



## Silicone Polymers in Controlled Drug Delivery Systems: A Review

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### ABSTRACT

In this paper some of the latest studies and research works conducted on silicone-based drug delivery systems (DDS) are reviewed and some of more specific and important novel drug delivery devices are discussed in detail. An overview on rapidly growing developments on silicone-based drug delivery systems is provided by presenting the necessary fundamental knowledge on silicone polymers and a literature survey including an introductory account on some of the drugs that are diffused through silicone polymers. The results based on vast investigations over a period of a decade indicate that intravaginal and transdermal routes of administration of the drugs using silicone-based DDS are more developed. It is also found that silicone polymers are suitable candidates for the release of hormonal steroids for controlling the estrous cycle. Finally, some commercially available silicone-based DDS are described.

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### Key Words:

silicone;  
veterinary devices;  
drug delivery systems;  
intravaginal devices;  
transdermal devices.

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## INTRODUCTION

Controlled drug delivery field is one of the most attractive and challenging areas in medical sciences, chemistry, materials science, engineering, pharmaceuticals, and other related biological sciences. Its application also covers diverse fields including medicine, agriculture, and biotechnology [1,2]. Recent growing interest and efforts of scientists in this area are due to DDS vitality in achievement of a better quality of life and health care for human beings. In addition to research on new drugs, a significant amount of pharmaceutical research works has been focused on designing novel methods of making drug dosages more effective. Many definitions of controlled drug delivery system are found in the literature, but all refer to a system consisting of two essential components of a drug and a drug carrier with the following purposes: the maintenance of drug levels within a desired therapeutic range, delivery of the drug locally to specific sites of a particular body compartment, to avoid possible toxicity, to minimize side effects, increasing patient compliance and comfort by decreasing the dosing frequency, and reducing manufacturing costs [3-5].

A variety of biomaterials such as polymeric materials have been designed and developed that can be used as a drug carrier. To use these materials in controlled drug delivery devices, they should meet the following conditions:

- Chemical inertness,
- Biocompatibility and minimum undesirable degradation byproducts,
- Non-leachability,
- Ease of fabrication and sterilization,
- To possess suitable mechanical properties [5,6].

Some of the more important polymers which have been recently developed and used for controlled drug delivery systems are as follows:

Poly(urethanes), poly(vinyl alcohol), poly(acrylic acid), polyamide, poly(methacrylic acid), poly(*n*-vinyl pyrrolidone), polylactides, poly(lactide-*co*-glycolides), polyanhydrides, polyorthoesters, and siloxanes [6].

For a drug to be successfully used in a controlled drug delivery system, the administration route plays a vital role. The choice of a delivery route depends on

some factors including:

- Patient acceptability,
- Properties of the drug (such as its solubility),
- Access ability to the treatment site,
- Effectiveness in dealing with a specific disease [7].

At present, the most accepted delivery routes as alternative to the traditional intravenous route are the nasal, transdermal, pulmonary buccal, ocular, vaginal, rectal, and oral. These administrations have been the focus of much academic and industrial research works [8].

The release of the drug occurs from a delivery system on the basis of diffusion, degradation, or swelling followed by diffusion. In a given DDS, the release may occur through any or all of these mechanisms [2].

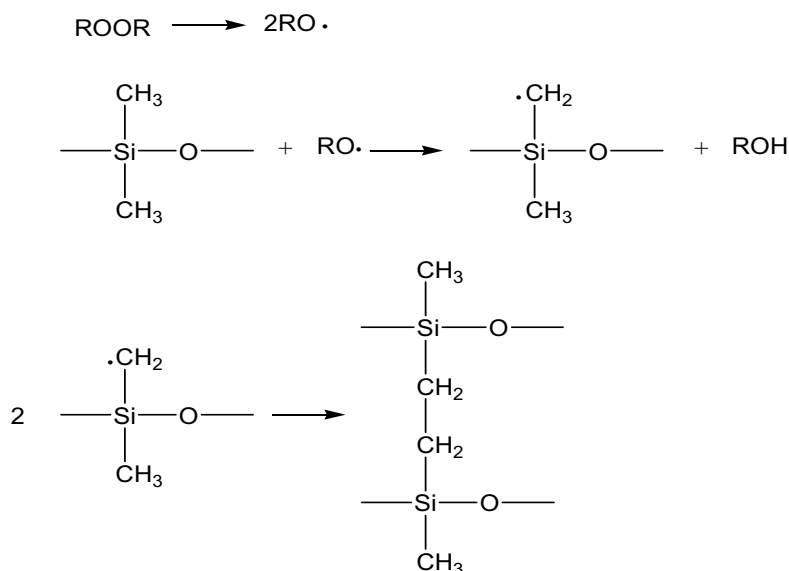
When a drug is released through a polymer, diffusion is usually observed. In degradation mechanism, release of the drug within the body occurs through biological processes which eliminate or remove the carrier system. In swelling control mechanism, water penetration into polymer causes swelling which controls drug release [1,9]. Usually, the release of a drug through silicone rubber as a carrier system occurs based on diffusion mechanism [5].

## SILICONE RUBBER POLYMERS

Polysiloxanes or silicones are important class of organo-silicon synthetic materials based on molecular chains of alternate silicon and oxygen atoms. Silicones as high technology materials have been used in many novel applications due to their unique combination of high temperature stability and low temperature elastomeric properties [10-13]. These compounds are produced in a wide range of properties all the way from water thin substances through heavy oil-like fluids to greases, rubbers, and solid resins by changing polymer chain length and the organic groups attached to silicon atoms. Silicone rubber is usually produced by hydrolysis of appropriate silanes and cross-linking the components produced via one of the methods described below [11]:

### Polydimethyl Siloxane Cross-linking Methods

Polydimethyl siloxane (PDMS) is a commercially



**Scheme I.** Peroxide curing mechanism for PDMS [17].

available polymer with rapidly increasing applications in DDS which has two methyl groups attached to each silicon atom. Cross-linking of PDMS is enhanced in polysiloxanes structure by a wide range of methods, including: (i) use of tri- or tetra-functional siloxane comonomers during polymerization, (ii) incorporation of a thermal initiator which would abstract hydrogen atoms from PDMS and result in cross-linking or, (iii) the exposure of PDMS to high energy irradiation [14].

As some of the drugs are sensitive to heat and moisture, they may impose limitations in DDS applications on the choice of curing methods for cross-linking process of silicone rubber. Recently, a curing method based on the use of platinum as catalyst has attracted considerable attention, due to its cost-effectiveness and safety [15]. This method is FDA approved, because of the absence of organic compounds or volatile by-products in the device [16].

#### Peroxide

Peroxide curing is used to produce high temperature vulcanized (HTV) silicone rubber. This process is

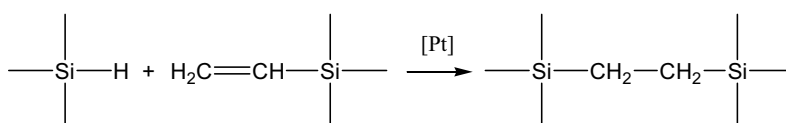
carried out on the basis of free radical mechanism, and a given amount of heat is necessary to generate organic peroxides free radicals for initiating the curing reaction (Scheme I) [17].

#### Addition

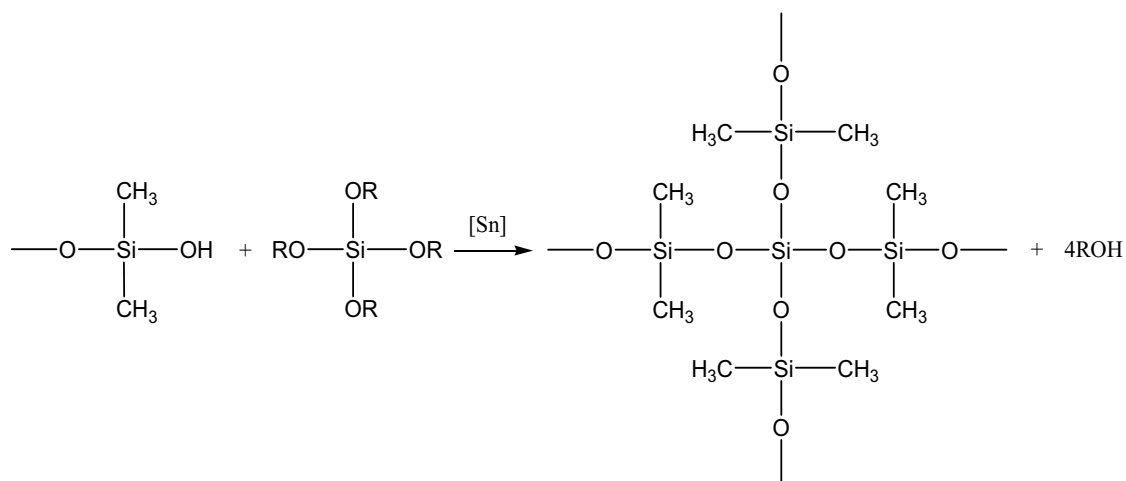
In room temperature vulcanization (RTV) method, cross-linked silicone rubber is produced via Si-H group attachment to double bonds. Platinum, palladium, or rhodium salts or their complexes can be used as the catalyst. By using platinum-olefin complexes as the catalyst, curing process takes place at room temperature (Scheme II) [17].

#### Condensation

There are two systems for condensation curing: one- and two-component systems. For one-component system the catalyst and cross-linking agent are incorporated in the base compound at the time of manufacturing; whereas in two-component system the cross-linker and catalyst must be added to the base compound consecutively just before use. The catalysts used for the above reactions are of organo-tin compounds.



**Scheme II.** Addition curing mechanism of silicone rubber [17].



**Scheme III.** Condensation curing mechanism of silicone rubber [17].

Condensation curing takes place at room temperature based on the mechanisms depicted in Scheme III. The silicone rubbers produced by this method are suitable for sealing, bonding, and coating applications due to their unique property [17].

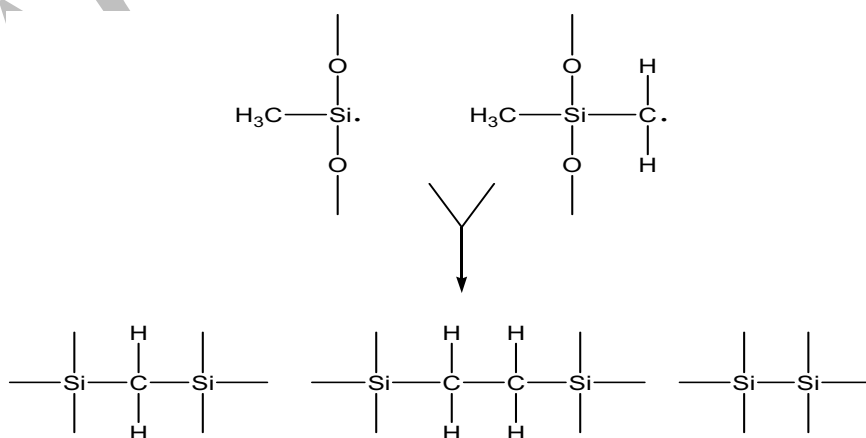
#### *Irradiation*

This curing method is suitable for radiation-induced cross-linking of elastomers. There are numerous published works describing the material properties of the irradiated silicone rubber. Nearly 50 years ago, silicone rubber was cross-linked by using high energy electron beam or gamma rays. The mechanical properties of irradiated silicone rubber have been investigated by Bopp et al. [18], Warrick [19], Przybyla [20], Vokal [21], Basfer [22] and more recently by Frounchi [23]. In addition, many scientists have studied the radiation chemistry of silicone rubber [14,

24-26], and a mechanism has been proposed for cross-linking reaction which is based on the scission of C-H and C-Si bonds in the side chains (Scheme IV) [14]. Somehow, the curing methods by irradiation are not as popular as other methods due to lack of knowledge on radiation/drug interactions.

### SILICONE-BASED DRUG DELIVERY SYSTEMS

Silicones or in more scientific term “siloxanes”, have been used in a wide range of biomedical applications during the past four decades, due to their physiological inertness, high blood compatibility, low toxicity, good thermal and oxidative stability, and low modulus [27,28]. In addition to drug delivery devices, medical applications based on siloxanes are as



**Scheme IV.** Irradiation curing mechanism of silicone rubber [14].

follows: blood pumps, cardiac pacemaker leads, mammary prostheses, drainage implants in glaucoma, artificial skin, maxillofacial reconstruction, replacement oesophagus, contact lenses, oxygenators, medical adhesives, finger joints, coating for cochlear implants, and catheters [29].

Due to unique structural features of silicone, this polymer plays an important role as matrix, membrane, and coating for DDS. Using siloxanes in controlled release delivery systems goes back to 1960s. The first work on the permeability of silicone to ordinary gases was published in 1957 by Kammermeyer [30].

In addition, it is found that oil soluble dye in powder form can diffuse through the silicone rubber tubing walls over a period of a few months. Further works in this field have led to the general conclusions that low molecular weight and lipophilic drugs easily diffuse through silicone rubber [31-35], while substantial efforts have been devoted to the release of high molecular weight and polar species via diffusion through silicone rubber [36,37].

The main structural feature of silicone system is the large atomic volume of the silicon atom itself as well as the size and position of the constituent groups which lead to complete freedom of rotation around the Si-O-Si bonds. Silicone polymers form helices, and the silicon-oxygen bond angles create large amounts of free volume in silicone elastomers. This free volume and the high compressibility of silicone compounds are responsible for their permeability to certain gases and liquids. The gas permeability of silicone rubber is around 100 times greater than that of the natural or butyl rubbers [38]. Also, silicone is cheap and easy to fabricate into many shapes by moulding and also it is curable without excessive heating. It is also chemically inert and non-toxic. This polymer as a drug carrier matrix does not degrade the drug due to its chemical inertness. The application of silicone based controlled release device also improves the patient's comfort for its simple administration and better compliance. In addition, pharmaceutical formulator parametric functions are based on silicone type and device size according to anatomical insertion inside the body to make optimum use of the polymer [39].

Silicone rubber performs suitably in releasing steroid molecules due to their relatively high solubility in the hydrophobic silicone and their relatively low

molecular weight/volume which allow a relatively rapid molecular diffusion. In particular, it is found that drug release depends primarily on the silicone elastomer diffusivity and solubility of the drug molecule, as it is shown by cumulative releases (eqns (1) and (2)) for matrix and reservoir-type devices [5,40]:

$$Q = \sqrt{D_p C_p (2A - C_p) t} \quad (1)$$

$$Q = \frac{D_p C_p}{h} t \quad (2)$$

where,

Q : cumulative amount of drug released per unit area ( $\text{mg}/\text{cm}^2$ ),

t : time (days),

A : initial amount of drug loading per unit volume in a matrix system ( $\text{mg}/\text{cm}^3$ ),

$D_p$  : diffusion coefficient of the drug in the polymer ( $\text{cm}^2/\text{day}$ ),

$C_p$  : solubility of the drug in the polymer ( $\text{mg}/\text{cm}^3$ ), and

h : thickness of the sheet layer in the reservoir-type system (cm).

Extensive work has been conducted on the measurements of  $D_p$  and  $C_p$ , and many researchers have studied the drug release behaviour using silicone matrices which lead to different products (Table 1).

### Modification of Silicone Rubber in Drug Delivery Systems

Though physico-chemical properties of silicone rubber makes it a good candidate for medical applications, but due to its hydrophobic properties, it is not suitable for some medical applications, so it should be modified to acquire some hydrophilic characteristics. PDMS rubber is used as a soft tissue substitute, because some problems occur when the silicone devices are kept implanted for a long time. For example, percutaneous devices are not immuned towards infection because there is a dead-space between the tissue and the implanted device. Such dead-space would not exist if the material surface could bond to the skin tissue [6,41,42].

For some biomedical applications surface and bulk modifications are necessary via suitable method to

**Table 1.** Silicone as drug carrier in DDS.

Drug	Drug function	System type	Ref. No.
Progesterone	Control of the estrous cycle(Antidepressants/Anxiolytics)	Matrix-type	[76-80]
Norgestomet	Control of the estrous cycle	Matrix-type	[81]
Desoxycorticosterone acetate (DCA)	Mineralocorticoid Hormone	Matrix-type	[82]
Indomethacin	Non-steroidal anti-inflammatory	Matrix-type	[83]
Brilliant blue	Model drug	Composite	[84]
Bovine serum albumin (BSA), Antipyrine (ANP), Indometacin (IDM), and Ketoprofen (KP)	Model drugs	Matrix-type	[85]
Hydrocortisone, Dapsone, and Estradiol	Anti-inflammatory, acne treatment, hormone	Tuneable silicones	[86]
Timolol maleate	Anti high blood pressure	Reservoir device	[87]
Acular	Nonsteroidal anti-inflammatory	Contact lens	[88]
Ketotifen	Antihistamine	Pressure sensitive adhesive (PSA) matrices	[89]
Nonoxynol-9- $\alpha$ -cyclodextrin	Spermicidal	Matrix-type	[90]
Genencor enzymes	Model drugs	Pressure sensitive adhesive	[91]
Vancomycin	Antibiotic	Amino-polysiloxane matrixes	[92]
Indomethacin and Dexamethasone	Non-steroidal and steroidal anti-inflammatory	Rods made of silicone rubber-poly lactide	[93]
Ibuprofen (IBU), Methyl paraben (MP) and Propyl paraben (PP),	Anti-inflammatory and antifungal	Colloidal microgels(butyl acrylate (10%) co-polyNIPAM (90%))	[94]
Ethinodiol diacetate	Hormonal contraceptives	Matrix-type	[95]
1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU)	Anticancer	Membrane	[96]
Gentamicin	Aminoglycoside antibiotic	Rod implant	[97,98]
Phenol	Model drug	Interpenetrating polymer network (IPN)	[99]
Testosterone	Hormone	Membranes	[100]
Nitroglycerine and scopolamine	Prevent angina and motion sickness	Transdermal	[101]
Levonorgestrel	Hormone	Matrix-type	[102]
Rifampicin	Antibiotic	Matrix-type	[103]
Salicylic acid and propranolol hydrochloride	Model drugs	Matrix-type	[104]
2-Pyridine aldoxime chloride (PAM-Cl)	Antidote	Matrix-type	[105-106]
Clindamycin, 17 $\beta$ -estradiol, 17 $\beta$ -estradiol-3-acetate, 17 $\beta$ -estradiol diacetate, metronidazole, norethisterone, norethisterone acetate, and oxybutynin	Model drugs	Intravaginal ring devices of matrix-type & reservoir	[107-108]
Oxybutynin	Anticholinergics	Intravaginal ring (IVR) of reservoir design	[109]

Continued

Drug	Drug function	System type	Ref. No.
Polyethylene glycols and Norethisterone acetate, Estradiol, Triclosan, Oleyl alcohol, and Oxybutynin	Different drug	Matrix (ring intravaginal drug delivery device)	[110]
Progestins	Hormone	Modelling	[111]
Timolol, Dexamethasone, and Dexamethasone 21-acetate	Model drugs	Composite	[112]
Nonoxynol-9 (N-9)	Spermicide	Matrix-type	[113]
Metronidazole, Acyclovir, Clotrimazole, Fluconazole, Terconazole, Azithromycin, Erythromycin, Doxycycline, Tetracycline, Minocycline, Clindamycin, Famcyclovir, Valacyclovir, and Clarithromycin	Antimicrobial agent	Matrix (ring intravaginal drug delivery device)	[114]
Ethynyl estradiol, Estradiol	Hormone	Matrix-type	[115]
Estradiol, Progesteron, Vitamin B6, Vitamin D, and Vitamin E	Model drugs	Silicone ring matrix	[116]
Fentanyl	Opioid analgesics	Reservoir- type	[117]
Metronidazole, Miconazole, Ciprofloxacin, and others	Microbicidal intravaginal	Silicone ring matrix	[118]

make silicone rubber hydrophilic in character. In controlled drug delivery systems bulk modification is preferred for drug transport throughout the polymer. Blending, copolymerization, formation of interpenetrating polymer network (IPN), and functionalization process are employed in bulk modification methods [43].

In IPN technique two interpenetrating three-dimensional networks are formed which are not covalently bonded [43]. An interpenetrating polymer network (IPN) is defined as an intimate combination of two or more polymers, both in network form; at least one of which is synthesized and/or cross-linked in the immediate presence of the other. There is a very promising technology based on hydrogel/PDMS IPN for transdermal drug delivery devices [44,45].

Another technique to make silicone rubber hydrophilic is to disperse hydrophilic polymer-hydrogel powder in the silicone rubber matrix. Many reports have been published that deal with the preparation and characterization of composites of PDMS having fine particles of hydrogels as dispersed phase. Silicone rubber and hydrogels based composite materials are two-phase polymeric systems. The composites show good mechanical properties of its compart-

ments: ease of fabrication of silicone rubber and hydrophilicity and water-permeable of hydrogels [46-54].

### Alternative Silicone Applications

#### PDMS Coatings

PDMS coatings are alternative silicone polymer applications in controlled drug release. One of the most important goals of pharmaceutical coatings is to control drug release by the use of polymeric materials. Surface coating provides an effective way to control the drug release. A drug-containing core or tablet is surrounded by a coated film, and the release rate of the drug is controlled by its diffusion through the film [55-58].

The use of PDMS as pharmaceutical tablet coating has shown potential for possible zero-order release (i.e., the highly desirable delivery of a constant drug dosage per unit of time). Drug release in these formulations is mainly dependent on the dispersion of domains of water-soluble substances such as low molecular weight polyethylene glycols within the PDMS films. Their dissolution provides channels for the release of drug molecules, thus a relatively large amount of water-soluble substances is necessary to

assure connectivity of the generated paths [59-68].

#### *PDMS in Drug-eluting Stents*

Silicone rubber is also used as drug bearing coating in drug eluting stents [69]. Usually several components are combined to make up the drug-coated stent platform. In drug-coated metallic stent with a polymer, the polymer functions as a drug carrier and a mixture of drug and polymer is applied as a coating on the abluminal surface of the metal stent. In drug-eluting stents, it is necessary to place a top-coat over the base coat. This top-coat is made up of another layer of polymer and acts as a diffusion barrier. Using this barrier a concentration gradient is created from stent to artery for controlled drug delivery [70]. It should be mentioned that the first organic material used for stenting was silicone rubber. However, silicone has low tensile and coil strengths and small inner to outer diameter ratio [71]. There are some reports on silicone or its copolymers with polyurethane drug-eluting stent for drug release (e.g., dexamethasone) [72-75].

### **DEVELOPMENTS OF SILICONE-BASED DRUG DELIVERY SYSTEMS**

Silicone-based drug delivery devices offer a new area with broad opportunities for scientists who are looking for novel methods of administering known drugs. In spite of substantial works and efforts that have been devoted to this rapidly growing field of research, most of these systems still remain as a laboratory curiosity. Some examples of studied silicone-based DDS are presented in Table 1.

### **COMMERCIALLY AVAILABLE SILICONE-BASED DRUG DELIVERY DEVICES**

A number of drug delivery devices have been developed for administration of drugs for human and livestock in different ways. It is interesting to note that most of the therapeutic systems have been derived from fundamental studies in laboratory. Some routes of the drug administrations are presented in the following sections.

### **Intravaginal Drug Delivery Devices**

In designing intravaginal drug delivery systems, anatomical and physiological considerations should be taken into account. The human trials have been focused primarily on the systemic delivery of contraceptives. Currently, the intravaginal delivery of therapeutic peptides and proteins has gained considerable attention. The main advantage of intravaginal drug delivery is that the hepatic first-pass metabolism is avoided by this route. General intravaginally platforms include creams, foams, pessaries, gels, tablets, and particulate systems. Typical examples of specifically designed intravaginal delivery systems are those employing solid polymeric systems, such as elastomers and hydrogels [8].

Vaginal rings, also known as intravaginal rings, or V-rings, are polymeric drug delivery devices designed in the shape of a doughnut to provide controlled release of drugs to the vagina over long periods of time. The main advantages of the vaginal rings are cost-effectiveness, patient compliance, and therapeutic efficacy due to the ability and versatility of these systems in providing long-term and continuous release of drug at constant predetermined rates. In spite of subdermally implantable systems which need surgical operation for placement, these rings can be placed in the vagina by woman herself [8,119]. Several types of human vaginal ring products are currently available: Estring and Femring [120-122].

Estradiol vaginal ring such as Estring is a slightly opaque ring with a whitish core containing a drug reservoir with 2 mg estradiol. A combination of estradiol, silicone, and barium sulphate forms the ring. When Estring is placed in the vagina, estradiol is released approximately 7.5 mcg per 24 h in a consistent stable manner over 90 days. The dimensions of Estring are: outer diameter 55 mm, cross-sectional diameter 9 mm, and core diameter 2 mm [121,123].

Estradiol acetate vaginal ring, Femring, is an off-white, soft, flexible ring with a central core containing estradiol acetate. Femring is made of cured silicone elastomer containing dimethyl polysiloxane, silanol, silica (diatomaceous earth), normal propyl orthosilicate, stannous octoate, barium sulphate, and estradiol acetate. The ring dimensions are: outer diameter 56 mm, cross-sectional diameter 7.6 mm, and core diameter 2 mm [122,124].



In the veterinary field, the major market for the application of drug delivery devices includes the fertility control via delivery of hormones. There are some older families of silicone based veterinary DDS. Progesterone releasing intravaginal device (PRID) is the first progesterone-releasing device of this kind for use in dairy cows. The PRID comprises a strip of stainless steel covered on both sides with a matrix of silicone and progesterone (1.55 g) in the form of a coil with a diameter of 4 cm and length of 12 cm (Figure 1a). It is manufactured by injection moulding a progesterone/silicone mixture around a stainless steel strip set in a dye such that both sides of the strips are coated by a matrix with defined and uniform thickness [125,126].

Controlled internal drug release (CIDR) is another device for release of progesterone from silicone matrix. CIDR devices are developed in different sizes; the so called CIDR-B and -G, for cattle and goats, respectively. CIDR-B is a T-shaped device with a wing tip-to-tip distance of 15 cm and body length of 13 cm comprising a silicone/progesterone (1.9 g progesterone) matrix that is injection moulded over a nylon spine (Figure 1b). Using this device, progesterone is released into the cow's bloodstream, and the ability to synchronize anestrous cows is substantially increased. The CIDR-G contains 0.33 g progesterone in silicone matrix. The T-shaped device is similar to CIDR-B with a 5.7 cm wing tip-to-tip width (Figure 1c) [127,128].

CueMate is (Figure 1d) a veterinary intravaginal

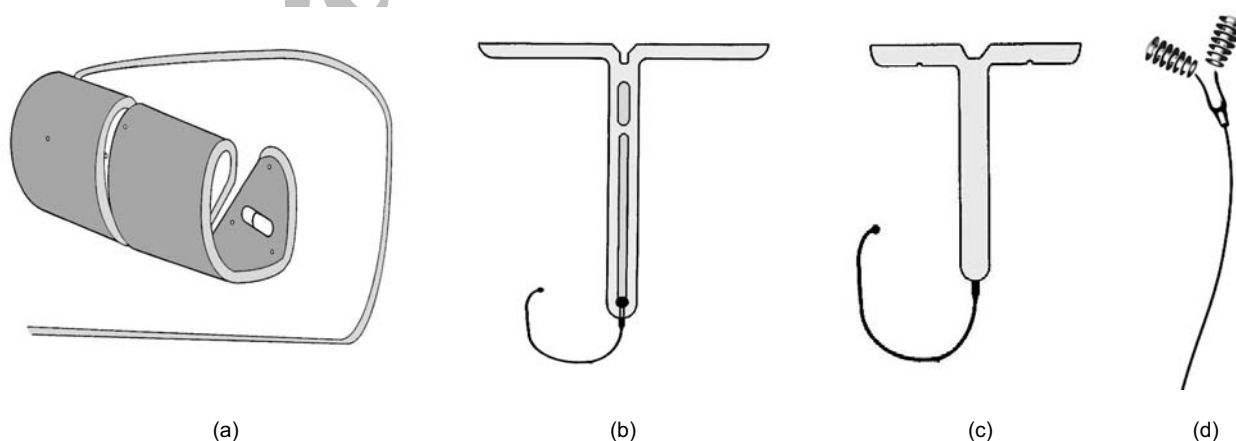
drug delivery system. In this device progesterone (1.56 g) is homogeneously distributed throughout silicone that is manufactured by injection moulding and then attached onto a wishbone shaped spine to facilitate drug administration, retention in the vaginal and removal after implantation [129].

### Subdermal Drug Delivery Devices

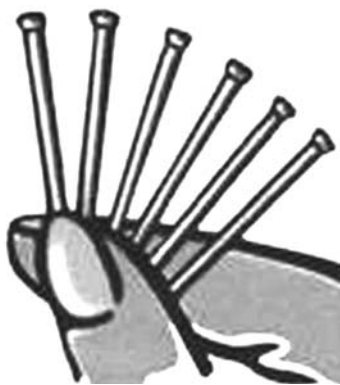
A drug delivery method involves implanting drug delivery system beneath the skin, subdermal or subcutaneous, and targeting specific tissues. In case of subdermal implants, flexible capsules are placed under the skin, and various hormones are administered in this way [130].

Norplant is a human contraceptive device that consists of six capsules of crystalline levonorgestrel encapsulated in silicone rubber (Figure 2). The rod-shaped devices are implanted in a fan-shaped array just below the dermis, usually in the upper arm over the triceps or biceps. Norplant is approved for use for 5 years. Levonorgestrel levels reach contraceptive strength within 24 h of insertion and decline slowly thereafter [131].

Compudose and Crestar are two commercially available animal ear implants. Compudose is implanted in the ear using the appropriate applicator. Compudose is a controlled release device made by coating non-medicated silicone rubber core with a thin layer of silicone rubber that contains oestradiol-17 $\beta$ . It has a surface area of 4.84 cm<sup>2</sup> and has been shown to release drug by a square-root-of-time



**Figure 1.** Commercially available controlled release intravaginal drug delivery systems in veterinary field: (a) PRID device, (b) CIDR -B, (c) CIDR-G, and (d) CueMate device.



**Figure 2.** Norplant.

mechanism. This is designed in four products range: Compudose 400, 200, 100, and -G to provide controlled release of drug over a period of 400, 200, 100, and 90-100 days, respectively [132,133].

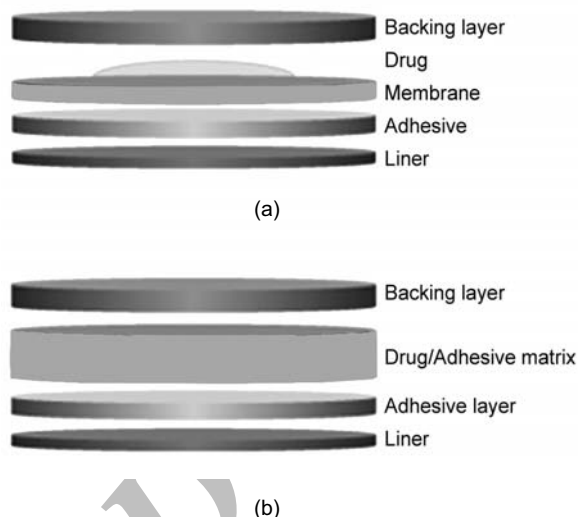
Crestar is an ear implant used for the control of estrous cycle in cattles. It is a small rod-shaped device containing 3 mg norgestomet dispersed throughout a silicone matrix. It is marketed with a 2 mL injection of 3 mg norgestomet and 5 mg estradiol valerate [134,135].

### Transdermal Drug Delivery Devices

The human skin is a readily accessible surface for drug delivery. Transdermal drug delivery systems (TDDS) are able to systemically deliver medicinal drugs through the skin. Skin is a protective membrane for body and consists of several complex layers which stratum corneum is the most impermeable of these layers. Skin penetration is very difficult and highly dependent on the particularity of drugs. Therefore, a few numbers of the drugs can be effectively delivered transdermally. Several penetration enhancers, such as oleic acid, oleic acid esters, and poly(ethylene glycol) have been added to transdermal formulation as an aid to pass skin [125,136].

Generally, the drug is contained in a transdermal patch which is applied to the skin similarly to a band aid. A patch system consists of four layers including: backing layer, membrane, adhesive layer, and liner [137]. Two major types of transdermal drug delivery system products are:

- Reservoir: the active ingredient is in a solution or suspension which is held between the backing layer and a rate-controlling membrane (Figure 3a).



**Figure 3.** Schematic of transdermal drug delivery systems: (a) reservoir and (b) matrix-type.

- Matrix: the drug as a suspension is dispersed in polymer and may be in contact with skin by using an adhesive applied to the perimeter of the system to be held to the skin (Figure 3b). Another refinement is drug-in-adhesive matrix in which the polymer is an adhesive containing the drug as dispersion [137].

For available drugs, transdermals may be considered as novel delivery systems. Only drugs which are given in relatively small daily doses can be administered through patches. Examples of such drugs include nitroglycerin (for chest pain), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), fentanyl (for pain relief), and estradiol [139].

Pressure sensitive adhesives (PSAs) are important components of TDDS, because they ensure intimate contact between the drug releasing area of a TDDS and the skin surface which is critical for controlled-drug delivery [137]. Usually, the bond formed between PSA and skin can be broken with a measurable force which leaves the substrate relatively free from damage [142]. The major classes of medical PSAs are acrylics, silicones, and polyisobutylenes. Transdermal patches have entered the pharmaceutical market since the early 1980s. The first transdermal patch known as Transderm Scop, marketed by CIBA Co., releases, scopolamine, the anti-motion sickness drug [138,139].

BIO-PSA 355 silicone pressure-sensitive adhesive

is well-suited as a contact adhesive in reservoir-type delivery systems. Its properties are somewhat compromised, however, when co-formulated with amino-functional agents. BIO-PSA Q7-2920 was developed to perform as amine resistance. PSA either functions as contact adhesive or may potentially act as drug-loaded adhesive matrix is conceptually simple, but technologically complex drug delivery system [140,141]. There are several transdermal patches that silicone adhesive is incorporated in their formulation: Vivelle-Dot (for estradiol release) by Noven Pharmaceuticals/Novartis Co. [142], Matrifen® transdermal pain patch (for fentanyl release) by Nycomed Co. [143], Duragesic (for fentanyl release) by Alza/Janssen Pharmaceutica Co. [144].

## SUMMARY

Some of the latest research works and studies on silicone-based drug delivery systems and biomedical applications such as novel drug delivery devices are the main focus covered in this review. With this in mind, drug delivery systems administration routes: subdermal, transdermal, and vaginal and the mechanisms of drug release are introduced and their differences are highlighted. Silicone rubber as a suitable drug carrier candidate in DDS is introduced and critical curing parameters, such as heat and moisture which play important roles in designing and processing of drug delivery devices are studied. Modifications of silicone rubber in drug delivery systems to impart some physico-chemical properties to make it suitable for specific medical applications are discussed, as well. The most informative part of this paper includes a survey on the developments of silicone-based drug delivery systems in relation to drug categories, their functions, and types. The last section includes a brief introductory of commercially available silicone-based drug delivery systems consisting of intravaginal, subdermal, and transdermal drug delivery devices. Transdermal drug delivery devices including reservoir and matrix types are discussed in more detail. It can be concluded that silicone polymers as important drug carriers have made great impact on the advancement of drug delivery science and technology.

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