Atrigel drug delivery system

Yasmeen Begum*, Nahid Fatima[1], Sana Ahmed[2]

*,1 Student, Deccan School of Pharmacy (Affiliated to OU)
2 Assistant professor, Deccan School of Pharmacy
Department of Pharmaceutics, Deccan School of Pharmacy, Dar-us-salam, Aghapura,Hyderabad-500001,Telangana,India.

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Corresponding author address

Yasmeen Begum*,
Student,
Department of Pharmaceutics,
Deccan School of Pharmacy,
Dar-us-salam, Aghapura
Hyderabad-500001,
Telangana,India

ABSTRACT

The Atrigel system could be a proprietary delivery system that may be used for each parenteral and site-specific drug delivery. once the liquid polymer system is placed within the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to make a solid implant. Atrigel system is formed of biodegradable polymers and biocompatible solvents so don't need removal. The solvents utilized within the Atrigel system to dissolve the compound ranges from the additional hydrophilic solvents like dimethyl sulfoxide, N-methyl-2-pyrrolidone(NMP), tetraglycol, and glycol furol.The wide effective and most typical style of drug delivery is parentral administration for active drug substance with poor bio-availability and therefore the drug with a narrow therapeutic index.this route maintains its values because of special benefits like faster onset of action just in case of emergency, target the drug quickly to desired site of action, hindrance of first pass metabolism etc. Development of associate degree Atrigel drug delivery system of a macromolecule drug helps in preventing denaturation of macromolecule in body fluids is studied in this article. It represents a desired alternate. this text complies the information on the in situ gel forming system i.e. Atrigel technology designed to produce drug unharness in sustained manner. the present Atrigel technology seems to produce efficacious product with important benefits over different existing delivery systems. However, certain enhancements been created to the technology embody simply to the lowest of pockets and fills even the smallest areas between teeth and gums. The pockets and areas wherever bacteria thrive wherever ATRIDOX begins to work. It releases the drug for weeks to months for complete bio-absorption with one injection.

Keywords: Epithelial Duct Controlled Delivery Systems, Atrigel, Perishable Polymers, Implants, Liposomes, In Place Gel Forming Systems

Introduction:

The Atrigel system is proprietary delivery system that can be used for both parenteral and site-specific drug delivery. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes. It solidifies upon contact with aqueous body fluids to form a solid implant. The solvents employed in the Atrigel system to dissolve the polymer ranges from the more hydrophilic solvents such as dimethyl sulfoxide, N-methyl-2-pyrrolidone(NMP), tetraglycol, and glycol furol to the more hydrophobic solvents such as propylene carbonate, triacetin, ethyl acetate, and benzyl benzoate. The most frequently used solvents is NMP because of its solvating ability and it's safety/toxicology profile. [1]

The number of drug delivery systems has been developed over the years , parenteral drug delivery system being one of them. Parenteral drug delivery refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestine mucosa. The limitations of oral route are circumvented. Action is faster and surer(valuable in emergency). Gastric irritation and vomiting is not provoked. It can be employed even in unconscious, uncooperative or vomitose patient. There are no chances of interference by food or digestive juices. Liver is also bypassed by this route . But this route specifically requires that the drug delivery system should be sterile , besides being invasive and painful, assistance of other person often being required (though self injection is possible, e.g. insulin by diabetics), there are chances of local injury and being more risky. Once administered, the action is difficult to revert back in case of side effects or toxicity. The different parenteral routes are subcutaneous, intravenous, intramuscular, intradermal and intraperitonial. Atrigel system was initially developed by Dunn and co-workers at southern research institute in Birmingham, Alabama in 1987. The technology was licensed to Vipont Research Laboratory(which later became Atrix Laboratories) for the sub gingival delivery of antimicrobials to treat periodontal disease.This system serves many advantages over conventional methods of drug administration including tablets , capsules etc[2]

Types of parentral controlled drug delivery system:

1. Surgical implants

Surgical implants can be made from biodegradable polymers using well-controlled manufacturing processes, such as extrusion, injection moulding, and compression moulding. These devices normally have very reproducible release profiles. However, because of their size, they require surgical implantation which often limits the product's market potential due to patient and physician acceptance issues.

2. Microspheres

Microspheres designed for parenteral delivery, on the other hand, can be injected into the body using conventional needles and syringes. Thus, they have been the most widely accepted biodegradable polymer system for parenteral uses. However, the manufacturing processes for microspheres are often complex and difficult to control. As a result, there are often questions involving costs and batch-to-batch product uniformity

3. Liposomes

Liposome's on the other hand are versatile carriers for both hydrophilic and lipophilic drug molecules but suffer from several disadvantages like, high production cost, leakage of drug, short half life and low solubility[3].

4. Injectable gels

Biodegradable injectable in situ gel forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within polymer matrix as it solidifies. Drug release occurs over time as polymer biodegrades.

Biodegradable polymers used in these systems are Polyhydroxyacids, polyanhydrides, polyorthoesters, polyesteramides and others (freed LE et al., 1994). Their importance will grow as numerous proteins will lose their patent protection in the future [4]

Mechanisms of action:

Atrigel® drug delivery system consists of biodegradable polymers dissolved in biocompatible carriers. Pharmaceuticals may be blended into this liquid delivery system at the time of manufacturing or, depending upon the product, may be added later by the physician atthe time of use. When the liquid product is injected into the subcutaneous space through a small gauge needle or placed into accessible tissue sites through a cannula, water in the tissue fluidscauses the polymer to precipitate and trap the drug in a solid implant. The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades with time (Hatefi A, Amsden B, 2002). [5]

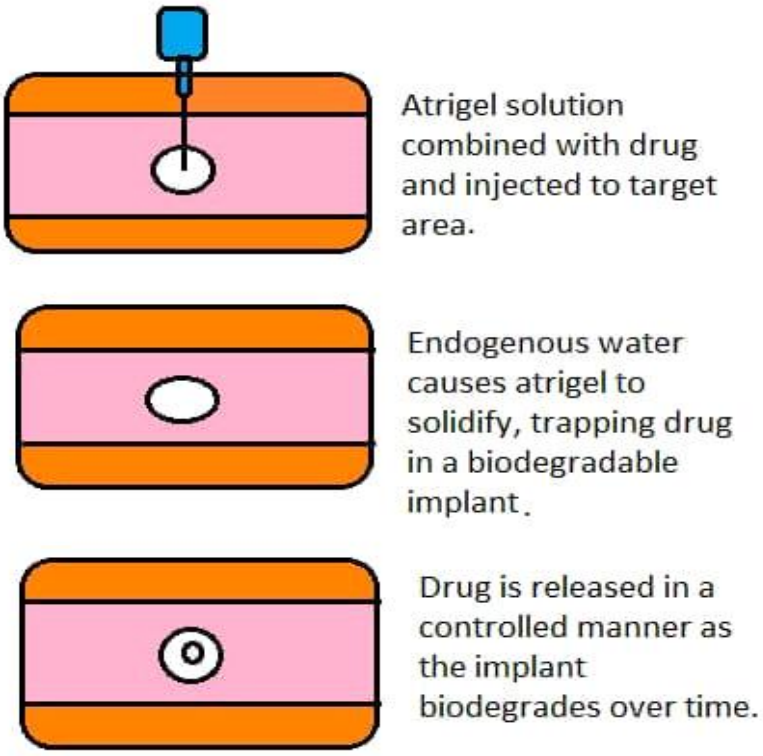

Figure.1: Controlled release by Atrigel system

Atrigel drug delivery platform:

Superior technology for extended delivery of peptides and small molecules: it is injected as a liquid which rapidly solidifies in tissues and usually applied by subcutaneous injection with syringe and needle.it releases the drug for weeks to months for complete bio-absorption.

Current internal programs:

>pyy3.36(obesity)-

•put peptide that reduces appetite and food intake

•obese subjects not resistant to anorectic effect

>resperidone (antipsychotic)-

•potential improved release kinetic vs risperdal consta(alkermes)

>ghrp-1 (growth promotion)-

•growth hormone releasing peptide-1

•potential indication: short stature,cachexia,muscle wasting

>micras(locally advancedtumors)-

•125iurd(thymidine analogue) delivered in atrigel

•incorporated in dna and emits radiation destroying cells.

Advantages & Disadvantages:

Advantages-

The Atrigel system is a proprietary delivery system that can be used for both parenteral and site specific drug delivery. Atrigel system was initially developed by Dunn and co-workers at southern research institute in Birmingham, Alabama in 1987.The technology was licensed to Vipont Research Laboratories (which later became Atrix Laboratories) for the sub gingival delivery of antimicrobials to treat periodontal disease.This system serves many advantages over conventional methods of drug administration including tablets, capsules etc. These include-

>The widely effective and most common form of drug delivery is parentral administration for active drug substance with poor bio-availability and the drug with a narrow therapeutic index.

>this route maintains its values due to special advantages like quicker onset of action in case of emergency, target the drug quickly to desired site of action, prevention pf first pass metabolism etc.

- **Compatibility with a broad range of pharmaceutical compounds-**

Water soluble and insoluble compounds and high and low molecular weight compounds like peptides and proteins, vaccines and natural products can be easily administered by atrigel systems.

- **Less invasive technique-**

The application is less invasive and painful compared to implants, which require local anaesthesia and a small surgical intervention.

- **Protection of drug-**

Development of an atrigel drug delivery system of a protein drug helps in preventing denaturation of protein in body fluids.

- **Sustained drug release-**

Helps in reduction of dose, achieve release for extended periods, so there is increase in patient compliance, important for those protein drugs having narrow therapeutic indices.

- **Biodegradable and biocompatible-**

Atrigel system is made of biodegradable polymers and biocompatible solvents so do not require removal.

- **Economic factors-**

Microspheres have to be washed and isolated after preparation; operating expenses for the production of in situ forming applications are marginal, thus lowering investment and manufacturing costs (cavalli r et al., 1993).

The technology for atrigel system is protected by 33 patents in the united states and 35 patents in the rest of the world. These patents cover the basic technology as well as process improvements.[6]

Disadvantages-

- High production cost, leakage of drug, short half life and low solubility.

- High melting temperature of thermoplastic pastes requiring injection temperature atleast 60°C
- parentral administration of drug is often critical and associated with problems such as limited number of acceptable excipients, stringent requirements of asceptic production process, safety issues and patient non-compliance.
- the manufacturing processes for microparticals are often complex and difficult to control leading to batch-to-batch ptoduct non uniformity.
- these method of administration often limit the product's market of potential due to patient and physician acceptance issues.

Formulation:

The formulation of these systems includes the dissolution of the water insoluble biodegradable polymer into a biocompatible solvent. The drug is next added to the solution where it dissolves or forms a suspension. This drug/ Polymer mixture is then easily and conveniently injected into the body where it forms a solid implant inside the tissue. Most commonly used polymers are poly (dl-lactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers because of their degradation characteristics and their approval by the Food and Drug Administration (FDA).These offer advantage that breakdown products are natural, biocompatible so no problem of toxicity. Various rates of biodegradation can be obtained depending on type of polymer, there combination and ratio. Polymer concentrations ranging from 10 to 80% by weight are used for preparation of Atrigel drug delivery system. The low molecular weight polymers at low polymer concentrations can be easily injected into the body using standard needles, and they can also be aerosolized for spray applications. The high molecular- weight polymers at high polymer concentrations may be used as it or putties that can be placed into sites in the body where they solidify and provide support. Some examples are depicted in table 1.

Table 1. Biodegradation time of different biodegradable polymers

Polymer	Types of biodegradable
Poly lactide	24-28 months
Poly dl-lactide	12-16 months
50:50 lactide/glycolide	50-60 days
85:15 lactide/glycolide	5 months

The solvents employed in the Atrigel system to dissolve the polymers range from the more hydrophilic solvents such as dimethyl sulfoxide, Nmethyl-2-pyrrolidone (NMP), tetraglycol, and glycol furol to the more hydrophobic solvents such as propylene carbonate, triacetin, ethyl acetate, and benzyl benzoate. The most frequently used solvent is NMP because of its solvating ability and its safety/toxicology profile. A Drug Master File on this solvent has been filed with the FDA. When this formulation is injected into the body the water miscible organic solvent dissipates and water penetrates into the organic phase. This leads to phase separation and precipitation of the polymer forming a depot at the site of injection as shown in Fig 1 Both in vitro and in vivo release studies were used to optimize the release characteristics of the formulations. For the in vitro studies, the drug is combined with the polymer solution and small drops of the mixture (about 50 mg) are added to phosphate-buffered saline solution. The receiving fluid is replaced at selected times with fresh solution, and the removed phosphatebuffer saline solution is analyzed for drug concentration using a variety of analytical methods.[7]

Methods of manufacturing:

In-situ forming drug delivery system (ISFD) injectable in-situ forming implants are classified into four categories based on the mechanisim of achieving solidification in-vivo.

1.Thermoplastic paste

2.In-situ cross linking system

3.In-situ polymer precipitation

4.Thermally-induced gelling system

5.In-situ solidifying organogel system

Evaluation and charactertization of in-situ gel system:

>Clarity-

The clarity of formulated solution determined by visual inspection under black and white background.

>Texture Analysis-

The firmness,consistency and cohesiveness of formulation are assessed using texture analyzer,which mainly indicates this syringe ability of sol so the formulation can be easily administered in-vivo.Higher values of adhesiveness of gels are needed to maintain an intimate contact with surface like tissues.

>Sol-gel transition temperature and gel time-

For in-situ gel forming system incorporating thermo reversible polymer,the sol-gel transition temperature may be defined as that temperature at which phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at specific rate.Gel formation is indicated by a lack of moment of meniscus on tilting the tube.

>Gel Strength-

This parameter can be evaluated using a rheometer.it depeneds on the mechanisms of the gelling of gelling agent used; a specific amount of gel is prepared in a beaker,from the salt form.this gel-containing beaker is raised at a certain rate,so pushing a probe slowly through the gel.the change in a load on the probe can be measured as a function of depth on immersion of the probe below the gel surface.

>Viscosity and rheology-

This is an important parameter for in-situ gels to be evaluated. the viscosity and the rheological properties of the polymeric formulation, either in solution or in gel made with artificial tissue fluid were determined with brook field rheometer or some other type of viscometer such as Ostwald's viscometer.

>Fourier Transforms Infrared Spectroscopy and Thermal Analysis-

During gelation process, the nature of interacting forces can be evaluted using this technique by emplyoing Potassium bromide(KBr)Pellet method.Thermo-gravimetric analysis(TGA)can be conducted for in-situ forming polymeric system to quantitate the percentage of water in hydro gel.Differential scanning calorimetry(DSC) is usedto observe any change in thermograms as compared with pure ingredients used thus indicates the interaction.

Application:

- **Human pharmaceuticals-**

a. Oral Drug Delivery-

Oral drug delivery is considered to be the holy grail of drug delivery because convenience results in high patient compliance. In the area of human Pharmaceuticals, controlled drug delivery had its beginnings in simple wax coatings, which prolonged the delivery of drugs taken orally.

b. Transdermal Drug Delivery -

Again, because convenience results in high patient compliance, transdermal drug delivery is another highly desirable means of controlled drug delivery. In transdermal drug delivery, the drug delivery device can be a reservoir-type or a matrix-type device. In a reservoirtype device, the device has an impermeable backing film on the outer side, followed by a reservoir containing the drug, then a semipermeable, ratecontrolling membrane, followed by an adhesive layer for attachment to the skin, and a final protective, removable inner film. in a polymeric matrix, laminated to the backing film and coated with an adhesive layer, followed by a protective, removable inner film.

c. Parenteral Delivery -

Perhaps the most complex of the controlled drug delivery systems are the human parenteral systems. Biodegradable microsphere and implantable-rod systems which deliver peptides for treatment of prostate cancer have been developed and approved in several countries. Implantable osmotic pumps are used in laboratory animals to conveniently evaluate the controlled delivery of active agents under a variety of conditions. Implantable silicone rods have also been developed and marketed for delivery of steroidal hormones.

d. Dental -

A biodegradable, in situ-forming implant containing doxycycline has been approved in the U.S. for treatment of periodontal disease. The polymer and drug are both dispersed in a water-soluble solvent. When injected into the periodontal pocket, the mixture sets by extraction of the solvent. The implant then delivers its payload and subsequently biodegrades. Nondegradablefibers containing tetracycline are also used to treat periodontal disease.[8]

Marketed products:

A number of marketed products based on this technology are enlisted in table 2. These products have been approved by FDA.

Table 2. Marketed products based on Atrigel technology

Marketed product	Active ingredient	Use	Marketed by
Atridox	8.5% Doxycycline	Periodontal treatment product with sub gingival delivery.	ZILA a tolmar company
Atrisorb D	4%Doxycycline	For periodontal tissue regeneration.	ZILA a tolmar company
Eligard	Leuprolide acetate	1-, 3-, and 4-month products for treatment of prostate cancer	TOLMAR
Lupron depot	Leuprolide acetate	2 and 4 month	ABBIVEENDOCRINE

		preparation for treatment of advanced prostate cancer	INC
Sandostatin	Octreotide acetate	Acromegaly	NOVARTIS

The current ATRIGEL technology appears to provide efficacious products with significant advantages over other existing delivery systems. However, certain improvements been made to the technology include modifications to lower the initial drug burst; use of new polymers and solvents in long-term drug release and tissue
compatibility. If these modifications, if, implemented successfully to the Atrigel technology, these will surely increase its uniqueness and its applicability to a wide variety of drug delivery products.

1) ATRIDOX® periodontal treatment product Dosage and administration:

The ATRIDOX product is a subgingival controlled-release product composed of a twosyringe mixing system. Syringe A contains 450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% N-methyl-2pyrrolidone (NMP). Syringe B contains 50 mg of doxycycline hyclate which is equivalent to 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentrationof 10% of doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days (Liversidge GG and Cundy KC, 1995).

Dosage and administration Steps:

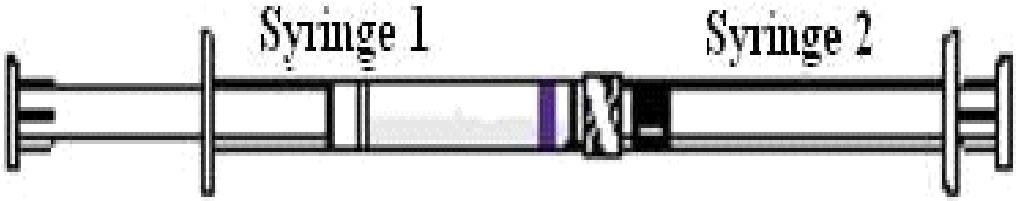

Figure 2. (a) Couple Syringe 1 (liquid delivery system) and Syringe 2 (drug powder).

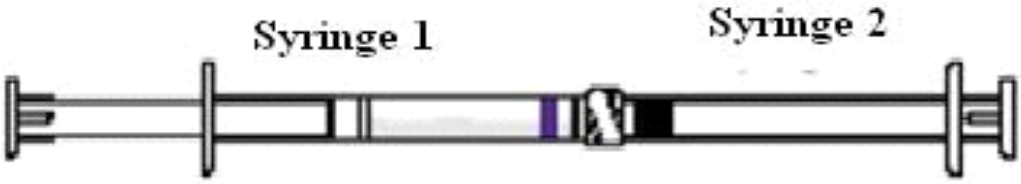

Figure 2.(b) Couple Syringe 1 (liquid delivery system) and Syringe 2 (drug powder).

Inject the liquid contents of Syringe 1 (indicated by purple stripe) into Syringe 2 (Doxycycline powder) and then push the contents back into Syringe 1. This entire operation is one mixing cycle.

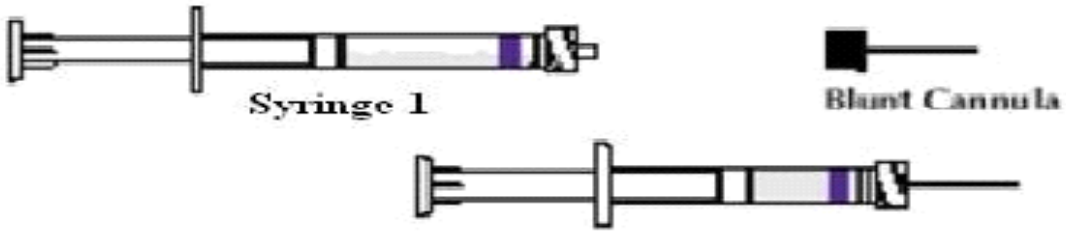

Figure 2. (c) Couple Syringe 1 (liquid delivery system) and Syringe 2 (drug powder).

1. If refrigerated, remove the product from refrigeration at least 15 minutes prior to mixing.
2. Couple Syringe A (liquid delivery system) and Syringe B (drug powder).
3. Inject the liquid contents of Syringe 1 (indicated by purple stripe) into Syringe B (doxycycline powder) and then push the contents back into Syringe 1. This entire operation is one mixing cycle.
4. Complete 100 mixing cycles at a pace of one cycle per second using brisk strokes.
5. If necessary, the coupled syringes can be stored at room temperature for a maximum of three days. Some of the Atridox systems are packaged in resealable pouches that can be used for this purpose. If the Atridox system is packaged in a try, use an airtight container.
6. After storage, perform an additional ten mixing cycles just prior to use.
7. The contents will be in Syringe 1 (indicated by purple stripe). Hold the coupled syringes vertically with Syringe 1 at the bottom. Pull back on the Syringe 1 plunger and allow the contents to flow down the barrel for several seconds.

8. Uncouple the two syringes and attach one of the provided cannulae to Syringe 1.

Product is now ready for application.

2) ATRISORB®- Free Flow Bioabsorbable (GTR) Barrier:

ATRISORBB Free Flow Bioabsorbable Barrier is a flowable gel that forms over a bone graft creating a barrier at the Guided Tissue Regeneration (GTR) surgical site which allows cell regeneration. It eliminates cutting, trimming, or handling of preformed barriers and reduces surgical time. ATRISORB is a unique flowable polymer that readily adapts to root morphology Rathbone J et al., 2000).

3).ATRISORB®-D Free Flow Bioabsorbable (GTR) Barrier :

ATRISORB-D contains all the advantages of ATRISORB, plus it is the only barrier that contains an antibiotic - doxycycline (4%). This provides a controlled release of doxycycline for a period of 7 days and is proven to prevent bacterial colonization of the barrier.

4).ATRIDOX® (doxycycline hyclate) 10% :

ATRIDOX is a Locally Applied Antibiotic (LAA) for the management of periodontal disease. When mixed, ATRIDOX becomes an easy to inject gel that flows minutes to prepare and administer at the chairside.[10]

Future developments:

- The current ATRIGEL technology appears to provide efficacious products with significant advantages over other existing delivery systems.
- However, certain improvements been made to the technology include easily to the bottom of pockets and fills even the smallest spaces between teeth and gums. It is these pockets and spaces where bacteria thrive and where ATRIDOX begins to work.
- It provides a controlled release of doxycycline for a period of 21 days 6 and is bioabsorbable - no removal required. Atridox takes only
- ATRIDOX is patient friendly, no anesthesia is required modifications to lower the initial drug burst.

- Use of new polymers and solvents in long term drug release and tissue compatibility. If these modifications, if implemented successfully to the Atrigel technology, these will surely increase its uniqueness and its applicability to a wide variety of drug delivery products.

Conclusion:

In conclusion, the market for drug delivery system has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of there drug molecules into new delivery system, thus providing numerous therapeutic and commercial advantages.A large number of compaines are involed in the development of new drug delivery system , which is evident by an increased number of products in the market and the number of patents grantes in the recent past. Tomorrow’s drug definitely will be more challenging in terms of the development of delivery system, and pharmaceutical scientists will have to be ready for a difficult task ahead.

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Yasmeen Begum

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