Acrylic Pressure-Sensitive Adhesive for Transdermal Drug Delivery Systems

Zbigniew Czech,[1] Rafał Kurzawa[2]

[1]*Institute of Organic Chemical Technology, Szczecin University of Technology, Szczecin, Poland*
[2]*Department of Reproductive Medicine and Gynecology, Pomeranian Medical University, Szczecin, Poland*

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ABSTRACT: This article describes the development in the area of resin-free acrylic pressure-sensitive adhesive (PSA) based on 2-ethylhexyl acrylate, methyl acrylate, acrylic acid, *N*-vinyl caprolactam, and pregnancy transdermal drug delivery systems, and shows the variety of polymer composition, residue monomers content, quality control of peel adhesion level and repeating during the time, biocompatibility of the acrylic PSA layer, and efficacy in clinical medicine. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 2398–2404, 2007

Key words: acrylic; pressure-sensitive adhesive; tack; peel adhesion; transdermal drug delivery systems; clinical medicine

INTRODUCTION

The aim of this work was to develop a solvent-based acrylic pressure-sensitive adhesives (PSAs) with high performances for medical application as transdermal drug delivery systems (TDDS). The exact specifications of this new acrylic PSA are characterized by the following properties:

- Medical grade acrylic polymer with very low concentration of residue-monomers ($\leq$0.3 wt %).
- Soft and constant adhesion level to skin.
- High cohesion.
- No PSA layer transfer on skin by removing.
- Biocompatibility of the acrylic PSA.
- Permeability of the water vapor or air.
- Minimal allergenic potential.

The focus of the development of self-adhesive medical products is on one hand directed toward customer-oriented requirements such as adhesion, biocompatibility, and permeability for water vapor or air. The customer wants highly tolerable, breathable products, which are also characterized by very good skin and optimal release. On the other hand, the economic targets of medical-product manufactures must be considered.[1]

The three domains, kind of raw material, technologies, and application, supply the basis for the trends of the development of adhesives for medical products. The use of highly tolerable substances with minimal allergenic potential is the primary factor with regard to raw materials. Additionally, the choice is limited by other external influences too.[2]

PSAs for stick-to-skin medical products are required to perform a wide variety of tasks under a range of conditions on a complex and highly variable substrate. The origins of something like PSA go back to ancient Egypt, and the first modern adhesive was patented in 1845.[3] Although, the materials have evolved, they had the elements that we recognize today, including an elastic polymer, an adhesion resin, filler, and plasticizer.

Nature rubber became a standard base for adhesives, and in 1899, Johnson and Johnson introduced a zinc oxide-containing cloth-backed tape.[4] Shortages of materials during World War II led to a proliferation of synthetic polymers, and by the 1960s, when polar comonomers were used to give cohesive strength to the polymer, acrylic adhesives began to dominate the medical field because of their inherent tack, good oxidative stability, and easy adaptability to a variety of needs.

Today, medical devices are called upon to meet a multitude of needs and are formulated accordingly. Tapes are used to secure dressing and devices, with gentleness, low cost, security, breathability or other characteristics being of primary importance, depending on the particular application. A so-called ''paper'' tape, which has a nonwoven backing coated with a thin and often porous coating of adhesive,[5] is chosen for low-stress applications such as securing a surgical dressing, where low cost is important and moderate adhesion is sufficient.

Correspondence to: Z. Czech (psa_czech@wp.pl).

Transparent dressings are widely used to cover and protect superficial wounds. They consist of thin, breathable polyurethane films coated with acrylic adhesives. Since they function as bacterial barriers, their generally high-moisture vapor transmission is accomplished by diffusion of water through the adhesive and backing layers. The more effective adhesives have hydrophilic character and are lightly crosslinked by gamma radiation during the sterilization process.

As a surface to which medical adhesives must stick, skin presents a substantial challenge. It is the largest organ of the body, averaging 3000 square inches and seven pounds in an adult. As the interface between the body and the outside world, it provides protection against microbial invasion, controls perspiration for temperature regulation, limits transpiration for moisture, and provides sensory information.[2]

Skin is a very complex organ. It is made up of two layers. The lower layer is the dermis, whose two major proteins, collagen and elastin, form a matrix that supports the outer layer called the epidermis. Skin is highly variable with gender, age, ethnicity, location on the body, and ambient conditions. It is also a structurally weak surface. The top layer, called the stratum corneum, is made of cells that migrated from the base of the epidermis and are being sloughed off as the skin renews and replenishes itself.

The body sheds roughly 10 million cells per day, or about 10,000 per minute of walking. Skin turns over completely in about 20 to 30 days. So medical adhesive devices must stick to a layer that is being shed. It is also a very rough surface, with hair, folds, creases, pores for sweat and oil glands, and wrinkles. The surface energy of skin is also low (Table I) and adhesion is further compromised by contamination with water, oil, salt, and loose debris. As a consequence of these characteristics, there is an upper limit on how much adhesion can be achieved,[6] since surface contact is limited and failure of the adhesion bond occurs mostly in the stratum corneum.

Self-adhesive qualities

PSAs for skin need to have a combination of traits that are unique compared to general-purpose adhesive products. Because a medical device is applied to a body that is compromised by acute, chronic, or systemic conditions, it is important that no component in the adhesive aggravate the system further. Obviously, there should be no toxic components that can be absorbed through broken or compromised skin but also there should be nothing that causes an allergic sensitization, response, or an acute chemical irritation. Common sources of concern are unreacted monomers, stabilizers, crosslinking agents, and residues from initiators, surfactants, and processing aids.

TABLE I
Skin as Low-Energy Surface

Material	Critical surface-energy (mN/m)	Polar (%)
Skin	25–29	40
Polyethylene	31	3
Teflon	18	0.2
Water	72	68

In use, an adhesive needs to have good water resistance, both to applied water from outside, such as from bathing or leaking tubes, and to water from under a tape or dressing in the form of perspiration, blood, or wound exudates. The self-adhesives need to retain sufficient cohesive strength when wet so that the device can be removed cleanly without leaving any adhesive residue and without relevant changes in removal force. In addition, because skin transpires water vapor into the air, an adhesive device also needs to allow enough water diffusion so that the skin tissue does macerate and eventually break down.[7]

Common self-adhesive polymers for medical applications

Natural or synthesized adhesives compounded with tackifiers, plasticizers, antioxidants, and zinc oxide were a mainstay for many years, but their low moisture permeability and harshness to skin now limit their desirability. Acrylic polymers are the most commonly used self-adhesives, having replaced compounded natural or synthetic resin. Acrylic offer oxidative stability and resistance to UV radiation are inherently tacky and can be adapted to a variety of uses by copolymerizing two or more monomers, including nonacrylates such as vinyl acetate, *N*-vinyl pyrrolidone, or *N*-vinyl caprolactame. PSAs for skin are often based on 2-ethylhexyl acrylate or butyl acrylate with acrylic acid (AA) or other high T_g monomers included to ameliorate cohesive strength.

Other polymers are occasionally used for specialized applications. Silicone polymers are inert and very hydrophobic but still have reasonable moisture permeability. Polyurethane adhesives reportedly have high adhesion and extended wear time. For certain specific applications, both the kind of polymers are increasingly being utilized. Polyolefin adhesives are inert, nonpolar, and have controllable peel strength. Collectively, these families of adhesives have been applied to a wide range of medical tapes, dressings, and other devices to solve a wide range of user and patient needs.

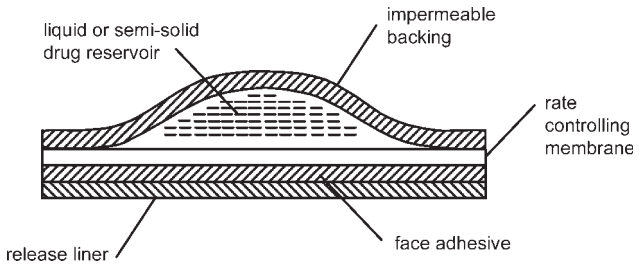

Figure 1 Reservoir transdermal system with face adhesive.

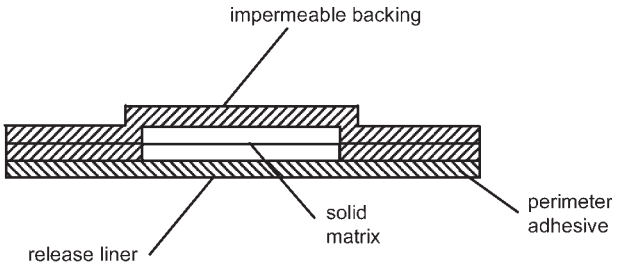

Figure 3 Solid matrix transdermal systems with perimeter adhesive.

The target function of self-adhesives, which are to be used for skin adhesion, can be concentrated on three basic characteristics:

- The fast skin wetting during initial adhesion.
- The secure adhesion on skin within the application time as well as the complete removability.
- A balanced relationship between these three basic characteristics is the primary aim of the formulation of PSAs for medical skin applications.

Transdermal delivery patches

TDDS constitute evolutionary step in the passage of active agents through the skin. Transdermal drug delivery is complex but essentially comprises a drug reservoir with a protective outer cover, a permeable membrane (sometimes), a self-adhesive, and a release liner. Figures 1–5 represent designs of the commercially available TDDSs.

Since they were first launched in the 1980s, sales of transdermal patches have been growing at a spectacular 20–30% per year. TDDS now represents a market worth more than US$1.5 billion a year.

Figure 6 shows the typical TDDS construction for diverse drugs usable in medical applications.

EXPERIMENTAL

The following experiments were conducted to study the use of the best synthesized acrylic PSA at Szczecin University of Technology for using as a ''therapeutic patch.'' Tack, peel adhesion, and shear strength were measured. These mentioned properties were determined by standard A.F.E.R.A. (Association des Fabricants Europeens de Rubans Auto-Adhesifs) procedures. Exact details can be found in AFERA 4015 (tack), AFERA 4001 (peel adhesion), and AFERA 4012 (shear strength). Administrative address: 60, rue Auber-94,408 Vitry Sur Seine Cedex, France.

The synthesis of medical acrylic PSA were performed in a typical organic solvent such as ethyl acetate (BASF). 2-Ethylhexyl acrylate (2-EHA), methyl acrylate (MA), and acrylic acid (AA) were available from BASF (Germany). *N*-vinyl caprolactam (VC) and AIBN were purchased from Tokyo Chemical Industry (Japan). The synthesized acrylic PSA for medical applications were crosslinked with aluminum acetyl acetonate (AlACA) purchased from Degussa (Germany).

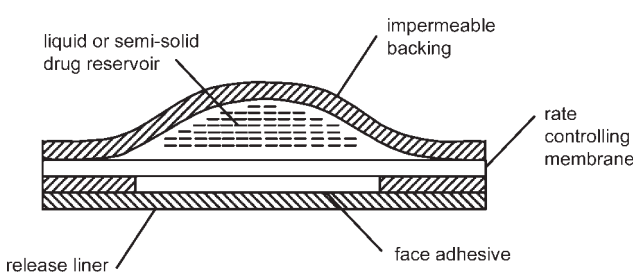

Figure 2 Reservoir transdermal system with perimeter adhesive.

RESULTS AND DISCUSSION

The basic solvent-borne acrylic PSA were synthesized in ethyl acetate at the boiling point temperature about 77°C with solid content on 50 wt %. The dosage time of the monomers mixture was 1 h and the postreaction time was 7 h. With measured concentrations of the residue monomers lower than 0.2 wt %, the synthesized acrylic self-adhesives have been tested using special mentioned medical applications. The synthesized investigated acrylic PSA and their main performance qualities are described in Table II.

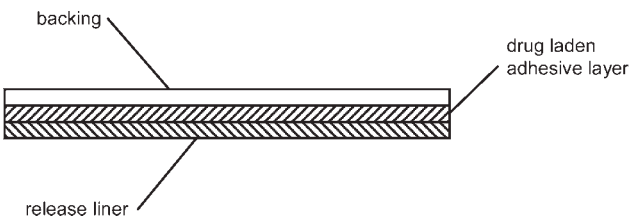

Figure 4 Drug-in-adhesive transdermal systems.

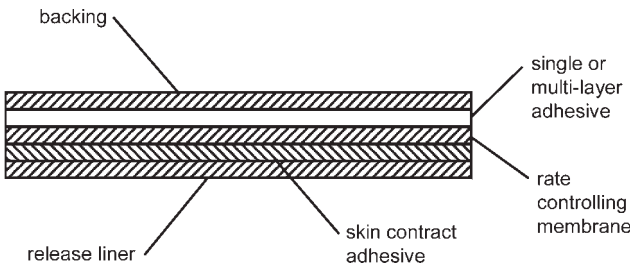

Figure 5 Multilayer drug-in-adhesive transdermal systems.

The greatest attention was attached to the tack and peel adhesion (Figs. 7 and 8). The influence of the AA and VC concentration on shear strength (cohesion) is presented in Figure 9.

From the experimental results, the following conclusions can be inferred:

- The increase of the AA and *N*-vinyl caprolactam content corresponds with the increase of viscosity of synthesized acrylic PSA (Table II).
- There is a direct proportional relation between AA and *N*-vinyl caprolactam content and the shear strength (cohesion) of resulted self-adhesives.

The solvent-borne acrylic PSA with relatively low content of AA show low values of tack and peel adhesion. After polymerization of a small amount of AA, the tack and peel adhesion begins to improve. The PSA structure is now compact, tack and peel adhesion increases, and in the course of the evaluation a maximum of tack and peel adhesion was observed. Finally, at higher concentrations of AA and *N*-vinyl caprolactam, the tack and peel adhesion levels were reduced.

The maxima of tack and peel adhesion are achieved for about 3 wt % of AA and about 5 wt % of *N*-vinyl caprolactam.

IMPLICATIONS IN CLINICAL MEDICINE

Health practitioners make every effort to ensure that patients actually complete the course of the prescribed medication therapy. If the treatment is in the form of self-administered oral drugs or injections, it is difficult to monitor compliance with the prescribed course. Therefore, the development of systems that allow the controlled delivery of drugs through the skin using a ''therapeutic patch'' was warmly welcomed by the medical profession.

Following the pioneering work by the California-based Alza Corp. with Ciba-Geigy in 1980s, the first commercial TDDS products were patches containing scopolamine for motion sickness and nitroglycerine (NTG) for angina sufferers. NTG TDDS significantly reduced the risk of myocardial infarction. This success stimulated the search for other drugs suitable for sustained transdermal delivery. At least 30 projects have been now known to be under development, including patches to treat sexual dysfunction, depression, Parkinson, and even Alzheimer disease. Besides the ongoing research, the following drugs are available in TDDS form: scopolamine, NTG, clonidine, nicotine, estradiol, testosterone, norethindrone acetate, fentanyl, lidocaine.

The benefits of transdermal route of drug delivery may be best seen in gynecology. This includes hormone replacement therapy (HRT) and contraception. Oral administration of estradiol derivatives is associated with a significant risk of vascular complications: thromboembolism and myocardial infarction. Women at major risk are smokers, patients with atherosclerosis and thrombophilias (carriers of clotting factor mutations), with a history of deep venous thrombosis or coronary heart disease. Oral administration of estrogens changes metabolism of liver dramatically. Some metabolic pathways are stimulated, while others are partially blocked. While administered orally, the first pass effect modulates synthesis of important clotting factors, which results in altered activity of factors II, VII, IX, and X as well as proteins S and C. This pathological state of ''hypercoagulation'' may lead to formation of thrombi and clinical complications like DVT, pulmonary embolism, myocardial infarctions, or cerbrovascular accidents.

The risk of oral HRT among menopausal women has its reflection in the results of women health initiative (WHI) study. Since the results have been published, the demand for the oral HRT has declined dramatically. On the other hand, the transdermal administration of estradiol and progestins avoids

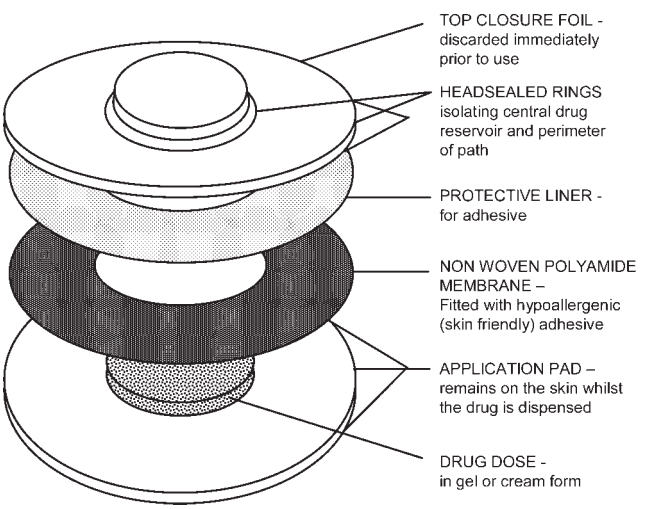

Figure 6 TDDS construction.

TABLE II
Important Properties of Synthesized Acrylic Pressure-Sensitive Adhesives

PSA	Monomers (wt %) 2-EHA	MA	AA	VC	η (Pa s)	Tack (N)	Peel adhesion at 20°C (N)	Shear strength at 20°C (N)
1	78	20	1	1	1.1	2.3	7.0	18
2	77	20	1	3	1.4	5.1	10.3	20
3	74	20	1	5	1.6	8.2	16.2	26
4	72	20	1	7	2.1	6.4	12.6	35
5	77	20	2	1	1.5	4.0	11.3	40
6	75	20	2	3	1.9	4.4	12.4	42
7	73	20	2	5	2.2	11.0	17.7	45
8	71	20	2	7	2.4	7.2	15.1	50
9	76	20	3	1	1.8	4.8	10.1	70
10	74	20	3	3	2.2	7.3	12.2	70
11	72	20	3	5	2.6	12.1	18.6	72
12	70	20	3	7	3.0	11.0	14.8	75
13	75	20	4	1	2.2	4,6	8.2	90
14	73	20	4	3	2.5	7.0	10.2	90
15	71	20	4	5	2.9	11.4	17.6	90
16	69	20	4	7	3.2	9.6	14.0	90
17	74	20	5	1	2.9	3.6	6.9	90
18	72	20	5	3	3.6	6.3	7.2	90
19	70	20	5	5	4.2	10.1	12.1	90
20	68	20	5	7	5.1	7.7	8.6	90

liver portal circulation, thus at least theoretically decreases the risks related to the hormonal treatment. However, the evaluation of the true safety of transdermal route of hormone administration awaits further meticulous research.

American data derived from women and health care practitioners indicate that women desire user-friendly contraception simplifying their lives. Despite enormous progress made in the field of contraception, in fact there are only two effective methods: hormonal contraception and intrauterine devices. The latter method bears significant risks; therefore, administration is narrowed to limit group of patients. On the other hand, hormonal contraception, also not completely free from potential complications, requires patients to be very compliant.

Data from clinical studies are surprising. At least 1/3rd of pregnancies are unplanned. Among this, 2/3rd happen in women using contraceptive methods. It has been established that among women taking combined oral contraceptive pills, at least 60% of unintended pregnancies resulted from errors of daily drug administration. Efficacy of contraception is measured by Pearl index (PI). PI is determined by the number of unintentional pregnancies related to 100 women years. For instance, a hundred women can use contraception for a year, each with a method that is going to be examined. If five pregnancies

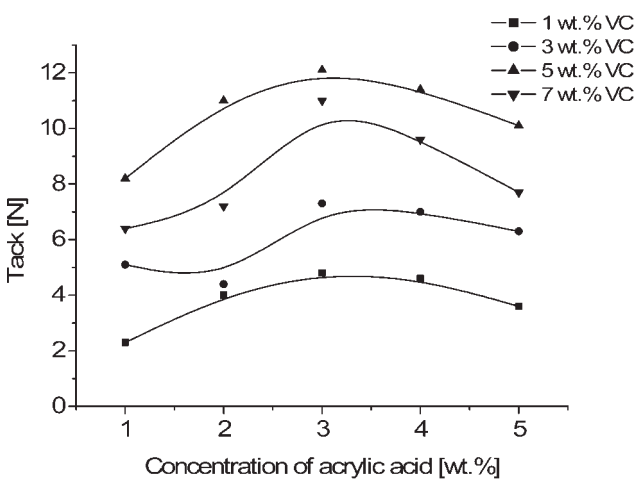

Figure 7 Effect of acrylic acid and *N*-vinyl caprolactam amount on tack.

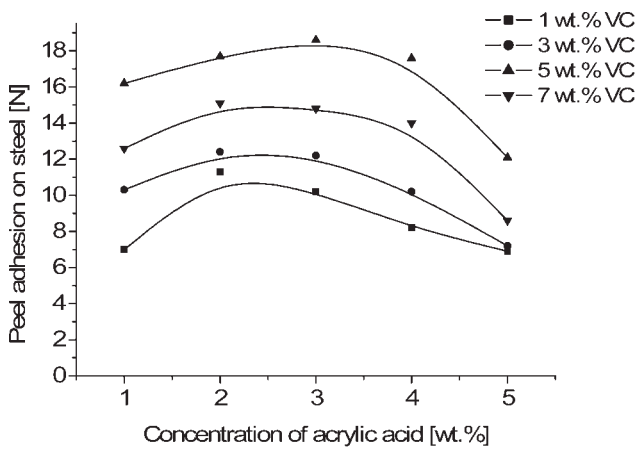

Figure 8 Effect of acrylic acid and *N*-vinyl caprolactam amount on peel adhesion.

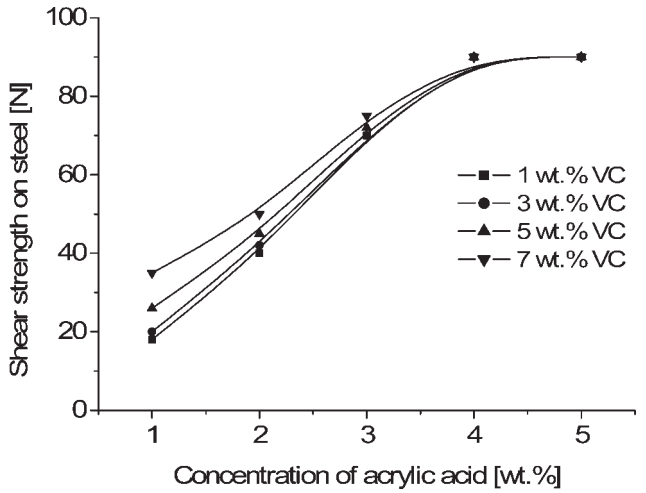

Figure 9 Effect of acrylic acid and *N*-vinyl caprolactam amount on cohesion.

occur during this time in this studied group, the PI is 5.0. The theoretical PI for oral combined contraceptives is 0.3, which reflects perfect use of the method. However, the practical PI may reach even 8.0, which reflects common errors made by pill users. About 10–30% of women forget up to three pills in the cycle. This observation helps explain the differences between theoretical and practical values. Figure 10 clarifies the detrimental consequences of noncompliance in pill users, and shows the benefits of transdermal administration of the hormones.

In TDDS, effective levels of serum hormones are reached a day following patch application and maintained within the therapeutic window throughout the 7 days of wear. When the patch is then removed on day 7, hormone levels decline, however are negligible only by day 10. This profile of steady levels of EE and NGMN throughout the 7 days of patch-wear stays in contrast to the daily peaks and troughs seen with a pill taken once a day. In pill users, the levels of hormones drop fast below the therapeutic level, which may lead to unintended pregnancy. This may not happen in TDDS users, who if make errors, usually forget to replace the patch. In such situations, blood serum hormone levels are found to remain within the therapeutic window least for 2 extra days. Sustained concentrations of EE and NGMN suggest that clinical efficacy can be maintained even if scheduled patch change is missed. This gives an extra time of 2 days of relative contraceptive safety, compared with 12 h given by the pill.

SUMMARY

Uniquely, and quite unlike other forms of drug dosage, the packaging components are an integral and functional part of a TDDSs. The importance of compatibility between the drug and the packaging components is therefore crucially important, and suppliers must ensure the chemical and physical stability of specific systems. To function properly, the packaging material must prevent unwanted diffusion of the active constituents, and at the same time permit their controlled penetration through the skin side of the patch.[8–12]

Medically, TDDS offer real, practical advantages to the patient by releasing precise amounts of medication through the skin directly into the blood stream. Once the patch is applied to the skin, no further action is required of the recipient—the patch continues to administer a uniform dosage over an extended period of time.

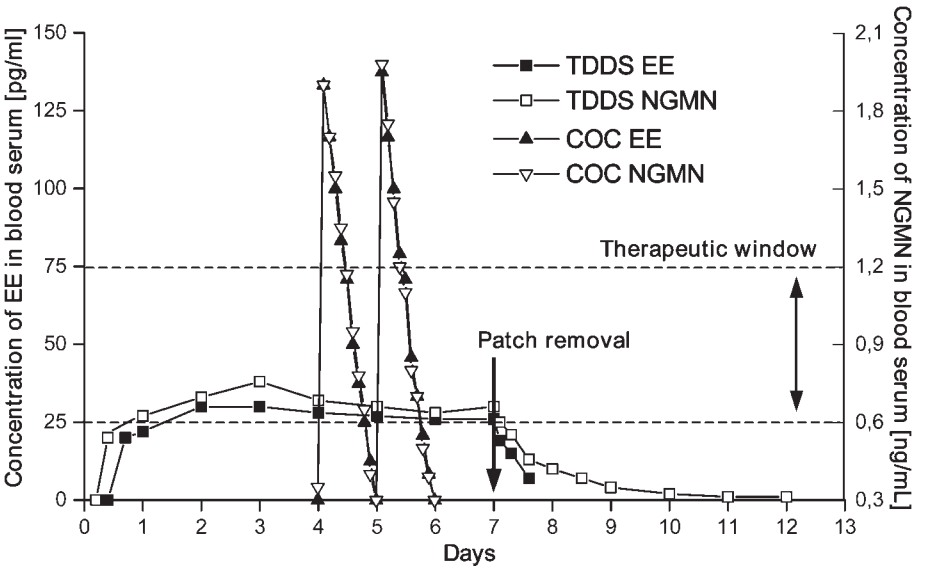

Figure 10 Pharmacokinetics of hormonal contraception in relation to the way of administration. TDDS, transdermal drug delivery systems; COC, combined oral contraceptives; EE, ethynyl estradiol; NGMN, norelgestromin.

Additionally, by bypassing the hepatic first pass metabolism, transdermal systems can afford the patients equivalent therapeutic benefits to capsules and tablets while utilizing significantly lower drug amounts, which in turn minimize side effects and adverse reactions.

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