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Survey on Nanofiber Material as Drug Delivery Systems

Ali Ashjaran* and Atefe Namayi

Department of Textile and Chemistry, From Young Researcher and Elite Club Shahre-Rey Branch, Islamic Azad University, Tehran, Iran.

ABSTARCT

Nanofibers, due to their high surface area and porosity, find applications as filter medium, adsorption layer in protective clothing, drug delivery, wound healing, tissue engineering, etc. Nanofiber drug delivery systems are able to improve therapeutic efficacy, reduce toxicity, and enhance compliance of the patients by delivering drugs at a controlled rate over a period of time to the site of action. In particular biodegradable polyesters and their copolymers demonstrated their potential as effective carriers for drug delivery. In this paper, the basic concepts and recent advances of self-assembly, phase separation, electrospinning are widely used to generation nanofibers.Also the different principles of drug delivery and the applications of nanofibers in drug delivery system are explained.

Keywords:Nanofiber, Drug Delivery Systems, Self-Assembly, Phases Separation, Elecrospinning

Corresponding Author

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INTRODUCTION

Nanofibers are important materials because of their surface area. There are lots of methods for producing of nanofibers such as drawing, template synthesis, phase separation, self-assembly, electrospinning, melt blown, etc. But phase separation, self- assembly and electrospinning are common and easy methods for producing nanofibers.

Drug delivery system (DDS),which includes the method of drug loading and different release mechanism, further it deals with the different application of nanofibers as drug delivery vehicle[1,2]. Drug delivery systems that can precisely controlthe release rates or target drugs to a specific body site have had an enormous impact on the health care system. Carriertechnology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc.[2-4].The first reports about electrospinning fibres as DDS were noted by kenway et al. Their studies are mostly focused on the use of nanofibers as medical applications[5-7].

In recent years, several studies focused on nanomaterial and nanofibers as drug delivery systems. These researches are concerned with the use of nanofibers in the fields of delivery of bioactive agent, nanocomposites, wound healing dressing, delivery of therapeutic molecules, tissue Engineering, nano environment materials, biometic electrospun for tissue Generation, flavour encapsulation and controlled release, nanofabrication, anti-adhesion in surgery, ultrafiltration, biomedicine and biotechnology, biohybrid Nano systems, nanotubes, core–shell fibers, hollow fibres and fabricate drug delivery systems [8-26]. This paper, introduces common method for producing nanofibers and nanofibers as Drug delivery material and drug loading and release systems briefly.

NANOFIBERS

During the last 5 years, several reviews related to nanofibers have appeared in the literature. Three distinct techniques have proven successful in routinely creating nanofibrous tissue structures: self-assembly, phase separation, and electrospinning[27-30].

Self-assembly

Self-assembly involves the spontaneous organization of individual components into an ordered and stable structure with preprogrammed non-covalent interactions, such as hydrogen bonds, van der Waals forces, hydrophilic interactions and electrostatic interactions [31]. Self-assembly, that is, the autonomous organization of molecules into patterns or structures without human intervention, are common throughout nature and technology. Self-assembly of natural or synthetic macromolecules produces nanoscaled supramolecular structures, sometimes nanofibers. Compared with electrospinning, self-assembly canproduce much thinner nanofibers only several nanometers in diameter, butrequires much more complicated procedures and extremely elaborate techniques. The low productivity of the self-assembly method is another limitation [1]. The self-assembly approach to fabricate shows in figure 1.

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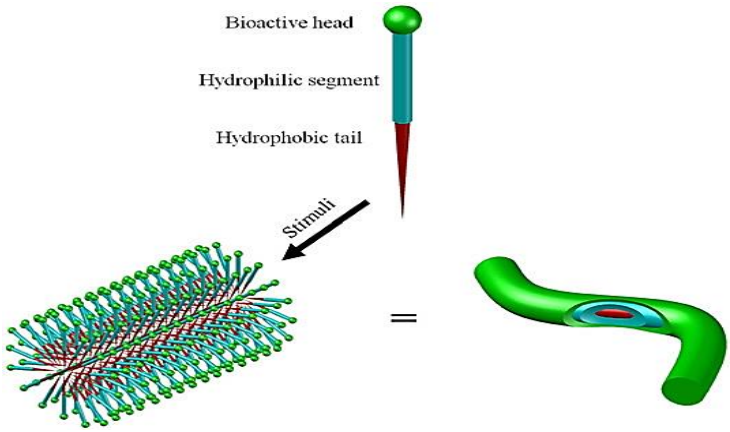

Figure 1: Schematic illustration showing the self-assembly approach to fabricate

Phase separation

Phase separation is a method frequently used to prepare 3-D tissue-engineering scaffolds. Phase separation of a polymer solution can produce a polymer rich domain and a solvent-rich domain, of which the morphology can be fixed by quenching under low temperature. Removal of the solvent through freeze drying or extraction can produce porous polymer scaffolds. Phase separation can be induced by changing the temperature orby adding nonsolvent to the polymer solution, thus called thermal induced or nonsolvent-induced phase separation, respectively. Unlike self-assembly, phase separation is a simple technique that does not require much specialized equipment. It is also easyto achieve batch-to-batch consistency and tailoring of scaffold mechanical properties and architecture is easily achieved by varying polymer/porogen concentrations. However, this method is limited to being effective with only a select number of polymers and is strictly a laboratory scale technique. Phase separation is a thermodynamic process [1,8].The Schematic of phase separation shows in figure 2.

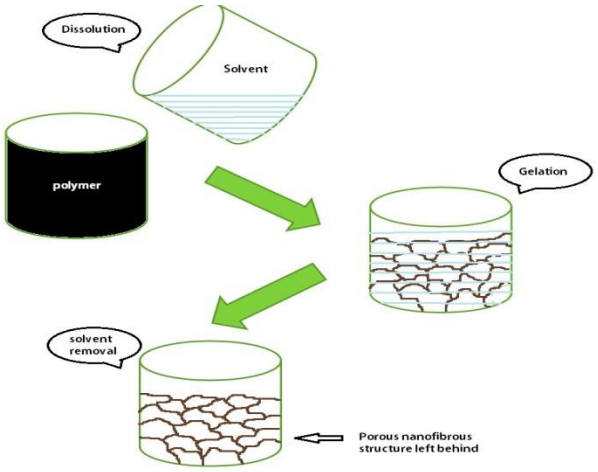

Figure 2: Schematic of phase separation

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Electrospinning

Electrospinning, firstly reported in 1934, has been used for more than 70 years, and yet is under developed in studying the fabrication of continuous nanofibers. The term “electrospinning”, derived from “electrostatic spinning”, was coined relatively recently. Since 1980s and especially in recent years, the electrospinning process has regained more attention probably due in part to a surging interest in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with diameters in the submicron/nanometer range can be easily fabricated using this process [31]. Electrospinning is a simple, scalable and versatile technique, using strong electrical fields to draw polymer solutions or meltsto produce fibers with diameters ranging from micrometers to nanometers that exhibit a highsurface area to volume ratio. Electrospun fibers have been the focus of research for such applications as tissue engineering scaffolds, wound dressings, drug delivery, artificial organs and vascular grafts [32]. Electrospun fibers are recognized to possess high surface areas andlarge aspect ratios. There are numerous possible applications of electrospun textiles that take advantage of the large amount of surface area[33]. In the generic design, an electrospinning setup consists of three major components (Figure 3): a high-voltage power supply, a spinneret, and an electrically conductive collector. For most experiments, an ordinary hypodermic metallic needle and a piece of aluminum foil work well as the spinneret and collector, respectively. The solution for spinning is loaded in a plastic syringe, which is connected to the metallic needle. In order to control the quality of electrospun fibers, the syringe is often connected to a syringe pump so that a constant and adjustable feeding rate of the solution can be maintained. Electrospinning is a technique based on electrostatic interactions [34, 35].

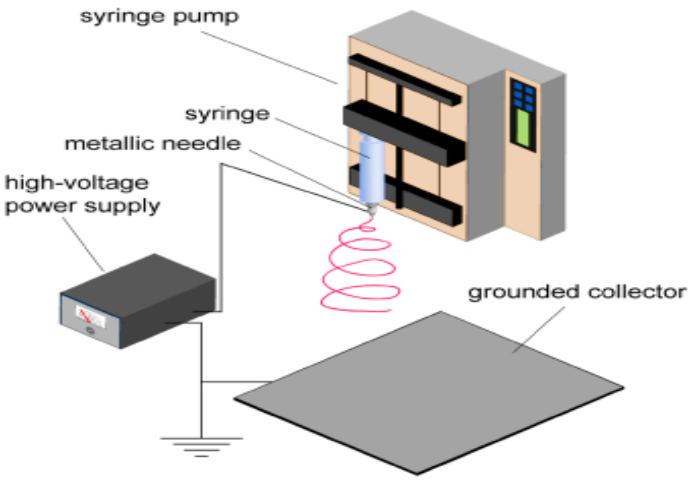

Figure 3: Schematic of a typical setup for electrospinning

DRUG DELIVERY SYSTEMES

Due to the flexibility in material selection a number of drugs can be delivered including: antibiotics, anticancer drugs, proteins, DNA,Small molecular drug, herbs, poorly water-soluble and water soluble drugs, gens, vaccines [1,31].

Physicochemical characteristics [36-37]

- Dose size
- Lionization, pKa and aqueous solubility
- Partition coefficient

Unsuitable drug Characteristics for extended-release [36, 37]

- Short elimination half-life, <2hr
- Long elimination half-life,>8hr
- Narrow therapeutic index
- Large doses
- Poor absorption
- Low or slow solubility
- Extensive first-pass clearance

Suitable drug Characteristics for extended-release [36, 37]

- Biological half-life
- Absorption
- Metabolism

Drawbacks of convention dosage forms[38-39]

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavailable fluctuations of drug concentration may lead to under medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index

Advantages of sustained release formulations include[40]

- Uniform release of drug substance over time.
- Reduction in frequency of intakes.
- Reduced adverse side effects.
- Better patient compliance.
- A sustained release dosage from Canbe created using lipid excipients to from either a water insoluble matrix or a hydrophobic film around an active drug.

Selection of Drugs

In the selection of a drug for formulation of magnetic microspheres, followingpoints are taken into consideration:

- The drug is so dangerous or labile that we cannot allow it to circulate freely in the blood stream.
- The agent is so expensive, that we cannot afford to waste 99.9% of it.
- Requires a selective, regional effect to meet localized therapeutic objective.
- Requires an alternative formulation essential to continue treatment in patient whose systemic therapy must be temporarily discontinued due to life threatening toxicity directed at selective organs [41].

Drug loading

Active substances can be incorporated inside the nanofibers, physically adsorbed or chemically bound to the surface (Figure 4). However, knowledge of the drug's behavior during its incorporation in the nanofibers and its subsequent release from the nanofibers is much more limited, compared to the knowledge available for drug incorporation and release from, for example, solid lipid nanoparticles. The loading of many different drugs and their localization in the lipid matrix have been systematically investigated. The results showed that the drug incorporation, localization and release depend on the physicochemical properties of the drug and the carrier matrix. Therefore, it is also expected that for nanofibers the loading mechanism will be governed by the drug solubility in the polymer solution and the drug–polymer interactions in the solid state [42].

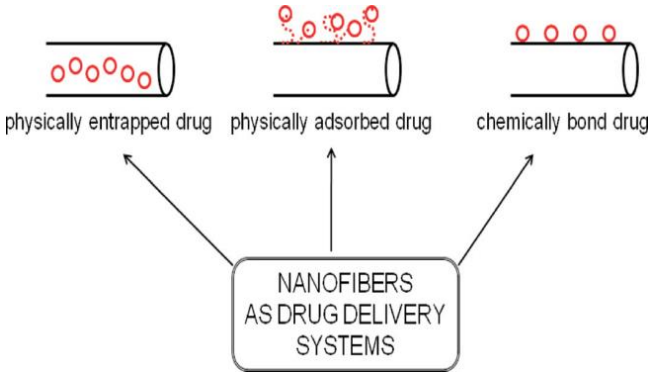

Figure 4: Scheme presenting the possibilities drug loading in/on nanofibers

The various loading possibilities, physical entrapment are currently the most widespread, since the drug in the nanofibers is protected against unfavourable environmental conditions and it offers good control over the drug's release. A typically observed release profile from such nanofibers exhibits an initial burst effect followed by an almost linear, sustained release. Furthermore, the preparation of core-shell nanofibers provides a drug-reservoir system with a shell barrier protecting the incorporated drug and controlling the drug diffusion rate. The burst effect from such nanofibers is small and the entire release profile is more sustained [42]. The incorporation of a drug in nanofibers, either in the form of a matrix or as a core-shell system, is relatively easy to perform, since the drug is simply dissolved in the polymer solution prior to electrospinning. The formation of an amorphous drug, which shows a higher solubility with respect to the crystalline form, is favoured, due to a very limited time being available for the drug's recrystallization during the electrospinning process. Furthermore, a reasonable question can be raised concerning the preservation of the chemical and biological integrity of the incorporated drug due to the application of a high voltage during the electrospinning. Various studies using H-NMR, DSC,

X-ray and IR spectroscopy have proven that the electrospinning process does not affect the structural integrity of the incorporated drug [43]. The physical adsorption of a drug on the surface of the preformed nanofibers is achieved by dipping the nanofibers into a solution of the drug, which associates with the nanofibrillar surface via electrostatic interactions. However, this techniqueis seldom used due to poor control over the drug's release and an undesirable competitive displacement of the drug with the components of biological fluids. The third approach to drug loading is the covalent immobilization of the drug on the nanofibrillar surface via the formation of chemical bonds. The latter is predominately used for the modification on the surface properties of nanofibers, since the technique is technically complex. However, there are some reports dealing with this approach for the delivery of active substances. The drug is released after the enzymatic or environmental degradation of the chemical bond [42]. However, the burst release may also be indicative of the drug being attached only on the surface. As the drug and carrier materials can be mixed together for electrospinning of nanofibers, the likely modes of the drug in the resulting nanostructed products are:

- Drug as particles attached to the surfaceof the carrier which is in the formof nanofibers,
- Both drug and carrier are nanofiberform;hence the end product will bethe two kinds of nanofibers interlacedtogether,
- The blend of drug and carrier materialsintegrated into one kind of fibers containingboth components, and
- The carrier material is electrospun intoa tubular form in which the drug particlesare encapsulated [1].

Drug release

Drug release from nanofibers can be described through three mechanisms: desorption from fiber surface, solid-state diffusion through fibers, and in vivo fiber degradation. Drug release tests from nanofibers are commonly conducted in phosphate-buffered saline (PBS) solutions. When the nanofiber drug carrier is subjected to PBS, the fibers will be surrounded by the solution. The solution will also penetrate the space in between individual nanofibers. When the nanofiber drug carrier is swollen by the aqueous phase, drugs or proteins attached to the fiber surfaces can be released. Drug release from nanofiber surface is a two-step mechanism, starting from desorption of drugs from the fiber surface, followed by fast diffusion into the aqueous phase. The desorption mechanism is not limited to the outer surface of the nanofibers but also includes drugs on the surfaces of the nanopores inside the nanofibers. Considering the nanometer size scale of the inner pores, and that the nanopores are most likely interconnected to some degree, the surface area would be much larger than the fiber outer surface area [43]

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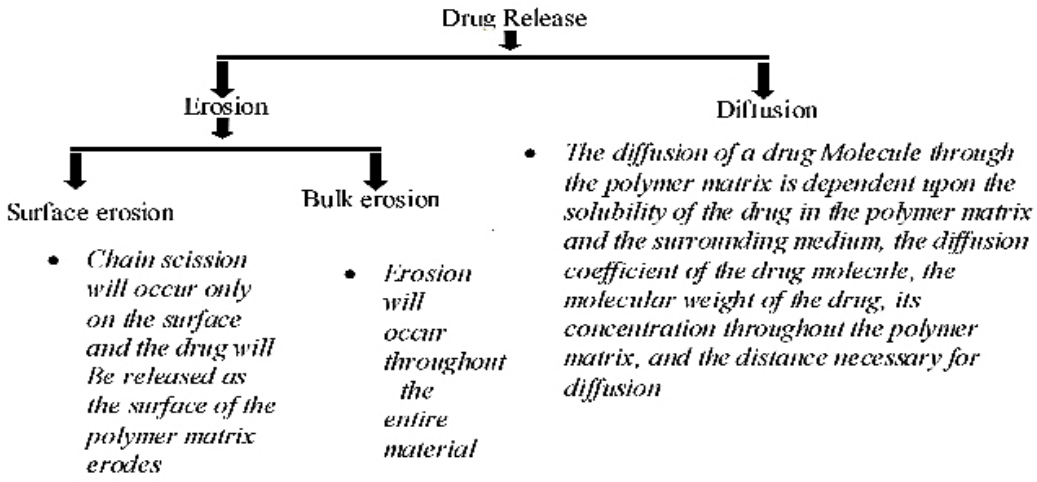


Figure 5: Different mechanism of drug release

Diffusion-controlled systems

Diffusion-controlled systems are the most widely used systems. They have been formulated in two basic configurations: reservoirs and matrix. In these systems, a core of drug is surrounded by a swollen or non-swollen polymer film, and diffusion of the drug through the polymer is the rate limitingsteps (figure 6). These systems include membranes, capsules, microcapsules, liposomes, and hollow fibers. While the last four systems have been effectively applied in various areas (e.g. enzyme immobilization, drug targeting), membranes have proven of greatest value in controlled-release applications [44].

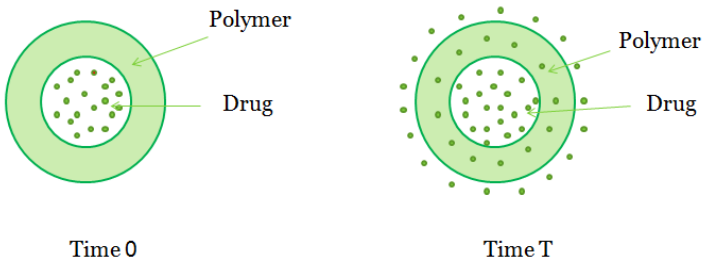


Figure 6: Idealized diffusion-controlled reservoir release system

Matrix systems

In these systems, the drug is uniformly distributed, throughout a solid polymer (figure 7)as in reservoir systems; drug diffusion through the polymer matrix is the rate-limiting step.From the standpoint of fabrication cost, the ease of accomplishing this distribution pattern represents a significant cost decrease compared to reservoir systems. However, because of the different way in which drug is distributed, release characteristics are not generally zero-order. Solution of Fick's equation for transient diffusion [44].

Case 1: The drug is molecularly dissolved in the polymer matrix and drug diffusion occurs via a solution-diffusion mechanism.
Case 2: The drug is dispersed in the polymer matrix (i.e., it is loaded above its solubility limit) and diffusion occur via a solution-diffusion mechanism.
Case 3: The drug is dissolved in the polymer matrix anddiffusion occurs through water-filled pores in the matrix.

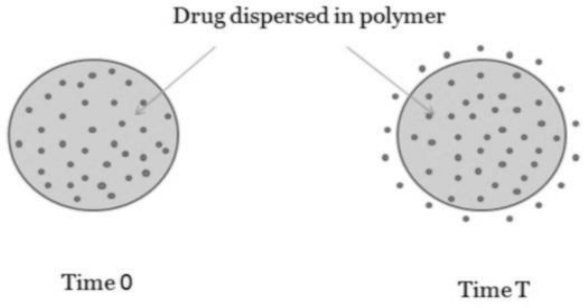


Figure 7: Idealized diffusion-controlled matrix release system

CHEMICALLY – CONTROLLED SYSTEMS

In these systems, the drug is distributed, ideally, uniformly, throughout a polymer in the same way as in matrix systems. The difference, however, relates to the fact that while the polymer phase in matrix systems remains unchanged with time and drug is released by diffusion, the polymer phase in bio erodible systems decreases with time. Consequently, as the polymer surrounding the drug is eroded, the drug escapes (Figure 8).

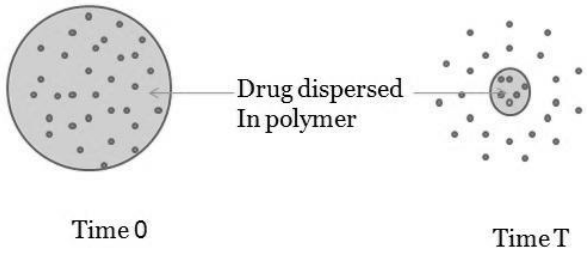


Figure 8: Idealized drug release from bio erodible systems

This property offers a significant advantage over non-erodible systems in many applications because biodegradable polymers are eventually absorbed by the body, obviating the need for surgical removal. However, this advantage must be weighed against the potential disadvantage that the absorption products may be toxic, immunogenic, or carcinogenic. Mathematical formulations for bio erodible systems may be obtained if the kinetics of the biodegradation reaction of the polymer is known. Hoffenberg4' has explored ideal situations where surface erosion is the only factor permitting drug release to occur. He has found that to obtain zero-order release it would be necessary to utilize geometry where the surface area did not change as a function of time. A slab (neglecting edge effects) is such

a shape. On the other hand, spheres and cylinders woulddisplay decreasing rates with time because their surface areas would diminish [44].

Pendant chain systems

In these systems, a drug is chemically bound to a polymer backbone-chain and is released by hydrolytic or enzymatic cleavage (Figure 9). The use of these therapeutic agents has received considerable attention in drug-related research. The major thrust so far has been the design of polymer-drug complexes for short term use that can reduce toxicity, increase therapeutic efficiency, or be targeted toward specific cells or organs. Many examples exist in the literature. While some studies have explored this type of system for prolonged administration(e.g.; hours), less attention has been paid to the use of these pendant chain systems for controlled long-term drug release. In its simplest form, the pendant chain system consists of drug attached to a polymer backbone. The polymer system can either be soluble or insoluble. Soluble backbone-chains are generally used for transport functions such as cell targeting; insoluble forms are more desirable for long-term controlled-release implants. The backbone may also be biodegradable or non-biodegradable. For in vivo use, it is important that the polymers do not cause immunological reactions and that the drugs, when coupled to the polymers, do not function as happens and induce allergic reactions. The drug itself can be attached directly to the polymer or it can be attached via a spacer group. The spacer group may be used to affect the rate of release and hydrophobicity of the system [44].

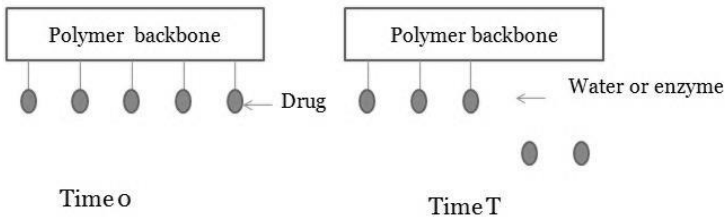


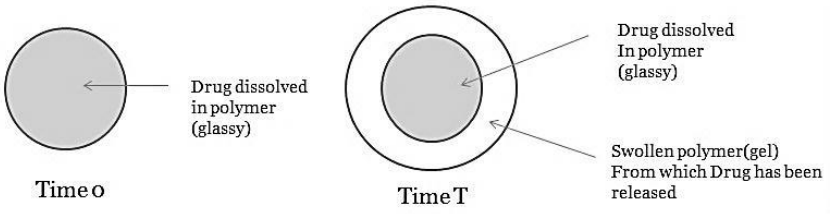
Figure 9: Idealized drug release from pendant chain systems

Swelling-controlled systems

Swelling-controlled release of potent drugs may be achieved by employing the glassy/rubbery transition of polymers inthe presence of a penetrant, and the macromolecularrelaxations associated with this transition.In these systems the drug is originally dissolved ordispersed in a polymer solution; the solvent is then evaporated,leaving the drug dispersed in a glassy (solvent-free)polymer matrix. There is no drug diffusion in the solidphase. As the dissolution medium (e.g. water) penetratesthe matrix, the polymer swells and its glass transitiontemperature is lowered below the temperature of theexperiment. Therefore, the swollen polymer is in a rubberystate and it allows the drug contained in it to diffuseoutward (Figure 10).Swelling-induced macromolecular relaxation of thepolymer is observed in the gel-like region near the moving front separating the glassy from the rubbery

state.Although diffusion in rubbery systems at equilibrium is generally Fickian, diffusion in a rubbery state which is not at equilibrium (due to the continuous swelling) may be Fickian or non-Fickian [44].

Figure 10: Idealized swelling controlled release system



Magnetically Controlled systems

In these systems, drug and small magnetic beads are uniformly dispersed within a polymer matrix (e.g., ethylene vinyl acetate copolymer). Upon exposure to aqueous media,drug is released in a fashion typical of diffusion-controlled matrix systems. However, upon exposure to an oscillating external magnetic field, drug is released at a much higherrate. The mechanism responsible for this magnetic modulation is unclear. It was mentioned previously that the incorporation of powdered drug into solvent-cast ethylene vinyl acetate copolymer caused porous channels to form within the matrix. It is possible that the beads cause alternating compression and expansion of the channels, thus facilitating drug release [44].

TYPES OF DRUG RELEASE

In general a few typical different types of release can be recognised relevant in nanofibers drug delivery systems; immediate release, extended release and triggered or delayed release the different mechanisms are[1].

Immediate release

- The drugs are available within a relatively Short time.
- his type of release is required in situations where immediate action is essential.

Extended release

- The availability of drugs is maintained at a lower concentration and for a prolonged time compared to immediate release systems.
- The drug is delivered at a (very) slow rate and for a prolonged period of Hours, days or even years, thereby usually reducing dosing frequency.

Trigged or delayed release

- The release of drugs from triggered or delayed release systems is determined by an (external) trigger/stimulus or time. The resulting release can be of the immediate type or slow-release type.

- The release of the drug from the delivery system might also be triggered by a specific event, situation, or change in the environment such as a change in pH, temperature, ionic strength or even by an externally controllable trigger- like ultrasound [1].

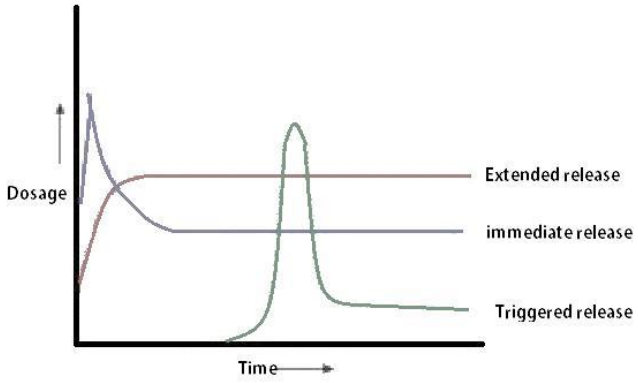


fig 11. Drug release profile

CONCLUSION

Nanomaterial have been attracting the attention of global materials research these days primarily due to their enhanced properties required for application in specific areas like catalysis, filtration, NEMS, nanocomposites, nanofibrous structures, tissue scaffolds, drug delivery systems, protective textiles, storage cells for hydrogen fuel cells, etc.

Nanofibers are defined as fibres with diameters on the order of 100 nm. Nanofibers, due to their high surface area and porosity are important. Nanofibers have applications in many different fields, such as protective textiles, filtration, drug delivery, tissue engineering, etc. To be a successful extended-release product, the drug must be released from the dosage from at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient, gastrointestinal residence time, and may be adsorbed at a rate and will replace the amount if drug being metabolized and excreted. In the nut shell, sustained-release formulations are a promising way to improve the patient's compliance by reducing dosing intervals and minimizing adverse effects.

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