Expert Opinion

Non-degradable polymer nanocomposites for drug delivery

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Introduction: The need to optimize therapeutic outcomes while minimizing side effects is a major driving force for research and development in the controlled drug delivery field. Polymer nanocomposites (NCs) are an emerging class of materials with remarkable potential for controlled drug delivery. There are a range of release mechanisms that characterize polymer NC systems, and these may be perturbed not only by the addition of nanofillers, but also by the type of drug and the interactions of the drug with the components of the system.

Areas covered: The focus of this review is on non-degradable polymer NC systems. In particular, the types of drug delivery approach from these polymer NCs and the theoretical models developed to describe those approaches are discussed. The importance of component interactions and factors affecting drug delivery from polymer NCs is also addressed.

Expert opinion: Despite the remarkable potential and extensive research being conducted on polymer NCs for use in drug delivery, commercialization and large-scale production are limited by the cost and difficulty in consistently producing fully exfoliated NCs. A continuing challenge for the field is to understand better the key interactions and structure–property relationships arising from different polymer, filler and drug combinations.

Keywords: biomedical, drug delivery system, drug interaction, nanocomposite, polymer

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1. Introduction

Composite materials are defined as materials that consist of two or more distinct components including a matrix and a filler that are combined on a macroscopic scale. These components are incorporated such that the resulting new material shows the desirable properties of its constituents, such as increased mechanical strength, stiffness, fatigue resistance and wear resistance. With mechanical properties being the major driver, composite materials have been widely used in automotive and aerospace applications where high strength-to-weight and stiffness-to-weight ratios are required [1].

Much like traditional composites, nanocomposites (NCs) consist of two or more components; however, at least one dimension, the length, width, or thickness, of one of the components is in the size range 1 – 100 nm [2]. Significant improvements in properties can be achieved using very low nanofiller loadings, typically 1 – 5 wt% in comparison with the 10 – 70 wt% filler content in conventional composites [3]. These filler nanoparticles reinforce and strengthen the matrix, which can be constructed of metallic, ceramic or polymeric base materials [4,5]. In this review the focus is on polymer matrices.

The origin of polymer NCs can be traced back to the early 1950s, when Hauser discovered that by replacing inorganic cations in nanoclays with an organic base, the ability of the clay to swell in water was diminished and the surfaces became organophilic [6]. This finding laid the foundation for the incorporation of such

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Article highlights.

- Polymer NCs are classes of material capable of producing different modes of drug release through different polymer, filler, surfactant and drug combinations.
- Permeability and drug release in polymer NCs can be modulated by adjusting filler content, surfactant, dispersion and drug–component interactions.
- Drug delivery using polymer NCs can be classified into four broad types on the basis of the manner in which the drug is incorporated and released.
- Uniform dispersion of nanofillers is crucial in property enhancement and is the major challenge in this field.
- A better understanding of key interactions between drug, polymer and nanofiller could contribute to the development of more accurate models in predicting drug release from a NC system.

This box summarizes key points contained in the article.

modified nanoclays into organic polymers, the modifier having a 'compatibilizing' effect on the normally hydrophilic clay. In the absence of surface modifiers, the ability to disperse typically polar nanofillers within a largely nonpolar organic matrix is limited.

Much research investigating the swelling behavior of layered clays and intercalation chemistry of polymers has been conducted [7-9], but the findings were not translated into NC applications until the 1990s. In 1993, researchers from the Toyota group successfully polymerized ε-caprolactam in cation-exchanged montmorillonite (MMT) to produce a nylon-6 clay-based NC [10,11]. The resulting NC was well dispersed and showed dramatic improvements in mechanical, physical and heat distortion temperature at very low layered silicate concentrations [10,11]. This enabled research into other potential fillers such as carbon nanotubes (CNT), carbon fibers (CNF), glasses and metals [12-14].

The improvements in material properties observed in polymer NC systems make them particularly attractive for biomedical applications. Having the ability to improve mechanical properties without altering the chemistry of the polymer matrix is a useful tool to overcome regulatory concerns with new chemistries in the biomedical environment. Similarly, barrier properties are known to be affected by the addition of nanofillers and this property may have significant implications in the field of drug delivery. Drug delivery systems typically aim to provide therapeutic levels of active agents at the target site in a controlled manner. Such systems theoretically provide appropriate concentrations of drug at a local site, which usually would not be possible through systemic administration. Control of drug release locally is also able to overcome issues of adverse side effects and systemic toxicity that can be associated with systemic drug delivery.

This review discusses the components of polymer NCs and properties relevant to drug delivery systems. The mechanisms of release and applications relating to the use of polymer NCs in drug delivery are discussed and categorized based on delivery approaches. In addition, the mathematical models developed in predicting permeability and the factors affecting drug delivery from polymer NCs are also presented. Although the focus is on non-degradable polymer systems that could be used for applications such as stent coatings, catheters and other such medical devices, the NC approach could equally be exploited in a degradable system [13,15-17].

2. Components of polymer nanocomposites

Polymer NCs consist of the polymer matrix material and the nanofiller, but in many cases a third component, the organic modifier, is required to enhance compatibility of the inorganic nanofiller with the organic polymer matrix, as illustrated in **Figure 1**.

Choice of polymer matrix often depends on the application, with much research concentrated on NCs based on epoxies [18], polyimide [19], polystyrene [20], polypropylene [21], polyethylene [22] and polyurethane [23]. Polymers have a variety of desirable attributes over metals and ceramics in medical applications, such as flexibility, toughness, weight/volume ratio, design flexibility and low electrical conductivity [24,25].

2.1 Nanofillers

Various types of nanoparticle filler have been used as reinforcement for rubber and plastics. This review discusses some of the common nanofillers reported in drug delivery systems or biomedical applications, such as metals, metal oxides, carbon nanotubes and nanofibers, silicates and layered double hydroxides (LDH) [26-28].

2.1.1 Metals and metal oxides

Metal oxides such as TiO_2 are spherical nanofillers that have been studied as fillers in various polymer types. Ng *et al.* [29] showed a dramatic increase in both modulus and scratch resistance using TiO_2 particles with an average diameter of 32 nm and 10 wt% loading in epoxy, whereas micrometer-sized TiO_2 demonstrated only increased modulus. In the field of bioengineering, TiO_2 can be used as a drug carrier for active drug molecules as a result of its oxidizing properties and chemical inertness. Nanocomposites based on poly(lactic acid) and nano-TiO_2 as a carrier of anticancer drugs showed more efficient delivery and potentially higher loading capacity owing to the large surface area. This was attributed to electrostatic interactions and non-covalent binding between the drug and TiO_2 creating a self-assembled surface that could readily adhere to the surface of the targeted cancer cells and enhance drug permeation [30]. In addition, there have been reports on the use of nano-Ti in urinary tract applications because of its encrustation-resistant properties and decreased adhesion of *Staphylococcus epidermidis* [31].

Both gold (Au) and silver (Ag) have been explored in NCs as fillers possessing desirable biological properties. An improvement in thermal and mechanical behavior was found

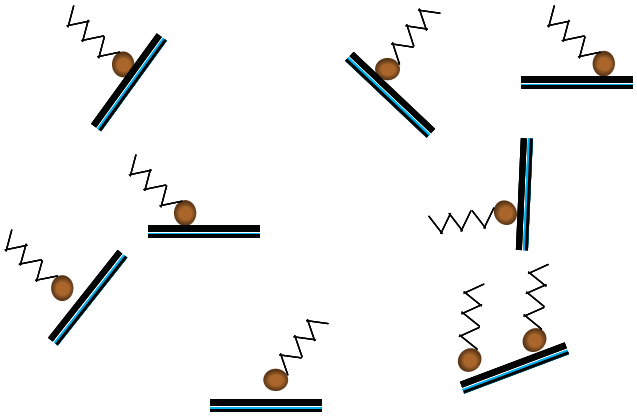

Figure 1. Polymer nanocomposite consisting of three components. The inorganic nanofillers (rectangular stacks) modified through electrostatic interaction with organic surfactants (sphere shaped head group and tail), both of which are incorporated in a polymer matrix.

by Hsu and co-workers when Ag/Au nanoparticles were incorporated in a polyether urethane. Following implantation in porcine models, these materials also demonstrated improved *in vivo* biostability compared with neat polyurethane, which was attributed to free radical scavenging by the Ag/Au nanoparticles [32,33]. Silver is well known for its antimicrobial ability and has been used in catheters to prevent infection [34]. Incorporation of silver nanoparticles in polyether urethane showed enhanced cellular proliferation, reduced monocyte activation and lower bacterial adhesion [35]. Gold, on the other hand, is a noble metal that is not cytotoxic and does not elicit pro-inflammatory cytokines. Gold-incorporated polyether urethane NCs also demonstrated lower bacteria adhesion and platelet activation [36].

2.1.2 *Carbon nanotube/fiber*

Carbon nanotubes and carbon fibers are unique structures with high aspect ratios and excellent mechanical (flexibility and strength), electrical and thermal properties, making them the subject of intensive research as reinforcements for polymer, metal and ceramic composites [37]. CNT were first discovered by Iijima in 1991 at the NEC fundamental research laboratory in Japan [38]. CNT can be visualized as rolled sheets of graphitic carbon either as a single-walled structure with diameter as small as 0.4 nm or multi-walled with outer diameter from 5 to 100 nm [27]. CNF can encompass a range of morphologies from disordered bamboo-like structures to layers of 'cup stacked' structures with diameter on the order of 50 – 200 nm. Polymer NCs based on CNT and CNF show improved mechanical strength at low volume fractions. Chang *et al.* [39] showed a factor of 3 modulus increase with 1 wt% CNT in polypropylene matrix, while a 13% improvement in fracture toughness and 33% improvement in bending strength were observed in CNF-reinforced alumina NC loaded with 2.5 and 5.0 (v/v), respectively [37].

2.1.3 *Layered double hydroxides*

LDH are anionic clays that can also accommodate organic compounds through ion-exchange reactions from their interlayer anions. The chemical formula for LDH can be generalized as $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}$ $(A^{n-})_{x/n} \cdot yH_2O$, where M^{II} and M^{III} are divalent and trivalent cations, respectively, and A^{n-} is the anion. The most commonly known natural occurring LDH is hydrotalcite, having the formula $Mg_6Al_2(OH)_{16}CO_3$ $4H_2O$, therefore LDHs are also known as hydrotalcite-like compounds [40,41].

2.1.4 *Smectite clays*

There are generally three types of layered silicate (phyllosilicate) used in the synthesis of polymer clay NCs. They are the 2:1 type, 1:1 type and layered silicic acids. The smectite group, or 2:1 type, are most widely used for the production of polymer NCs because of their high strength and high aspect ratio along with their remarkable ability to exchange ions [42,43]. Smectites commonly used in NCs are shown in **Table 1**.

So far, montmorillonite is the most widely used layered silicate because of its abundance in nature, low cost, ease of chemical modification and, most importantly, MMTs have silicate layers 0.96 nm thick and ~ 100 to several hundred nanometers in length [44-46]. This high surface area (~ 750 m^2/g) and nanoscale dimension eliminate any size differences between the filler and polymer, resulting in decreased ductility, poor surface smoothness and degradation properties seen in conventional composites [47].

The structure of MMT consists of a repeating triple layer composed of two silica tetrahedral sheets sandwiching an octahedral sheet of alumina. Isomorphic substitution of Si^{4+} for Al^{3+} in the tetrahedral layer and Al^{3+} for Mg^{2+} in the octahedral sheet will generate negative charges within the layers. This behavior is then counterbalanced by cations such as Na^+, Ca^{2+} and Li^+ occupying the 'interlayer' or 'gallery' [45,48]. The layers with high aspect ratio are stacked by means of weak dipole forces and the galleries are generally occupied by cations (e.g., Na^+, Ca^{2+} and Li^+), which are responsible for the swelling of clay in water [49]. The ability of these cations to undergo ion exchange makes them potentially attractive for biomedical applications [17,50].

2.2 Surfactant

As noted earlier, a practical problem in the synthesis of polymer NCs is to disperse the inorganic nanofiller in an organic polymer matrix. The principle underlying organic modification of nanofillers is that an amphiphilic molecule can interact both with charged surfaces of the filler and with the nonpolar matrix. For example, cationic-organic surfactants, such as alkylammonium cations, are commonly used in rendering clays organophilic [2,20,51]. They lower the surface energy by

Table 1. Notation and chemistry of common smectites [42,63].

2:1 type	Substitution	Cell formula
Natural		
Montmorillonite	Octahedral	$(Na,Ca)_{0.33}(Al,Mg)_2Si_4O_{10}(OH)_2 \cdot nH_2O$
Hectorite	Octahedral	$Na_{0.3}(Mg,Li)_3Si_4O_{10}(OH)_2$
Saponite	Tetrahedral	$(Ca_{0.5},Na)_{0.3}(Mg,Fe^{2+})_3(Si,Al)_4O_{10}(OH)_2 \cdot 4(H_2O)$
Synthetic		
Fluorohectorite	Octahedral	$Li_{1.12}[Mg_{4.88}Li_{1.12}][Si_8O_{20}]F_4$
Laponite	Octahedral	$Na_{0.7}[Mg_{5.4}Li_{0.4}]Si_8O_{20}(OH)_4$

reducing the van der Waals interaction of the clay layers, which allows organic species to diffuse into the layers and achieve separation of the silicate layers [49]. The degree of dispersion is dependent on alkyl chain length [10,18], degree of quaternization [52,53] and the amount of alkylammonium ions. On the other hand, anionic surfactants such as dodecyl sulfate, dodecyl benzenesulfonate and laurate are commonly used to modify the positively charged surfaces on LDH nanofillers [40]. Carbon nanotubes undergo similar aggregation and can be dispersed with surfactants such as triton X100 and anionic sodium dodecyl chloride, with dispersion dependent on the nature and surface charge of the surfactant [54,55].

3. Morphology of nanocomposites

Varying degrees of nanoparticle dispersion are usually achieved in polymer NCs. In the case of clay particles in polymer NC, three broad types of morphology exist, conventional composite, intercalated NC, or exfoliated NC, as illustrated in **Figure 2**. In conventional composites, clay particles exist in agglomerated stacks or tactoids and there is no intercalation of polymer between clay layers [5,49]. In intercalated NC, polymer chains are inserted into the gallery of the clay minerals resulting in a well-ordered multilayer morphology with a repeating distance of a few nanometers. Exfoliated NCs occur when the clay platelets are completely separated and dispersed in a continuous polymer matrix. The expansion of the layered silicate is so large that the interaction between the layers is not strong enough to keep the ordered morphology [56].

The ideal exfoliated morphology is where the individual silicate layers are completely separated and uniformly dispersed in the polymer matrix. Practically, morphologies of fabricated NC usually lie between these idealized morphologies and a partially exfoliated structure is the result [57]. **Figure 3** shows transmission electron microscopy (TEM) images of polymer NCs at various magnifications to illustrate typical morphologies observed. To optimize the benefits that NCs have to offer with regards to material properties, filler particles should be exfoliated throughout the matrix material to increase the number of available reinforcing elements that can carry applied load and deflect cracks. Complete exfoliation is difficult to achieve and most NCs have been found to contain some intercalation in their structure. Uniform separation of nanofillers is reflected not only by their enhanced mechanical performance but also by their significant decreases in gas or water permeability. This is a useful property in terms of drug delivery applications and is discussed below.

4. Exploitation of barrier properties for drug delivery

Barrier properties refer to those characteristics of a material that prevent permeation of molecules such as gas, water vapor and liquids. Materials with good barrier properties are resistant to or can retard diffusion of the permeating molecule. This is especially important in packaging of food and beverages where the loss of carbon dioxide in carbonated soft drinks and moisture penetration into sealed foods can lead to product spoilage. Materials with good barrier properties can be particularly useful in drug delivery systems when prolonged dosage and controlled release to prevent fluctuations in drug concentration are required. Polymers are often used as drug carriers but may not provide sustained therapeutic doses within the desired time frame and release mechanisms are mainly via diffusion. Diffusion can be perturbed by several approaches, such as adjusting the composition of the polymer, coating with an extra layer of polymer, or covalently attaching the drug to the polymer backbone [17,58].

Nanofillers have the capacity to alter the barrier properties of the base polymer either by acting as obstacles and retarding permeation of molecules, or by enhancing penetration by acting as carriers of penetrants. The alteration in barrier properties is potentially beneficial for drug delivery purposes as this can have a direct influence on dissolution rate, release mechanisms and drug uptake. Many polymers, such as polyethylene terephthalate (PET), polyurethane, nylon, high-density polyethylene (HDPE) and epoxy, demonstrate a reduction in permeability up to an order of magnitude with a low percentage of fillers added [59,60]. An example given by Xu and co-workers, showed that water vapor permeability of polyurethanes could undergo fivefold reduction at 20 wt% silicate loading even under conditions where the NCs were not fully exfoliated [61,62].

Altered barrier properties of polymer NCs, in particular significantly reduced permeability of moisture and gases, have been explored for packaging materials and containers,

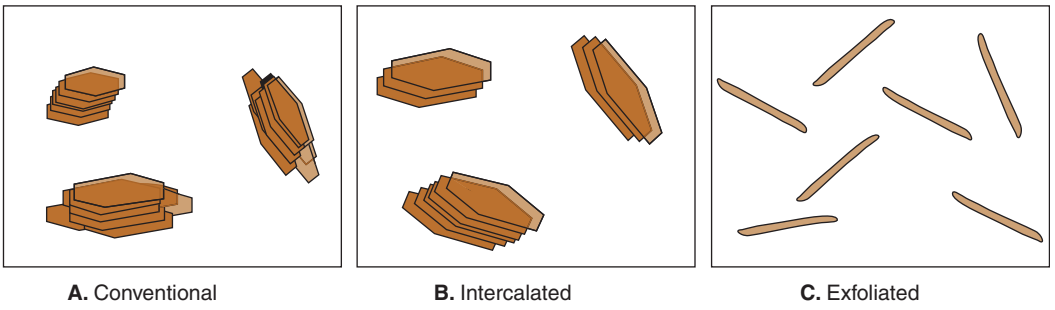

Figure 2. Illustration of (A) conventional, (B) intercalated and (C) exfoliated polymer clay nanocomposite.

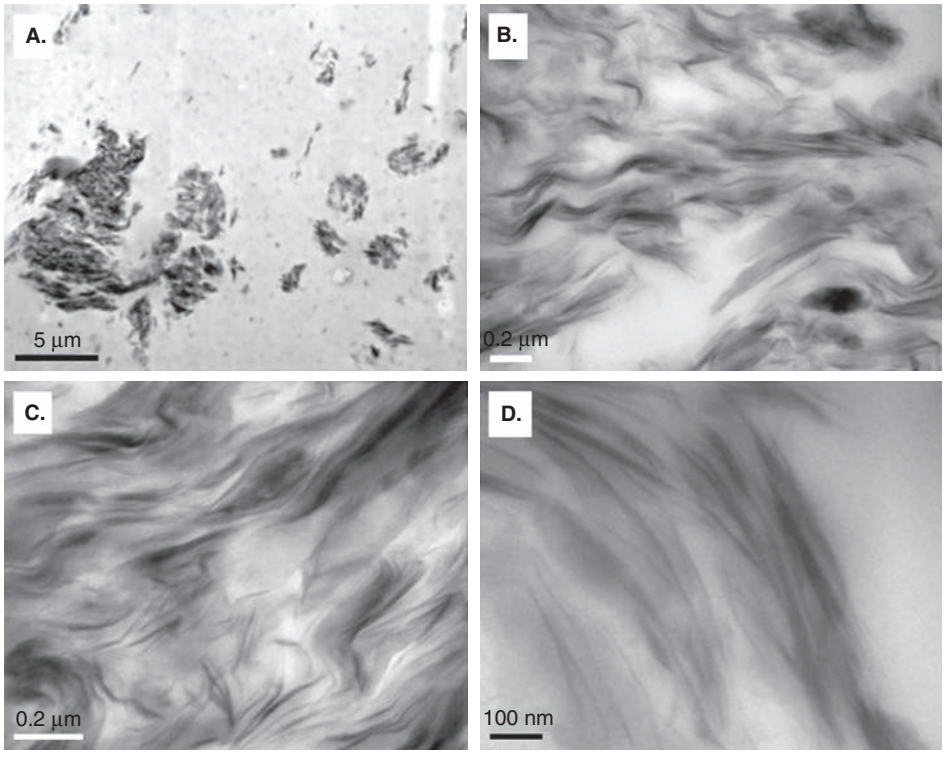

Figure 3. Morphology of polymer silicate nanocomposite showing (A) tactoids and agglomerated stacks, (B, C) intercalated morphology and (D) partially exfoliated structure showing individual silicate sheets at ×5000, ×60,000, ×100,000 and ×150,000 magnification, respectively.

and in a variety of food and beverage products. However, these properties have not been widely exploited for medical applications [14,59,63]. The following sections first outline the types of drug delivery approach and applications for non-degradable polymer NCs. The mathematical models developed to predict the permeability are then presented, and the factors that can influence drug delivery in polymer NCs are outlined.

4.1 Drug delivery approaches in polymer nanocomposites

Drug delivery approaches using polymer NC can be broadly categorized into four types, as illustrated in **Figure 4**. All delivery types are based on non-degradable polymer NC systems where release is by means of diffusion or from activation through external stimulus. Depending on the various filler and surfactant combinations, the drug release could be fast, pulsatile, or sustained.

4.1.1 Type 1

Type 1 approaches represent cases where the nanoparticle is the drug. Drugs are released by diffusion from the polymer matrix, and release can be modulated by modifying the polymer composition or concentration of the drug. This type of drug delivery approach is prevalent in antibacterial applications, such as urinary catheters, joint arthroplasty and

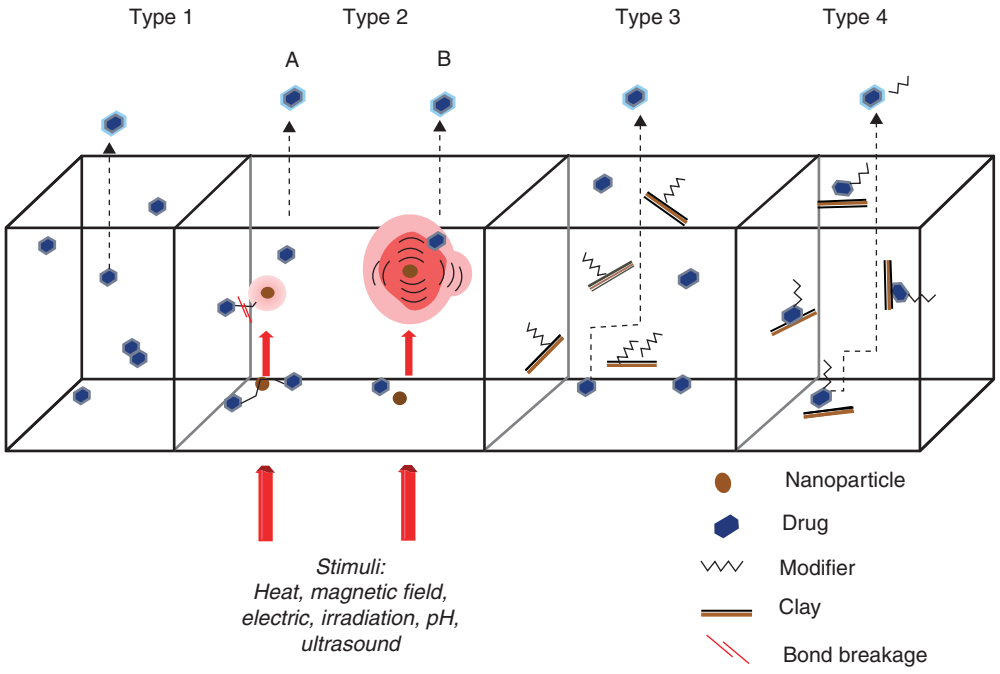

Figure 4. Types of approach for drug delivery in non-degradable polymer nanocomposite. Dotted lines represent the pathway of release. Nanoparticles activated by external stimuli are highlighted in red. Type 1 approach is when the nanoparticle is the drug. Type 2 requires an external stimulus for drug delivery. Activated nanoparticles can cleave the bonded drug (type 2A) or cause a physical change to the polymer (type 2B), thereby inducing release. Type 3 is where drugs are added as a fourth component. Finally, in the type 4 approach, the drug is used as the modifier or a component of the modifying system.

medical packaging [64,65]. Damm *et al.* [65] compared the antimicrobial efficiency of silver nanoparticles and silver microparticles incorporated in polyamide 6. The NC was able to eliminate *Escherichia coli* completely within 24 h of release at a loading of 0.06 wt%, whereas polyamide silver microcomposites killed only 80% of bacteria in the same time with loadings much higher than NC. The silver released from NCs was therapeutically active and released at a higher concentration than from microcomposites owing to the larger surface area of nanoparticles. Hung and Hsu [35], on the other hand, incorporated either silver or gold particles in polyether urethanes. These silver and gold NCs showed much lower bacterial adhesion and reduced monocyte activation compared with neat polyurethane [35]. In addition, following implantation in porcine models, these materials also demonstrated improved *in vivo* biostability compared with neat polyurethane as a result of their capacity for free radical scavenging [32,36].

4.1.2 *Type 2*

Type 2 drug delivery represents polymer NCs that require an activator or external stimulus to assist release. This type can be separated further into two subtypes, where the nanoparticles are bound to the drug and can be activated to release the drug (type 2A), or stimuli-responsive nanoparticles could cause a reversible physical or chemical change to the polymer matrix, thereby enhancing release (type 2B). Nanoparticles that respond to external stimulation have attracted significant interest in the last few years owing to their potential applications in drug delivery [66,67]. By responding to specific external stimuli and releasing drugs in a pulsatile manner, the release is independent of the biological environment and can provide trigger-precise drug doses [68,69]. Drug release under non-stimulated states is dependent on diffusion as well as interactions between the drug and nanoparticle. While under stimulation, a burst release of drug occurs. So far, systems have been developed to respond to irradiation [68-71], heat [72], magnetic fields [73-77], magnetic induced heat [78], pH [79], ultrasound [80], electrical stimuli [81] and even combinations of some of the above [82]. Although the nanoparticles in this type 2 are often used alone or incorporated within a stimuli-responsive polymer hydrogel, this approach can also be applied to non-hydrogel polymers to minimize the loss of drug after repetitive stimulation and potential leaching of cytotoxic nanoparticles.

Electromagnetic radiation in the range 380 – 2500 nm has been applied externally to NC to switch drug release on and off [68]. Wavelengths in the visible light range typically cannot penetrate > 1 cm in the skin owing to scattering, therefore near-infrared (NIR) light (650 – 900 nm) is often used to allow deeper penetration into the tissue [83]. Tanaka and co-workers [71] reported coumarin-modified mesoporous silica

nanoparticles loaded with the steroid cholestane, which respond to UV light. Mesoporous silica nanoparticles are cylindrical structured materials containing a hexagonal array of pores (0.5 – 1.5 cm^3/g) that allow easy loading of drugs. The release of cholestane was achieved through cleavage of the cyclobutane ring of the coumarin dimer by applying UV light at a wavelength of 250 nm [71]. Similarly, Wu *et al.* [69] reported a light responsive silica nanoparticle prepared by covalent conjugation of photoactive *o*-nitrobenzyl bromide molecules with amino groups on the particle surface. Drugs with carboxylic, phosphate, or hydroxyl groups were covalently attached and irradiated at 310 nm. On irradiation, the photoactive groups transformed to cause an irreversible cleavage of the drug–particle bond, inducing drug release [69]. Gold-filled NCs are also materials that display remarkable potential in activated drug delivery systems [66]. The incorporation of NIR-sensitive gold nanorods into a temperature-sensitive hydrogel was reported by Wei *et al.* [72]. NIR-radiated gold nanorods delivered localized heat to the polymer matrix and induced a phase transition of the polymeric chains from coiled to globular. The drug release was observed to be faster in periods of NIR exposure as a result of the breakage of hydrogen bonds between drug and polymer from heat-induced conformational change [72].

The concept of using external magnetic fields to achieve pulsatile release from polymer composites was first investigated by Kost *et al.* [73]. Insulin release was demonstrated from a magnetic bovine zinc insulin ethylene-vinyl acetate copolymer (EVA) composite through a low frequency oscillating magnetic field [73]. This is a very attractive technique because the use of magnetic nanoparticles linked to insulin can provide a sudden influx to the patient when required, such as after a meal. The remaining insulin can then be released more slowly at other times [73]. Alternatively, heat-responsive magnetic nanoparticles are also gaining interest in hyperthermia cancer treatment and areas of chemotherapy where imprecise targeting can be overcome and drugs can be localized and triggered precisely [84]. Magnetically modulated release can be accomplished by either: i) aggregation of magnetic particles embedded in a polymer matrix, leading to shape deformation to promote release [74,75]; or ii) magnetic heating of nanoparticles embedded in a thermally responsive polymer [78]. In i), problems can arise from insufficient force to create an opening in the polymer matrix and chain loosening from repeated friction between the nanoparticles and matrix [75]. Problems related to case ii) would be the loss of drug after each burst and the mesh size eventually becoming comparable to or less than the drug so no release of drug will happen. Therefore, for implantable drug delivery, which requires drug delivery from weeks to months, further improvement of this type of approach is required [78].

4.1.3 Type 3

Type 3 represents cases where the drug is added in polymer NCs that contain inorganic nanofillers, most commonly silicates. Drugs are released through diffusion but are forced to follow a longer path owing to the presence of impermeable nanoparticles. Mathematical models developed to predict barrier properties of this type are the most common in the literature and are discussed in later sections. Drugs in this type of NC delivery system are added as a fourth component in the system [85]. Specific examples of applications of this type of drug delivery system can be found in anti-inflammatory agent delivery systems [86,87]. Studies on the incorporation of dexamethasone into polyurethane clay NC showed that the drug did not lead to a disturbance in morphology and demonstrated an adequate reduction in inflammatory response over 14 days [86]. Similarly, a study by Cypes *et al.* [87] also showed that the controlled release of dexamethasone in this system was achieved by addition of silicate and there was a dependence on silicate loading [87].

Oral chemotherapy is another area of drug delivery that may benefit from NC delivery approaches. Methylmethacrylate chloromethylstyrene copolymer NC (PMMA-MMT) incorporated with active 1,2,4-triazine derivatives were investigated by Salahuddin *et al.* [88] for this purpose. The incorporation of cationic 1,2,4-triazine and their derivatives resulted in a range of release profiles that varied according to pH and the condition of the buffer (acidic or neutral) [88]. Another interesting area using NCs as drug delivery systems is in transdermal pressure-sensitive adhesives. This is to obtain better control over the drug release kinetics and to improve adhesive properties in pressure-sensitive patches [89]. A model dye, solvent blue 35, with physiochemical characteristics similar to commercial drugs in transdermal systems, was used to study the release kinetics. Up to 75% reduction in dye released was observed with 10 wt% clay over a 10-day period with little burst effect. Shear strength also showed a 2.5-fold increase due to the reinforcement of polydimethysiloxane (PDMS) matrix [89].

4.1.4 Type 4

Finally, in type 4 approaches the drug is used as the modifier or a component of the modifying system. Polymer molecules that have the ability to interact with the charged nanofiller surface and also regions that can interact with the polymer matrix can conceivably be used to compatibilize the nanofiller with an organic polymer. A new approach different from other types is where the therapeutic activity was achieved through selection of organic molecules that have a dual function, being a modifier and drug at the same time [90,91]. The use of chlorhexidine (CHX) as both a drug and modifier in PDMS and polyurethane clay NC have been reported [91,92]. Polyurethane clay NC modified with CHX resulted in a range of morphologies that depended on the amount of clay and saturation level of CHX. In both cases where MMT was 100% ion-exchanged with CHX and where free CHX was added, the bacterial number of *S. epidermidis* dropped almost two orders of magnitude [91]. Styan *et al.* [90] previously reported that modifiers such as Ethoquad® O/12PG (EQ)

and 1-aminoundecanoic acid (AUA) possess biological activity either used alone or co-modified. Whereas AUA alone showed no inhibition of bacterial growth but maintained cell viability, an increase in EQ resulted in an increase in activity against *S. epidermidis* but decreased cell growth, suggesting the possibility of controlling antibacterial activity by adjusting levels of EQ [90].

4.2 Mathematical models in describing release

Mathematical models predicting the permeability of polymer NCs are often applied to assess diffusion through polymer matrices with added fillers (type 3). Theoretical models developed for this type of system are the focus of this section and are more complicated than types 1 and 2, where diffusion is through a non-degradable, non-swelling or swelling type polymer membrane [59,93]. Enhanced barrier properties can be explained by the concept of tortuous paths, as shown in **Figure 5**, where nanoparticles act as impermeable barriers forcing the permeating molecules to travel around and follow the longer and more tortuous pathway in order to diffuse through the NC. The tortuosity factor is defined as the ratio of the actual distance the penetrant has to travel to the shortest distance it would travel in the absence of obstacles and is expressed as:

$$t = \frac{\text{Actual distance}}{\text{Shortest distance}} = 1 + \frac{L}{2W}$$

From this expression, it can be seen that the sheet-like morphology of silicates is likely to be more efficient than spherical particles in maximizing the path length owing to the large length-to-width ratio [12,59].

Accurate predictions from various mathematical and computer simulations of barrier properties and drug release behavior are difficult because of the complexity of polymer NC systems. A model commonly referred to in the literature is the tortuous path theory developed by Nielsen [94]. Although highly simplified, it is often used as a preliminary estimation of the permeability behavior in NCs as well as the starting point for the development of further mathematical/computer-based permeability models. It assumes that nanoparticles in the form of platelets with length L and thickness W are distributed evenly and aligned perpendicular to the diffusion direction, as shown in **Figure 5**. The equation is as follows:

$$\frac{P_c}{P_p} = \frac{V_p}{1 + \frac{L}{2W} V_f}$$

where P_c is the permeability of the composite, P_p is the permeability of the polymer, V_p is the volume fraction of the polymer and V_f is the volume fraction of the filler. This relationship shows that the relative permeability of NC decreases with increasing amount of filler and increasing aspect ratio. The limitations of Nielson's model are that it is valid only if the clay loading is < 1 wt% and the assumption of uniform dispersion, size and orientation is often not the case in reality. Several other models that have been proposed to predict the barrier properties of NC are shown in **Table 2**. Many of these are similar to Nielson's model, but have also considered factors such as particle orientation [95], particle shape [96-98], state of aggregation, resistance [99] and polymer–clay interactions within the NC system [100].

The experimental deviation in Neilson's model was observed by Yano *et al.* [101] when the permeability of polyimide–clay hybrid incorporated with four different types of clay mineral was examined. Hectorite and saponite were shown to contain aggregates and were not fully exfoliated, therefore calculated values overestimated the permeability of these respective NCs [101]. Several studies have noted that although the predicted curve based on Nielson's model did not completely match the experimental result as it did not take into account the degree of dispersion, the agreement is satisfactory and can provide a general trend in the permeability behavior in polymer NCs [102,103]. In particular, a study conducted by Choudalakis and Gotsis [93] compared several mathematical models as a function of platelet volume fraction and aspect ratio. It was concluded that Nielson's simple model is adequate in describing the reduction in the relative permeability in polymer NCs.

In summary, most of the models assume that the fillers are a regular and uniform shape in a regular array in space. The assumption is also that fillers are in complete exfoliation and that the physical characteristics of the polymer remain unchanged with the addition of the inorganic particles. The arrangements are usually perpendicular or have an average orientation at an angle to the main direction of diffusing gas molecule. Despite these shortcomings, these models can provide a preliminary guide to the relative permeability of polymer NCs and be used to design systems with desired outcome.

4.3 Factors affecting drug delivery in polymer nanocomposite

The addition of inorganic nanofillers does not always result in a decrease in permeability. Reductions in permeability are highly dependent on the dispersion of the NC. Gorrasi *et al.* [104] observed that the initial decrease in water vapor permeability plateau with increasing filler concentration. Also, a slight increase in permeability was observed at the highest filler concentration, which could be due to filler aggregation. In fact, the largest reduction in permeability can often be correlated with samples showing the best dispersion [105-107]. The presence of non-uniformly dispersed nanofillers affects all delivery types discussed, but in particular the types 3 and 4 approaches. As types 3 and 4 can potentially be used to deliver sustained and controlled therapeutic doses, the drug release is highly dependent on the structure of NCs. However, an exfoliated structure is difficult to achieve as the morphology is easily influenced by factors such as filler content, surfactant type and compatibility between each of the components [108]. Without uniform dispersion, the drug

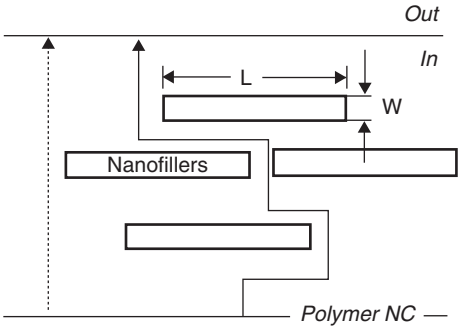

Figure 5. The concept of the tortuous pathway showing the actual distance (filled line) a molecule has to travel in the presence of nanofillers as compared with the shortest distance (dotted line).

release cannot be sustained, controlled and accurately predicted. Uniform dispersion is also important, albeit to a lesser extent, in the types 1 and 2 delivery approaches. Modulation of release from type 1 is largely governed by polymer composition, drug concentration and drug–polymer interaction. As nanoparticles also act as the drug, agglomerated drugs could create fluctuations in drug concentration that could lead to periods of overdose and underdose. Similarly for type 2, if the nanoparticles bound to (type 2A) or situated around (type 2B) the drugs were not uniformly dispersed, the required drug concentration could not be delivered on stimulation.

Another major factor that can influence drug delivery in polymer NCs is component interactions. As mentioned previously, the often adapted tortuous pathway model and most other mathematical models that describe the barrier properties of polymer NCs do not consider the interactions between the diffusing molecule and the polymer, filler or modifier. Several studies in the literature have described drug delivery from polymer NCs where release properties were mainly dependent on the quantity of fillers, aspect ratio, level of exfoliation, charge and the ionic strength of the medium [87,109-112]. However, few studies have examined the interaction between the drug and the constituents of the NC system and how that affects structure and release behavior. It is well known that interactions arising from hydrophobic, van der Waals, hydrogen bonding and cation-exchange processes between the clay and drugs could affect drug release [50]. By using ion-exchange processes, layered clay minerals can accommodate polar organic compounds between the layers and form a variety of intercalated compounds [113]. Basic drugs or molecules tend to form stronger bonds to MMT that retard the release. On the other hand, anionic and non-ionic drugs have much weaker interactions with MMT, resulting in faster release [50].

In the case of polymer clay NCs, where most of the material consists of the polymer matrix, interaction between the drug and polymer could become more dominant than the interactions with clay. One of the few studies that explored this effect in hydrogel NCs was based on negatively charged clays (MMT [112] and bentonite [111], and positively charged clay: hydrotalcite [110,114]) when a variety of model dyes were added. By adding uncharged vitamin B2 to the negatively charged gel, loading and release was dependent on crosslinking density and the swelling ratio of the hydrogels [110,111]. The release of positive crystal violet decreased owing to attractive forces with anionic gel, whereas negative phenol red released rapidly owing to electrostatic repulsion [112,115]. If the charge between the drug and the system is the same, then the release ratio is likely to be higher. For polymer NCs to be used in controlled drug delivery where the polymer matrix is usually neutrally charged, the addition of a fourth component will further complicate the system. These processes are not well understood at present and should be taken into consideration as they can affect the resulting release mechanisms. These studies demonstrated that the enhancement in permeability from polymer NCs is dependent on dispersion, filler content, compatibility and interactions between each of the components in the system. A good theoretical understanding of the likely interactions between components combined with experimental confirmation of the NC structure–property relationships is required to develop a robust NC drug delivery system.

5. Conclusion

Over the last 20 years, polymer NCs have been widely investigated owing to dramatic increases in their mechanical and thermal properties. Furthermore, these improvements can be achieved at filler concentrations much lower than conventional composites, greatly reducing the mass of the material. The main challenge in NCs is to achieve uniform dispersion in order to prevent the particulates acting as stress concentrators, thus affecting rigidity, strength and elongation properties. The marked improvement observed in mechanical properties of NCs initially sparked interest in the automotive and aerospace industry. However, the subsequent discovery of altered barrier properties has resulted in the study of NCs as alternatives to existing medical device materials. In particular, a variety of nanofillers and polymers for polymer NCs is being investigated for use in drug delivery systems. Some of these nanofillers, such as smectite clays, LDH and CNT, do not contain any biological activity but are intended to improve the mechanical and barrier properties of NCs. They can then be modified to provide biological activity or used alongside a biological molecule for therapeutic purposes. Smectite clays still remain the most commonly used nanofiller in polymer NCs as they are inexpensive and easily modified and the sheet-like morphology is optimal for both barrier and mechanical improvements.

Drug delivery in polymer NCs can be categorized into four broad types, all of which have different delivery approaches (diffusion or activation) and intended purposes (fast, pulsatile or sustained release). In the case where the nanoparticle is the drug, the type 1 delivery approach is more suited to

Table 2. Theoretical models in predicting barrier properties of polymer nanocomposites [14,93,95-98,116].

Model	Filler type	Formula
Nielson	Ribbon	$\frac{P_c}{P_p} = \frac{1-\Phi}{1+\frac{\alpha}{2}\Phi}$
Cussler (regular array)	Ribbon	$\frac{P_c}{P_p} = (1+\frac{\alpha^2\Phi^2}{1-\Phi})^{-1}$
Cussler (random array)	Ribbon	$\frac{P_c}{P_p} = (1+\frac{\mu'\alpha^2\Phi^2}{1-\Phi})^{-1}$
Fredrickson-Bicerano	Disk	$\frac{P_c}{P_p} = \frac{1}{1+\mu\alpha^2\phi^2}$ where $\mu = \frac{P^2}{16\ln^2\alpha}$
Gusev and Lusti	Disk	$\frac{P_c}{P_p} = \exp\left[-\left(\frac{\alpha\phi}{3.47}\right)^{0.71}\right]$
Bharadwaj	Ribbon	$\frac{P_c}{P_p} = \frac{1-\Phi}{1+\frac{\alpha}{2}\Phi\left(\frac{2}{3}\right)\left(S+\frac{1}{2}\right)}$

For ribbon α: Length/thickness; For disk α: Radius/thickness; Φ: Volume fraction of the filler; P_c: Permeability of composite; P_p: Permeability of polymer; α: Aspect ratio (width to thickness); μ': Geometric factor; S: Orientation factor (from -1/2 to 1).

short-term applications involving fast release. These can include coatings for drug eluting balloons and devices that only need anti-inflammatory/anti-thrombotic effects during or after implantation. Types 2 – 4 should be considered in applications where the main objective is to control drug release. The stimuli-responsive nature in type 2 has rapidly gained attention in the last few years as 'bursts' of drugs can be released when needed. Gold, iron particles and mesoporous silica are all nanoparticles widely investigated in this type and are able to release the drug through direct cleavage or by causing a conformational change to the polymer matrix.

The initial driving force for research of polymer NCs in drug delivery arose from type 3 delivery systems. This is one of the most commonly used NC-based delivery approaches in releasing therapeutic molecules. The drug release behavior in this type can be modulated through adjusting filler concentration, level of dispersion and potential drug interactions. Related to this are type 4 approaches, which have the active agent acting in dual roles as both surfactant and bioactive molecule. Achieving uniform dispersion and understanding the interactions between constituents in these two types of system is of critical importance for the development of a robust, predictable delivery system. Release behavior can deviate from mathematical predictions as fillers are typically not 'perfectly' exfoliated and the addition of clay may in fact actively promote or retard release due to drug–clay or drug–polymer interactions.

In summary, polymer NCs offer the flexibility to accommodate a wide range of therapeutic drugs. Through careful selection of drug and filler/polymer combination, a release profile that optimally addresses the intended application can be provided.

6. Expert opinion

The major advantages of polymer NC include improved mechanical and thermal properties combined with the ability to modulate barrier properties. However, only a few polymer NCs have been manufactured and used commercially, with the most publicized application being a timing belt cover developed by Toyota. The reasons for the slow uptake of this technology in medical applications are mainly related to limited theoretical knowledge and, consequently, poor understanding about how to control nanofiller dispersion, a key factor in determining NC properties. Different combinations of polymer, filler, surfactant and modification technique result in different properties and modes of drug release. Also, the greatest hurdle in large-scale manufacturing is the development of a universal processing technique to produce NCs with required or even tailored properties for a specific application. This requires not only extensive laboratory testing but also a fundamental understanding of the structure–property relationship of NCs. Without a universal processing technique, the properties of NCs cannot be controlled or replicated.

The observation that barrier properties may be modulated in NCs is of high interest in developing materials for drug delivery. Depending on the intended purpose, drug delivery from polymer NCs can be fast and short lived, sustained or trigger-precise. Fillers from different approaches can act as reinforcement, possess biological features, or both. The delivery approaches described in types 3 and 4 are by far the most commonly studied both experimentally and theoretically in the literature. This is because both mechanical and barrier properties can be improved at the same time. A key issue that remains unresolved, particularly with type 3 and 4 systems, is nanofiller dispersion. As modulation of release occurs through the addition of nanofillers, increasing the nanofiller content will inevitably increase the likelihood of clumping. Therefore, there is an optimum amount of nanofiller content to reduce permeability but still maintain dispersion.

As in industrial applications, polymer NCs, although studied extensively as drug delivery systems, have not yet been widely used in biomedical devices. The challenges presented for developing these materials for the typically lower volume biomedical applications are in part similar to those for larger scale applications. The drug permeability in polymer NC can be significantly perturbed by the varied properties of the components that affect drug diffusion and partitioning (or interaction). The addition of drug to the NC can also have

a detrimental impact on the dispersion of the nanofiller. A continuing challenge for the field is to understand better the key interactions between the drug and the polymer, nanofiller and/or the surfactant. This knowledge will contribute to the development of more accurate models that will ultimately allow prediction of the behavior of the drug in a NC system

Declaration of interest

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