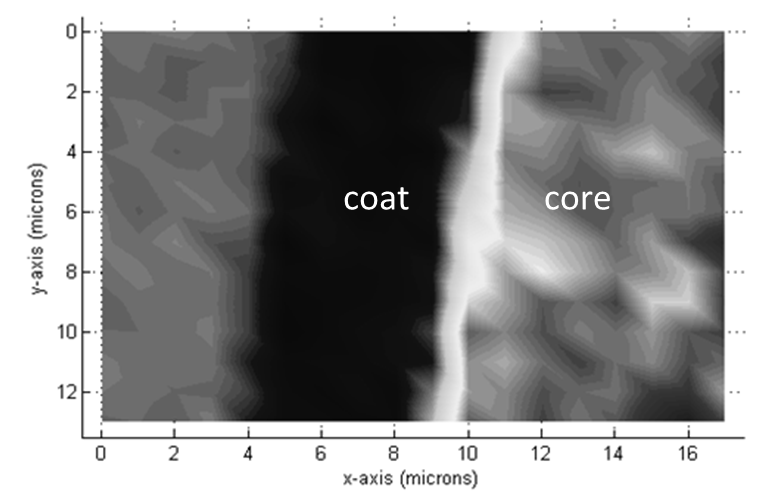
**Fig. 5** Adhesion mechanisms: a) mechanical interlocking; b) molecular bonding; c) thermodynamic adhesion.

**

**Fig. 6** Tensile test for co-extruded mini-tablets.



**Fig. 7** Raman map of the core/coat intersection of a co-extruded dosage form representing the abundance of the drug incorporated in the core and the absence of this drug in the coat.



**Table 1:** Overview and composition of pharmaceutical products manufactured via hot-melt co-extrusion.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Dosage form | Layer 1 | | Layer 2 | | Ref. |
|  | Drug | Carrier | Drug | Carrier |  |
| Oral | theophylline | soy protein isolate | - | soy protein isolate | [[14](#_ENREF_14)] |
|  |  |  |  |  | [[15](#_ENREF_15)] |
|  | theophylline | polyethylene glycol | theophylline | microcrystalline wax | [[1](#_ENREF_1)] |
|  | metoprolol tartrate | polycaprolactone | hydrochlorothiazide | polyethylene oxide | [[22](#_ENREF_22)] |
|  | diclofenac sodium | polycaprolactone | diclofenac sodium | polyethylene oxide | [[79](#_ENREF_79)] |
|  | diclofenac sodium | ethylcellulose | diclofenac sodium | Soluplus® | [[79](#_ENREF_79)] |
|  | troglitazone | povidone | - | ethylcellulose | [[72](#_ENREF_72)] |
|  | CI-1017 | povidone | - | Eudragit® RS PO | [[72](#_ENREF_72)] |
|  | perindopril tert- butylamine salt | Eudragit® E 100 | - | Eudragit® RL PO | [[73](#_ENREF_73)] |
|  | naltrexone HCl | Eudragit® RS PO | - | Eudragit® RS PO | [[75](#_ENREF_75)] |
|  |  |  |  |  |  |
| Implant | etonogestrel | ethylene vinyl acetate | - | ethylene vinyl acetate | [[13](#_ENREF_13)] |
|  | flucinolone acetonide | polycaprolactone / polyvinyl acetate | - | poly(lactic-co-glycolic acid) / ethylene vinyl acetate | [[55](#_ENREF_55)] |
|  | macrocyclic lactone | ethylene vinyl acetate | - | ethylene vinyl acetate | [[57](#_ENREF_57)] |
|  |  |  |  |  |  |
| Vaginal ring | etonogestrel + ethinyl estradiol | ethylene vinyl acetate | - | ethylene vinyl acetate | [[65](#_ENREF_65)] |
|  |  |  |  |  |  |