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Review Article

TRANSDERMAL DRUG DELIVERY SYSTEM: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT
The human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body. Over the past decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The human skin surface is known to contain, on an average, 10- 70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body. There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The present review article explores the overall study on transdermal drug delivery system (TDDS) which leads to novel drug delivery system (NDDS).
Key words: TDDS, NDDS, Penetration enhancers, Animal Models, In vitro, In vivo.

INTRODUCTION

Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of administration. Recently, it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation[1].To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. It is exemplified by the development and marketing of scopolamine-releasing transdermal therapeutic system for 72-hr prophylaxis or treatment of motion-induced nausea[2],of nitroglycerin and isosorbide dinitrate-releasing trans-dermal therapeutic systems for once-a-day medication of angina pectoris[3], and of clonidine-releasing transdermal therapeutic system for weekly treatment of hypertension[4].The intensity of interests in the potential biomedical applications of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems for long term continuous infusion of therapeutic agents, including antihypertensive, anti-anginal, anti-histamine, anti-inflammatory, analgesic, anti-arthritic, steroidal, and contraceptive drugs[5].

Transdermal Permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration[2]. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows[3-4]:

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

Basic Components Of TDDS

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status[5].

Drug

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery[17-18]. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be

non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day)[19].

Permeation Enhancers

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate[20]. Penetration enhancers interact with structural components of stratum corneum *i.e.,* proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability[21]. Over the last 20 years, a tremendous amount of work has been directed towards the search for specific chemicals, combination of chemicals, which can act as penetration enhancers.

Pressure sensitive adhesives

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tachy, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue[12]. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs[13]. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemically and biologically compatible and should not alter drug release[14].

Backing Laminate

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate[16]. Examples of some backing materials are vinyl, polyethylene and polyester films.

Release Liner

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g.* paper fabric) or occlusive (*e.g.* polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates[18].

Other excipients

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir[14,]. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[4].

Preparation Of Different Types Of Transdermal Patches

Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types

- Matrix type
- Reservoir type
- Membrane matrix hybrid
- Micro reservoir type
- Drug in adhesive type

Matrix type

Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer. The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly. The medicated polymer formed is then moulded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature. The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film[20].

Reservoir Type

The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unreachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e. g. ethanol). The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate[54].

Membrane matrix

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate[43]. Examples of marketed preparations are Catapress® and TransdermScop®.

Micro reservoir type

The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol. The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unreachable microscopic drug reservoirs (micro reservoirs). The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane[61-62]. This system is exemplified by development of Nitrodisc®.

Evaluation Of Transdermal Patches

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order

to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- In vitro evaluation
- In vivo evaluation

Physicochemical Evaluation

Thickness

The thickness of transdermal film is determined by traveling microscope[12], dial gauge, screw gauge[15] or micrometer[6] at different points of the film.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight[12].

Drug content determination

An accurately weighed portion of film (about 100 mg) is dissolved in 100 mL of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution[14].

Content uniformity test

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Moisture content

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula[24].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Moisture Uptake

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below[23] .

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100 \qquad (1)$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value[13].

Tensile Strength

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation[16].

$$\text{Tensile strength} = F/a.b\ (1+L/l) \qquad (2)$$

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point

In another study, Tensile strength of the film was determined with the help of texture analyzer[22]. The force and elongation were measured when the films broke.

Water vapor transmission studies (WVT)

For the determination of WVT, Rao *et al*., (1997) weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch[14].

In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated[23].

$$WVT = W/ST$$

W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time

Microscopic studies

Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope[12].

Adhesive studies

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors[23]:

Peel Adhesion properties

It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a

single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate. Minghetti *et al.*, (2003) performed the test with a tensile testing machine Acquati model AG/MC 1.

Tack properties

It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer[75-78].

Thumb tack test

The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

Quick stick (Peel tack) test

The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.

Probe tack test

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

Shear strength properties or creep resistance

Shear strength is the measurement of the cohesive strength of an adhesive polymer *i.e.*, device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti *et al*., (2003) performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification[74]

In vitro release studies

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system *e.g.*, Higuchi, First order, Zero order and Peppas and Korsenmeyer model. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug.

There are various methods available for determination of drug release rate of TDDS.

The Paddle over Disc: (USP apparatus 5/ PhEur 2.9.4.1) This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C

The Cylinder modified USP Basket: (USP apparatus 6 / PhEur 2.9.4.3) This method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C.

The reciprocating disc: (USP apparatus 7) In this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method (PhEur 2.9.4.2) may be used.

Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell: In this method transdermal system is placed in between receptor and donor compartment of the diffusion cell. The transdermal system faces the receptor compartment in which receptor fluid *i.e.,* buffer is placed. The agitation speed and temperature are kept constant. The whole assembly is kept on magnetic stirrer and solution in the receiver compartment is constantly and continuously stirred throughout the experiment using magnetic beads. At predetermined time intervals, the receptor fluid is removed for analysis and is replaced with an equal volume of fresh receptor fluid. The concentration of drug is determined spectrophotometrically .

The pH of the dissolution medium ideally should be adjusted to pH 5 to 6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when skin is covered). PhEur considers 100 rpm a typical agitation rate and also allows for testing an aliquot patch section. The latter may be an appropriate means of attaining sink conditions, provided that cutting a piece of the patch is validated to have no impact on the release mechanism. The dissolution data obtained is fitted to mathematical models in order to ascertain the release mechanism[15].

In vitro permeation studies

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages[17]. Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug. So permeation study involves preparation of skin, mounting of skin on permeation cell, setting of experimental conditions like temperature, stirring, sink conditions, withdrawing samples at different time intervals, sample analysis and calculation of flux *i.e.,* drug permeated per cm^2 per second[15].

Preparation of skin for permeation studies

Hairless animal skin and human cadaver skin are used for permeation studies. Human cadaver skin may be a logical choice as the skin model because the final product will be used in humans. But it is not easily available. So, hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex.

Intact Full thickness skin

Hair on dorsal skin of animal are removed with animal hair clipper, subcutaneous tissue is surgically removed and dermis side is wiped with isopropyl alcohol to remove residual adhering fat. The skin is washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20C till further use. The skin is defrosted at room temperature when required.

Separation of epidermis from full thickness skin

The prepared full thickness skin is treated with 2M sodium bromide solution in water for 6 h. The epidermis is separated

by using a cotton swab moistened with distilled water. Then epidermis sheet is cleaned by washing with distilled water and dried under vacuum. Dried sheets are stored in desiccators until further use[19].

In vivo Studies

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

- Animal models
- Human volunteers

Animal models

Considerable time and resources are required to carryout human studies, so animal studies are preferred at small scale[17]. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted lead us to a conclusion that hairless animals are preferred over hairy animals in both in vitro and in vivo experiments[13]. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in man[25].

Human models

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers and phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population and phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources but they are the best to assess the performance of the drug.

Skin irritation studies

White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin[13,53]. Mutalik and Udupa (2005) carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema[24].

Stability studies

The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

Conclusion

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. Transdermal patches can be divided into various types like matrix, reservoir, membrane matrix hybrid, micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. After preparation of transdermal patches, they are evaluated for physicochemical studies, *in vitro* permeation studies, skin irritation studies, animal studies, human studies and stability studies. But all prepared and evaluated transdermal patches must receive approval from FDA before sale. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care .

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